ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2019 January 23; 8(1): 1-8

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Irregular Volume 8 Number 1 January 23, 2019

EDITORIAL

Contents

World Journal of Critical Care Medicine

Volume 8 Number 1 January 23, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Edward A Bittner, FACE, FCCP, MD, PhD, Associate Professor, Staff Physician, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA 02114, United States

AIMS AND SCOPE

World Journal of Critical Care Medicine (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCCM covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, *etc.*

We encourage authors to submit their manuscripts to *WJCCM*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Critical Care Medicine (*WJCCM*) is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Ying-Na Bian* **Proofing Editorial Office Director:** *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
Kam Lun Ellis Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
January 23, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 January 23; 8(1): 1-8

DOI: 10.5492/wjccm.v8.i1.1

ISSN 2220-3141 (online)

EDITORIAL

Expiratory flow-limitation in mechanically ventilated patients: A risk for ventilator-induced lung injury?

Antonia Koutsoukou, Matteo Pecchiari

ORCID number: Antonia Koutsoukou (0000-0002-1536-3205); Matteo Pecchiari (0000-0003-0513-9311).

Author contributions: Koutsoukou A conceived the study; Koutsoukou A and Pecchiari M drafted the manuscript; both authors approved the final version of the article.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Manuscript source: Invited manuscript

Received: July 13, 2018
Peer-review started: July 13, 2018
First decision: August 3, 2018
Revised: August 24, 2018
Accepted: October 17, 2018
Article in press: October 17, 2018
Published online: January 23, 2019

Antonia Koutsoukou, ICU, 1st Department of Respiratory Medicine, National and Kapodistrian University of Athens Medical School, Athens 11527, Greece

Matteo Pecchiari, Dipartimento di Fisiopatologia e dei Trapianti, Università degli Studi di Milano, Milan 20133, Italy

Corresponding author: Antonia Koutsoukou, PhD, Professor, ICU, 1st Department of Respiratory Medicine, National and Kapodistrian University of Athens Medical School, "Sotiria" Hospital for Diseases of the Chest, 152 Mesogion Av, Athens 11527, Greece. koutsoukou@yahoo.gr
Telephone: +30-210-7763718
Fax: +30-210-7781250

Abstract

Expiratory flow limitation (EFL), that is the inability of expiratory flow to increase in spite of an increase of the driving pressure, is a common and unrecognized occurrence during mechanical ventilation in a variety of intensive care unit conditions. Recent evidence suggests that the presence of EFL is associated with an increase in mortality, at least in acute respiratory distress syndrome (ARDS) patients, and in pulmonary complications in patients undergoing surgery. EFL is a major cause of intrinsic positive end-expiratory pressure (PEEPi), which in ARDS patients is heterogeneously distributed, with a consequent increase of ventilation/perfusion mismatch and reduction of arterial oxygenation. Airway collapse is frequently concomitant to the presence of EFL. When airways close and reopen during tidal ventilation, abnormally high stresses are generated that can damage the bronchiolar epithelium and uncouple small airways from the alveolar septa, possibly generating the small airways abnormalities detected at autopsy in ARDS. Finally, the high stresses and airway distortion generated downstream the choke points may contribute to parenchymal injury, but this possibility is still unproven. PEEP application can abolish EFL, decrease PEEPi heterogeneity, and limit recruitment/derecruitment. Whether increasing PEEP up to EFL disappearance is a useful criterion for PEEP titration can only be determined by future studies.

Key words: Expiratory flow-limitation; Mechanical ventilation; Ventilator-induced lung injury; Acute respiratory distress syndrome; Positive end-expiratory pressure; Intrinsic positive end-expiratory pressure

Core tip: Expiratory flow limitation (EFL), the inability of expiratory flow to increase despite increasing driving pressure, is a common unrecognized occurrence during mechanical ventilation in a variety of intensive care unit conditions. It implies cyclic compression/decompression of the airways, is associated with intrinsic positive end-expiratory pressure (PEEPi) and inhomogeneous filling, and is often concomitant with cyclic recruitment/derecruitment. In acute respiratory distress syndrome, the development of abnormally high stresses is potentially injurious for the lung. External PEEP abolishes EFL and decreases ventilation and intrinsic PEEP heterogeneity, improving gas exchange. Moreover, external PEEP prevents cyclic airway collapse/reopening, possibly protecting the parenchyma from low lung volume ventilator-induced lung injury.

Citation: Koutsoukou A, Pecchiari M. Expiratory flow-limitation in mechanically ventilated patients: A risk for ventilator-induced lung injury? *World J Crit Care Med* 2019; 8(1): 1-8
URL: https://www.wjgnet.com/2220-3141/full/v8/i1/1.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i1.1

MAIN TEXT

Expiratory flow limitation (EFL) is present when, at a given lung volume, expiratory flow cannot be augmented by increasing the driving pressure, which is the difference between the pressure at the entrance of the respiratory system and the alveoli[1,2].

During a forced expiratory vital capacity maneuver, EFL is reached after the peak expiratory flow[3] or even during the peak[4]. When EFL is established, flow can not be increased by increasing the expiratory effort and thus is maximal[5].

In most normal subjects, EFL is absent even during maximal exercise[6]. Conversely, in patients with respiratory disorders, it may appear at moderate levels of exercise or even at rest, during tidal breathing[7].

Traditionally, in spontaneously breathing subjects, EFL has been detected by superimposing the flow-volume loop recorded during a tidal breath with that of the same loop recorded during a forced vital capacity maneuver, when the expiratory flow is maximal[8]. If the expiratory flows during tidal breathing are less than the maximal expiratory flow at each volume, tidal EFL is absent. Mead-Whittenberger's method and the forced oscillation technique method infer the presence of EFL from the increase of alveolar pressure in front of a decreasing flow and from a within-breath difference between inspiration and expiration in terms of reactance, respectively. Both these findings are suggestive but not demonstrative of the presence of EFL[9]. A plethysmographic method for EFL detection not requiring the introduction of an esophageal balloon is under development[10].

The Hyatt's method requires the subject's cooperation, and it is affected by methodological problems related to gas compression and variable volume history[11]. To overcome these issues, a new method, the negative expiratory pressure (NEP) technique, was developed a few decades ago[12]. During a test breath, the driving pressure is artificially increased by the application of a small negative pressure (-5 cmH_2O) during the expiration, and the resulting flow-volume trajectory is compared with one recorded without NEP application: the superimposition of the two trajectories indicates the presence of tidal EFL. The extent of EFL is quantified as the proportion of tidal volume (V_T) over which the expiratory flow with and without NEP superimpose and is expressed as a percentage of the control V_T[12]. The NEP technique is currently considered the gold standard for EFL detection in spontaneously breathing subjects.

The NEP technique can also be applied to mechanically ventilated patients[12] (Figure 1), but it requires a special apparatus connected with the ventilator. A study using a fixed level of NEP rose concerns regarding the possibility that the NEP technique overestimates the extent of EFL in mechanically ventilated subjects by causing airway collapse[13], but it remains to be determined if the problem can be solved by reducing the level of NEP. Alternatively, EFL can be detected by comparing the expiratory flow-volume loops recorded with two different levels of positive end-expiratory pressure (PEEP) or with PEEP and zero end-expiratory pressure (ZEEP)[14,15]. If at a given volume expiratory flow does not change despite the change in driving pressure, EFL is present. Clearly, the last two techniques cannot be used to

detect EFL in patients mechanically ventilated at ZEEP. The driving pressure for expiration can be increased by manually compressing the abdomen, as done in both spontaneously breathing[16] and mechanically ventilated subjects[17]. The interrupter technique can give indications of EFL in mechanically ventilated patients but is demanding in the clinical settings[13]. Additionally, tidal EFL can be assessed as the lack of change in the expiratory flow-volume loop after the insertion a resistance on the expiratory limb of the ventilator[13]. The so called atmosphere method consists of disconnecting the ventilator expiratory limb at end-inflation, a maneuver in patients with tidal EFL that does not elicit any effect in terms of expiratory flow-volume loop[18].

An in-depth discussion of the mechanisms responsible for the genesis of EFL may be found elsewhere[9]. Briefly, EFL may stem from two mechanisms: (1) the coupling between airways compliance and convective acceleration of gas (wave-speed theory)[19]; or (2) the coupling between airways compliance and viscous pressure losses[20]. In a normal subject, the former mechanism, non-dissipative and gas density-dependent, predominates at high lung volumes, whereas the latter, dissipative and gas viscosity-dependent, predominates at low lung volumes.

In pathological conditions, tidal EFL may occur due to a decrease of maximal expiratory flows or to an increase of the expiratory flows secondary to an increased ventilatory demand. Moreover, as maximal expiratory flows are volume-dependent (*i.e.*, they decrease with decreasing lung volume), any decrease of lung volume facilitates the occurrence of tidal EFL.

During spontaneous breathing in the seated position, tidal EFL at rest is present in many chronic obstructive pulmonary disease (COPD)[1,2,7] and in some cystic fibrosis patients[21], conditions characterized by a marked reduction of the maximal expiratory flow. EFL has been detected in 20% of sitting patients with acute heart failure[22], while it is absent in subjects with chronic heart failure in the same position[23,24]. Reducing the ventilatory demand by increasing ventilatory efficiency may cause EFL to disappear in COPD patients[25].

On turning to supine position, the prevalence of EFL increases in COPD and acute heart failure patients[22,26], and EFL appears in chronic heart failure patients[23,24]. Positional changes markedly affect the prevalence of tidal EFL in massively obese subjects, increasing the percentage of subjects with EFL from 22 (sitting) to 59 (supine)[27].

A limited number of studies have investigated the prevalence and severity of tidal EFL in critically ill patients, but the evidence collected so far shows that tidal EFL is a common occurrence in the intensive care unit (ICU).

At ZEEP, tidal EFL is present in the majority of COPD patients requiring mechanical ventilation during an exacerbation[13,28] and in two-thirds of morbidly obese patients who had undergone abdominal surgery[29]. In the former group, tidal EFL may be attributed to the decrease of maximal expiratory flow, whereas in the latter group, the occurrence of tidal EFL should be a consequence of the reduction of functional residual capacity (FRC), compromised by anesthesia, paralysis, abdominal surgery, and supine position[30].

Similarly, the reduction of FRC after induction of anesthesia may in part explain the finding that 30% of patients undergoing major surgery exhibited tidal EFL intraoperatively[31].

Armaganidis *et al*[32], using the NEP technique, showed that 11 out of 13 patients with acute respiratory failure resulting from pulmonary diseases exhibited tidal EFL. A larger cohort found that about 60% of 100 patients enrolled exhibited tidal EFL at ZEEP[33].

Tidal EFL has also been detected by the NEP technique in the majority of acute respiratory distress syndrome (ARDS) patients mechanically ventilated on ZEEP[34,35]. The prevalence of tidal EFL decreases up to 20% with 5 cmH_2O PEEP[18].

A study on 64 ARDS patients found that mortality at the time of discharge was greater in patients with tidal EFL (8/13) than in those without it (12/51)[18]. Moreover, the presence of EFL intraoperatively is a strong predictor of postoperative pulmonary complications[31]. Overall, these data suggest that tidal EFL may play a role in determining outcome. This suggestion is supported by the known clinical consequences of tidal EFL in the ICU settings.

Tidal EFL is associated with pulmonary hyperinflation and intrinsic PEEP (for an excellent review of the topic, see Laghi and Goyal, 2012)[36]. Hyperinflation causes alveolar overdistension, decreases compliance, and worsens diaphragm function by decreasing the zone of apposition[37]. In mechanically ventilated patients, flattening of the diaphragm may facilitate mechanical ventilation-induced diaphragmatic damage[38]. Moreover the presence of PEEPi represents a threshold inspiratory load, which the inspiratory muscles should overcome in order to produce inspiratory flow[39], making weaning difficult and contributing to patient-ventilator asynchrony[40].

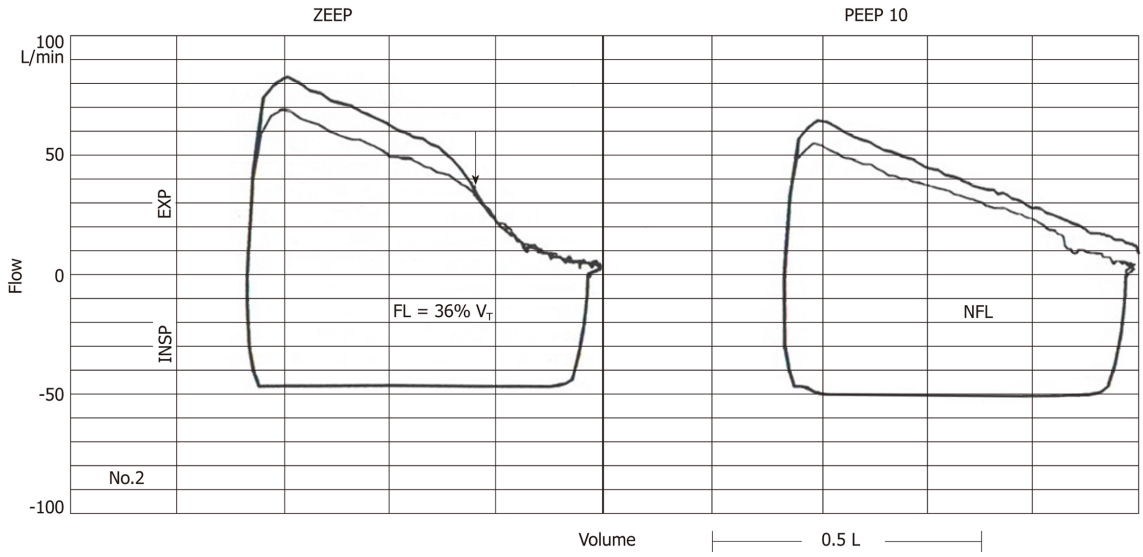


Figure 1 Flow-volume loops of negative expiratory pressure test breath and preceding control breath for two representative acute respiratory distress syndrome patients, one with expiratory flow limitation exceeding 35% of control tidal volume (left side) and the other without expiratory flow limitation (right side). Thin lines: Control breath; heavy lines: Negative expiratory pressure. In the expiratory flow limitation (EFL) patient, onset of EFL is heralded by an inflection point on the expiratory flow-volume curve (arrow). Reproduced with permission of the American Thoracic Society[34]. ZEEP: Zero end-expiratory pressure; PEEP: Positive end-expiratory pressure; V_T: Tidal volume.

Additionally, PEEPi can increase intrathoracic pressure (decreasing preload) and pulmonary vascular resistance (increasing the afterload of the right ventricle)[41], with resultant hemodynamic depression[42].

In patients with acute respiratory failure, PEEPi was on average six times greater in patients with tidal EFL than in patients without it (7.1 *vs* 1.2 cmH_2O)[32], and significant correlations were found between PEEPi and the percentage of the V_T in which EFL was present in semirecumbent and supine ARDS patients mechanically ventilated at ZEEP[34]. Similar correlations were found at ZEEP in morbidly obese subjects[29], reinforcing the notion that EFL is the major determinant of PEEPi in most clinical conditions. When PEEPi was measured in semirecumbent and supine ARDS patients, it was lower in the former than in the latter position.

In COPD patients, PEEPi may be reduced by bronchodilators[43], which cause the maximal expiratory flows to increase, reducing hyperinflation, despite the persistence of EFL[44]. To the contrary, pharmacological treatment is limited in ARDS patients[45], and thus the effects of regional or global EFL should be managed by carefully adjusting ventilator settings.

A PEEP of 10 cmH_2O abolished EFL and improved arterial blood oxygenation[34] in 10 ARDS patients. Notably, the distribution of regional PEEPi was inhomogeneous in these patients, as indicated by the low ratio between dynamic PEEPi (the pressure that should be applied at the beginning of inspiration to produce the inspiratory flow, PEEPi, dyn) and static PEEPi (the pressure that can be measured after the equilibration of PEEPi in all the communicating lung units, PEEPi, st)[35], indicating that in the presence of EFL, lung emptying is non-homogeneous with consequent ventilation/perfusion mismatch and gas exchange abnormalities[35]. Actually, PEEP application resulted in a decrease of inhomogeneity of regional PEEPi, and in patients with EFL, it improved oxygenation proportionally to the increase of the ratio between PEEPi,dyn and PEEPi,st. Thus, the reduction of PEEPi inequality can be one mechanism by which the application of external PEEP to mechanically ventilated ARDS patients improves oxygenation.

The decrease of FRC and the reduction of the number of functional lung units, which are typical characteristics of the ARDS lungs, may in part explain the diminished expiratory flow reserve and, thus, the occurrence of EFL in these patients. In this regard, it should be noted that breathing at low lung volume promotes airway closure and gas trapping, with further reduction in expiratory flow reserve. Surfactant deficiency should also promote small airway closure in these patients[46,47]. In ARDS patients, the onset of EFL is heralded by a distinctive inflection on the flow-volume curve[34,35], suggesting a reduction in the number of functional units due to small airway closure. Recently, massive reopening of airspaces in ARDS patients have been documented[48], and a reopening pattern on the volume-pressure curve was noted in 11 on 13 ARDS patients with EFL (the same pattern was present in only 10 on 52

patients without EFL)[18]. Note that if a substantial number of units are not in communication with the central airways, PEEPi,st underestimates the average alveolar pressure at end-expiration[48].

Cyclic opening and closing of airspaces during tidal ventilation has several detrimental effects on the lungs in addition to worsened ventilation/perfusion mismatch. In 1984, Robertson *et al*[49] suggested that ventilation at low lung volume may cause lung injury as a result of shear stresses caused by cyclic opening and closing of peripheral airways. This idea was later substantiated by Muscadere and coworkers[50], who, in an *ex vivo* model of lavaged rat lung, demonstrated that ventilation with physiologic V_T at ZEEP resulted in a significant increase of the injury scores of respiratory and membranous bronchioles relative to ventilation from a PEEP above the lower inflection point on the static inflation pressure-volume curve of the lung. Subsequent experimental research showed that surfactant deficiency is not a prerequisite for this kind of injury, which was also detected in normal open-chest or closed-chest rabbits and rats ventilated with physiological V_T below FRC[51-54]. These studies confirmed that ventilation at low lung volume causes epithelial necrosis and sloughing at the bronchial level. Moreover, they showed in the same condition that alveolar-parenchymal uncoupling is produced, that is rupture of the alveolar walls connected to the outer surface of bronchioles, probably as the result of abnormal stresses developing in the heterogeneous parenchyma. Indeed, when aerated lung areas are adjacent to collapsed ones, they function as stress-concentrators, generating excessive strain at the interface between collapsed and expanded alveoli[55]. Bronchiolar and parenchymal damage was associated with leukocytes recruitment in the alveolar septa[52]. Low volume mechanical ventilation has been found to induce transient ruptures of the cell membrane at the level of bronchioles and alveolar septa, with the number of bronchiolar lesions correlating with the increase of airway resistance[56].

All these phenomena may be relevant in mechanically ventilated ARDS because of the reduction of FRC and the gross mechanical heterogeneity of the lung parenchyma. Not surprisingly, small airway abnormalities in ARDS have been confirmed in autopsy studies[57].

Finally, the potential role of tidal EFL in eliciting ventilator-induced lung injury remains a concern.

When EFL develops, choke points appear that move along the tracheobronchial tree as the lung volume decreases. At the choke points, cross-section is small, and velocity is high. Downstream the choke points, the cross-section may further decrease, velocity may become supercritical, and the excess of energy be dissipated in a region where the cross-section suddenly increases together with lateral pressure[9]. Moreover, in the same region, flutter can appear[9]. Are the shear stresses and local deformations so generated sufficiently high to damage lung parenchyma? To the best of our knowledge, there have been no experimental studies specifically aimed to demonstrate a direct injurious effect elicited by this mechanism independently of parenchymal heterogeneity and airway collapse. However, some evidence suggests that this possibility is worth investigating. Indeed, a modeling study showed that heterogeneous narrowing of small airways can amplify several-fold shear stress on the epithelial layer of the airways[58], and, during mechanical ventilation with physiological V_T and normal end-expiratory lung volume, parenchymal distortion by itself is able to elicit an inflammatory response in normal animals[59].

In conclusion, EFL during tidal breathing is a frequent occurrence in the ICU. It implies cyclic compression/decompression of the airways, and it is often associated with cyclic recruitment/derecruitment together with inhomogeneous filling of airspaces. In ARDS lungs, this probably entails the development of abnormally high stresses with the risk of low lung volume injury[34,35]. This risk may not be confined to ARDS but could be present in all patients who exhibit EFL during mechanical ventilation, such as morbidly obese patients[29]. The application of external PEEP abolishes EFL[34], improving lung emptying and decreasing the heterogeneity of ventilation distribution and of PEEPi, with a resultant improvement in gas exchange[35]. Even if the NEP technique is no longer available as a clinical tool, EFL can be easily detected in the ICU using simpler methods, such as comparing the expiratory flow-volume loops recorded with two different levels of PEEP or the atmosphere method. Detection of tidal EFL in the ICU may not be of only prognostic value: for example, increasing the external PEEP until the disappearance of tidal EFL may become a useful complementary procedure of PEEP optimization. Only more experimental studies can establish if the prompt recognition of tidal EFL can be useful to optimize the management of patients under mechanical ventilation and improve the outcome.

REFERENCES

1 **Eltayara L**, Becklake MR, Volta CA, Milic-Emili J. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; **154**: 1726-1734 [PMID: 8970362 DOI: 10.1164/ajrccm.154.6.8970362]

2 **Koulouris NG**, Dimopoulou I, Valta P, Finkelstein R, Cosio MG, Milic-Emili J. Detection of expiratory flow limitation during exercise in COPD patients. *J Appl Physiol (1985)* 1997; **82**: 723-731 [PMID: 9074955 DOI: 10.1152/jappl.1997.82.3.723]

3 **HYATT RE**, SCHILDER DP, FRY DL. Relationship between maximum expiratory flow and degree of lung inflation. *J Appl Physiol* 1958; **13**: 331-336 [PMID: 13587411 DOI: 10.1152/jappl.1958.13.3.331]

4 **Tantucci C**, Duguet A, Giampiccolo P, Similowski T, Zelter M, Derenne JP. The best peak expiratory flow is flow-limited and effort-independent in normal subjects. *Am J Respir Crit Care Med* 2002; **165**: 1304-1308 [PMID: 11991884 DOI: 10.1164/rccm.2012008]

5 **Volta CA**, Ploysongsang Y, Eltayara L, Sulc J, Milic-Emili J. A simple method to monitor performance of forced vital capacity. *J Appl Physiol (1985)* 1996; **80**: 693-698 [PMID: 8929617 DOI: 10.1152/jappl.1996.80.2.693]

6 **Mota S**, Casan P, Drobnic F, Giner J, Ruiz O, Sanchis J, Milic-Emili J. Expiratory flow limitation during exercise in competition cyclists. *J Appl Physiol (1985)* 1999; **86**: 611-616 [PMID: 9931198 DOI: 10.1152/jappl.1999.86.2.611]

7 **D'Angelo E**, Santus P, Civitillo MF, Centanni S, Pecchiari M. Expiratory flow-limitation and heliox breathing in resting and exercising COPD patients. *Respir Physiol Neurobiol* 2009; **169**: 291-296 [PMID: 19770071 DOI: 10.1016/j.resp.2009.09.009]

8 **HYATT RE**. The interrelationships of pressure, flow, and volume during various respiratory maneuvers in normal and emphysematous subjects. *Am Rev Respir Dis* 1961; **83**: 676-683 [PMID: 13717137]

9 **Pedersen OF**, Butler JP. Expiratory flow limitation. *Compr Physiol* 2011; **1**: 1861-1882 [PMID: 23733691 DOI: 10.1002/cphy.c100025]

10 **Radovanovic D**, Pecchiari M, Pirracchio F, Zilianti C, D'Angelo E, Santus P. Plethysmographic Loops: A Window on the Lung Pathophysiology of COPD Patients. *Front Physiol* 2018; **9**: 484 [PMID: 29765337 DOI: 10.3389/fphys.2018.00484]

11 **Calverley PM**, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. *Eur Respir J* 2005; **25**: 186-199 [PMID: 15640341 DOI: 10.1183/09031936.04.00113204]

12 **Valta P**, Corbeil C, Lavoie A, Campodonico R, Koulouris N, Chassé M, Braidy J, Milic-Emili J. Detection of expiratory flow limitation during mechanical ventilation. *Am J Respir Crit Care Med* 1994; **150**: 1311-1317 [PMID: 7952558 DOI: 10.1164/ajrccm.150.5.7952558]

13 **Lourens MS**, Berg BV, Hoogsteden HC, Bogaard JM. Detection of flow limitation in mechanically ventilated patients. *Intensive Care Med* 2001; **27**: 1312-1320 [PMID: 11511944 DOI: 10.1007/s001340101010]

14 **Rossi A**, Polese G, Milic-Emili J. Monitoring respiratory mechanics in ventilator-dependent patients. In: Tobin MJ. Principles and practice of intensive care monitoring. New York: McGraw-Hill; 1998; 597-616

15 **Marangoni E**, Alvisi V, Ragazzi R, Mojoli F, Alvisi R, Caramori G, Astolfi L, Volta CA. Respiratory mechanics at different PEEP level during general anesthesia in the elderly: a pilot study. *Minerva Anestesiol* 2012; **78**: 1205-1214 [PMID: 22772859]

16 **Ninane V**, Leduc D, Kafi SA, Nasser M, Houa M, Sergysels R. Detection of expiratory flow limitation by manual compression of the abdominal wall. *Am J Respir Crit Care Med* 2001; **163**: 1326-1330 [PMID: 11371396 DOI: 10.1164/ajrccm.163.6.2004150]

17 **Lemyze M**, Favory R, Alves I, Perez T, Mathieu D. Manual compression of the abdomen to assess expiratory flow limitation during mechanical ventilation. *J Crit Care* 2012; **27**: 37-44 [PMID: 21798707 DOI: 10.1016/j.jcrc.2011.05.011]

18 **Yonis H**, Mortaza S, Baboi L, Mercat A, Guérin C. Expiratory Flow Limitation Assessment in Patients with Acute Respiratory Distress Syndrome. A Reappraisal. *Am J Respir Crit Care Med* 2018; **198**: 131-134 [PMID: 29466674 DOI: 10.1164/rccm.201711-2326LE]

19 **Dawson SV**, Elliott EA. Wave-speed limitation on expiratory flow-a unifying concept. *J Appl Physiol Respir Environ Exerc Physiol* 1977; **43**: 498-515 [PMID: 914721 DOI: 10.1152/jappl.1977.43.3.498]

20 **Shapiro AH**. Steady flow in collapsible tubes. *J Biomech Eng* 1977; **99**: 126-147 [DOI: 10.1115/1.3426281]

21 **Goetghebeur D**, Sarni D, Grossi Y, Leroyer C, Ghezzo H, Milic-Emiri J, Bellet M. Tidal expiratory flow limitation and chronic dyspnoea in patients with cystic fibrosis. *Eur Respir J* 2002; **19**: 492-498 [PMID: 11936528 DOI: 10.1183/09031936.02.00220702]

22 **Duguet A**, Tantucci C, Lozinguez O, Isnard R, Thomas D, Zelter M, Derenne JP, Milic-Emili J, Similowski T. Expiratory flow limitation as a determinant of orthopnea in acute left heart failure. *J Am Coll Cardiol* 2000; **35**: 690-700 [PMID: 10716472 DOI: 10.1016/S0735-1097(99)00627-0]

23 **Pecchiari M**, Anagnostakos T, D'Angelo E, Roussos C, Nanas S, Koutsoukou A. Effect of heliox breathing on flow limitation in chronic heart failure patients. *Eur Respir J* 2009; **33**: 1367-1373 [PMID: 19164349 DOI: 10.1183/09031936.00117508]

24 **Torchio R**, Gulotta C, Greco-Lucchina P, Perboni A, Avonto L, Ghezzo H, Milic-Emili J. Orthopnea and tidal expiratory flow limitation in chronic heart failure. *Chest* 2006; **130**: 472-479 [PMID: 16899847 DOI: 10.1378/chest.130.2.472]

25 **Theodorakopoulou EP**, Gennimata SA, Harikiopoulou M, Kaltsakas G, Palamidas A, Koutsoukou A, Roussos C, Kosmas EN, Bakakos P, Koulouris NG. Effect of pulmonary rehabilitation on tidal expiratory flow limitation at rest and during exercise in COPD patients. *Respir Physiol Neurobiol* 2017; **238**: 47-54 [PMID: 28109942 DOI: 10.1016/j.resp.2017.01.008]

26 **Pecchiari M**, Pelucchi A, D'Angelo E, Foresi A, Milic-Emili J, D'Angelo E. Effect of heliox breathing on dynamic hyperinflation in COPD patients. *Chest* 2004; **125**: 2075-2082 [PMID: 15189924 DOI: 10.1378/chest.125.6.2075]

27 **Ferretti A**, Giampiccolo P, Cavalli A, Milic-Emili J, Tantucci C. Expiratory flow limitation and orthopnea in massively obese subjects. *Chest* 2001; **119**: 1401-1408 [PMID: 11348945 DOI:

10.1378/chest.119.5.1401]
28 **Alvisi V**, Romanello A, Badet M, Gaillard S, Philit F, Guérin C. Time course of expiratory flow limitation in COPD patients during acute respiratory failure requiring mechanical ventilation. *Chest* 2003; **123**: 1625-1632 [PMID: 12740283 DOI: 10.1378/chest.123.5.1625]
29 **Koutsoukou A**, Koulouris N, Bekos B, Sotiropoulou C, Kosmas E, Papadima K, Roussos C. Expiratory flow limitation in morbidly obese postoperative mechanically ventilated patients. *Acta Anaesthesiol Scand* 2004; **48**: 1080-1088 [PMID: 15352952 DOI: 10.1111/j.1399-6576.2004.00479.x]
30 **Hedenstierna G**, Strandberg A, Brismar B, Lundquist H, Svensson L, Tokics L. Functional residual capacity, thoracoabdominal dimensions, and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. *Anesthesiology* 1985; **62**: 247-254 [PMID: 3977112 DOI: 10.1097/00000542-198503000-00007]
31 **Spadaro S**, Caramori G, Rizzuto C, Mojoli F, Zani G, Ragazzi R, Valpiani G, Dalla Corte F, Marangoni E, Volta CA. Expiratory Flow Limitation as a Risk Factor for Pulmonary Complications After Major Abdominal Surgery. *Anesth Analg* 2017; **124**: 524-530 [PMID: 27537927 DOI: 10.1213/ANE.0000000000001424]
32 **Armaganidis A**, Stavrakaki-Kallergi K, Koutsoukou A, Lymberis A, Milic-Emili J, Roussos C. Intrinsic positive end-expiratory pressure in mechanically ventilated patients with and without tidal expiratory flow limitation. *Crit Care Med* 2000; **28**: 3837-3842 [PMID: 11153623 DOI: 10.1097/00003246-200012000-00015]
33 **Natalini G**, Tuzzo D, Rosano A, Testa M, Grazioli M, Pennestrì V, Amodeo G, Berruto F, Fiorillo M, Peratoner A, Tinnirello A, Filippini M, Marsilia PF, Minelli C, Bernardini A; VENTILAB group. Effect of external PEEP in patients under controlled mechanical ventilation with an auto-PEEP of 5 cmH2O or higher. *Ann Intensive Care* 2016; **6**: 53 [PMID: 27306887 DOI: 10.1186/s13613-016-0158-0]
34 **Koutsoukou A**, Armaganidis A, Stavrakaki-Kallergi C, Vassilakopoulos T, Lymberis A, Roussos C, Milic-Emili J. Expiratory flow limitation and intrinsic positive end-expiratory pressure at zero positive end-expiratory pressure in patients with adult respiratory distress syndrome. *Am J Respir Crit Care Med* 2000; **161**: 1590-1596 [PMID: 10806160 DOI: 10.1164/ajrccm.161.5.9904109]
35 **Koutsoukou A**, Bekos B, Sotiropoulou C, Koulouris NG, Roussos C, Milic-Emili J. Effects of positive end-expiratory pressure on gas exchange and expiratory flow limitation in adult respiratory distress syndrome. *Crit Care Med* 2002; **30**: 1941-1949 [PMID: 12352025 DOI: 10.1097/00003246-200209000-00001]
36 **Laghi F**, Goyal A. Auto-PEEP in respiratory failure. *Minerva Anestesiol* 2012; **78**: 201-221 [PMID: 21971439]
37 **Laghi F**, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003; **168**: 10-48 [PMID: 12826594 DOI: 10.1164/rccm.2206020]
38 **Ottenheijm CA**, Heunks LM, Dekhuijzen PN. Diaphragm muscle fiber dysfunction in chronic obstructive pulmonary disease: toward a pathophysiological concept. *Am J Respir Crit Care Med* 2007; **175**: 1233-1240 [PMID: 17413128 DOI: 10.1164/rccm.200701-020PP]
39 **Smith TC**, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. *J Appl Physiol (1985)* 1988; **65**: 1488-1499 [PMID: 3053583 DOI: 10.1152/jappl.1988.65.4.1488]
40 **Thille AW**, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med* 2006; **32**: 1515-1522 [PMID: 16896854 DOI: 10.1007/s00134-006-0301-8]
41 **Gottfried SB**. The role of PEEP in the mechanically ventilated COPD patient. In: Roussos C, Marini JJ. Ventilatory failure. Berlin: Springer; 1991; 392-418 [DOI: 10.1007/978-3-642-84554-3_23]
42 **Pepe PE**, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. *Am Rev Respir Dis* 1982; **126**: 166-170 [PMID: 7046541 DOI: 10.1164/arrd.1982.126.1.166]
43 **Dal Vecchio L**, Polese G, Poggi R, Rossi A. "Intrinsic" positive end-expiratory pressure in stable patients with chronic obstructive pulmonary disease. *Eur Respir J* 1990; **3**: 74-80 [PMID: 2178961]
44 **Tantucci C**, Duguet A, Similowski T, Zelter M, Derenne JP, Milic-Emili J. Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. *Eur Respir J* 1998; **12**: 799-804 [PMID: 9817148 DOI: 10.1183/09031936.98.12040799]
45 **Boyle AJ**, Mac Sweeney R, McAuley DF. Pharmacological treatments in ARDS; a state-of-the-art update. *BMC Med* 2013; **11**: 166 [PMID: 23957905 DOI: 10.1186/1741-7015-11-166]
46 **Eissa NT**, Milic-Emili J, Pochen EJ, Granier EG, Green E. Effects of positive end-expiratory pressure in adult respiratory distress syndrome. Pochen EJ, Granier EG, Green E. *Pulmonary radiology*. Boston: The Fleischner Society; 1993; 169-178
47 **D'Angelo E**, Pecchiari M, Gentile G. Dependence of lung injury on surface tension during low-volume ventilation in normal open-chest rabbits. *J Appl Physiol (1985)* 2007; **102**: 174-182 [PMID: 16959911 DOI: 10.1152/japplphysiol.00405.2006]
48 **Chen L**, Del Sorbo L, Grieco DL, Shklar O, Junhasavasdikul D, Telias I, Fan E, Brochard L. Airway Closure in Acute Respiratory Distress Syndrome: An Underestimated and Misinterpreted Phenomenon. *Am J Respir Crit Care Med* 2018; **197**: 132-136 [PMID: 28557528 DOI: 10.1164/rccm.201702-0388LE]
49 **Robertson B**. Lung surfactant. In: Robertson B, Van Golde L, Batenbourg J. Pulmonary surfactant. Amsterdam: Elsevier; 1984; 384-417
50 **Muscedere JG**, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994; **149**: 1327-1334 [PMID: 8173774 DOI: 10.1164/ajrccm.149.5.8173774]
51 **D'Angelo E**, Pecchiari M, Baraggia P, Saetta M, Balestro E, Milic-Emili J. Low-volume ventilation causes peripheral airway injury and increased airway resistance in normal rabbits. *J Appl Physiol (1985)* 2002; **92**: 949-956 [PMID: 11842025 DOI: 10.1152/japplphysiol.00776.2001]
52 **D'Angelo E**, Pecchiari M, Saetta M, Balestro E, Milic-Emili J. Dependence of lung injury on inflation rate during low-volume ventilation in normal open-chest rabbits. *J Appl Physiol (1985)* 2004; **97**: 260-268 [PMID: 15020576 DOI: 10.1152/japplphysiol.01175.2003]
53 **D'Angelo E**, Pecchiari M, Della Valle P, Koutsoukou A, Milic-Emili J. Effects of mechanical

ventilation at low lung volume on respiratory mechanics and nitric oxide exhalation in normal rabbits. *J Appl Physiol (1985)* 2005; **99**: 433-444 [PMID: 15761084 DOI: 10.1152/japplphysiol.01368.2004]

54 **D'Angelo E**, Koutsoukou A, Della Valle P, Gentile G, Pecchiari M. Cytokine release, small airway injury, and parenchymal damage during mechanical ventilation in normal open-chest rats. *J Appl Physiol (1985)* 2008; **104**: 41-49 [PMID: 17962576 DOI: 10.1152/japplphysiol.00805.2007]

55 **Retamal J**, Bergamini BC, Carvalho AR, Bozza FA, Borzone G, Borges JB, Larsson A, Hedenstierna G, Bugedo G, Bruhn A. Non-lobar atelectasis generates inflammation and structural alveolar injury in the surrounding healthy tissue during mechanical ventilation. *Crit Care* 2014; **18**: 505 [PMID: 25200702 DOI: 10.1186/s13054-014-0505-1]

56 **Pecchiari M**, Monaco A, Koutsoukou A, D'Angelo E. Plasma membrane disruptions with different modes of injurious mechanical ventilation in normal rat lungs*. *Crit Care Med* 2012; **40**: 869-875 [PMID: 22001586 DOI: 10.1097/CCM.0b013e318232da2b]

57 **Morales MM**, Pires-Neto RC, Inforsato N, Lanças T, da Silva LF, Saldiva PH, Mauad T, Carvalho CR, Amato MB, Dolhnikoff M. Small airway remodeling in acute respiratory distress syndrome: a study in autopsy lung tissue. *Crit Care* 2011; **15**: R4 [PMID: 21211006 DOI: 10.1186/cc9401]

58 **Nucci G**, Suki B, Lutchen K. Modeling airflow-related shear stress during heterogeneous constriction and mechanical ventilation. *J Appl Physiol (1985)* 2003; **95**: 348-356 [PMID: 12651864 DOI: 10.1152/japplphysiol.01179.2001]

59 **Pecchiari M**, Monaco A, Koutsoukou A, Della Valle P, Gentile G, D'Angelo E. Effects of various modes of mechanical ventilation in normal rats. *Anesthesiology* 2014; **120**: 943-950 [PMID: 24270126 DOI: 10.1097/ALN.0000000000000075]

P- Reviewer: Drabek T, Santomauro M, Willms DC
S- Editor: Dou Y **L- Editor:** Filipodia **E- Editor:** Bian YN

Published By Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2019 February 21; 8(2): 9-17

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Irregular Volume 8 Number 2 February 21, 2019

ORIGINAL ARTICLE

Retrospective Study

Contents

World Journal of Critical Care Medicine

Volume 8 Number 2 February 21, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Marc G Jeschke, MD, PhD, Associate Professor, Senior Scientist, Department of Surgery, Sunnybrook Research Institute, Toronto ON M4N 3M5, Canada

AIMS AND SCOPE

World Journal of Critical Care Medicine (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCCM covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, *etc*.

We encourage authors to submit their manuscripts to *WJCCM*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Han Song* **Proofing Editorial Office Director:** *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
Kam Lun Ellis Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
February 21, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 February 21; 8(2): 9-17

DOI: 10.5492/wjccm.v8.i2.9

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Study

Neutrophil-lymphocyte ratio: A prognostic tool in patients with in-hospital cardiac arrest

Vishal H Patel, Philip Vendittelli, Rajat Garg, Susan Szpunar, Thomas LaLonde, John Lee, Howard Rosman, Rajendra H Mehta, Hussein Othman

ORCID number: Vishal H Patel (0000-0002-3057-8896); Philip Vendittelli (0000-0002-9129-8433); Rajat Garg (0000-0003-1343-9939); Susan Szpunar (0000-0003-2375-8941); Thomas LaLonde (0000-0003-3566-933X); John Lee (0000-0002-5563-2334); Howard Rosman (0000-0003-0400-6752); Rajendra H Mehta (0000-0001-8478-8648); Hussein Othman (0000-0002-5345-3666).

Author contributions: Patel VH, Lee J, Rosman H, Mehta RH contributed to study conception and design; Patel VH, Vendittelli P, Garg R, Szpunar S contributed to data acquisition, data analysis and interpretation; Patel VH, Rosman H, Mehta RH and LaLonde T contributed to editing, reviewing and final approval of the article.

Institutional review board statement: Approval obtained from Ascension-St John Hospital IRB committee.

Informed consent statement: Waiver of informed consent for human study subjects may be justifiable under certain rare and specific conditions. This retrospective review demonstrated minimal risk and as such, patients were not required to give informed consent to the study as determined by the IRB as some of the subjects may have moved, died, provided incorrect information or no longer be patients at Ascension St John Hospital and Medical center, it would be impracticable to attempt

Vishal H Patel, Philip Vendittelli, Thomas LaLonde, Howard Rosman, Hussein Othman, Department of Cardiovascular Medicine, Ascension-St John Hospital and Medical Center, Detroit, MI 48236, United States

Rajat Garg, Department of Internal Medicine, Cleveland Clinic, Cleveland, OH 44915, United States

Susan Szpunar, Department of Biomedical Investigations and Research, Ascension-St John Hospital and Medical Center, Detroit, MI 48236, United States

John Lee, Department of Critical Care Medicine, Ascension-St John Hospital and Medical Center, Detroit, MI 48236, United States

Rajendra H Mehta, Duke Clinical Research Institute, Duke University Medical Center, Durham, NC 22705, United States

Corresponding author: Vishal H Patel, MD, MSc, Academic Fellow, Department of Cardiovascular Medicine, Ascension-St John Hospital and Medical Center, 22101 Moross Rd, 2nd Floor VEP, Cath Lab, Detroit, MI 48236, United States. vishal.patel@ascension.org
Telephone: +1-313-6095931
Fax: +1-313-4170542

Abstract

BACKGROUND

In-hospital cardiac arrest (IHCA) portends a poor prognosis and survival to discharge rate. Prognostic markers such as interleukin-6, S-100 protein and high sensitivity C reactive protein have been studied as predictors of adverse outcomes after return of spontaneous circulation (ROSC); however; these variables are not routine laboratory tests and incur additional cost making them difficult to incorporate and less attractive in assessing patient's prognosis. The neutrophil-lymphocyte ratio (NLR) is a marker of adverse prognosis for many cardiovascular conditions and certain types of cancers and sepsis. We hypothesize that an elevated NLR is associated with poor outcomes including mortality at discharge in patients with IHCA.

AIM

To determine the prognostic significance of NLR in patients suffering IHCA who achieve ROSC.

to contact them.

Conflict-of-interest statement: All authors declare no conflict of interest.

Manuscript source: Unsolicited manuscript

Received: December 13, 2018
Peer-review started: December 13, 2018
First decision: January 5, 2019
Revised: January 24, 2019
Accepted: January 29, 2019
Article in press: January 30, 2019
Published online: February 21, 2019

METHODS

A retrospective study was performed on all patients who had IHCA with the advanced cardiac life support protocol administered in a large urban community United States hospital over a one-year period. Patients were divided into two groups based on their NLR value (NLR < 4.5 or NLR ≥ 4.5). This cutpoint was derived from receiving operator characteristic curve analysis (area under the curve = 0.66) and provided 73% positive predictive value, 82% sensitivity and 42% specificity for predicting in-hospital death after IHCA. The primary outcome was death or discharge at 30 d, whichever came first.

RESULTS

We reviewed 153 patients with a mean age of 66.1 ± 16.3 years; 48% were female. In-hospital mortality occurred in 65%. The median NLR in survivors was 4.9 (range 0.6-46.5) compared with 8.9 (0.28-96) in non-survivors (P = 0.001). A multivariable logistic regression model demonstrated that an NLR above 4.55 [odds ratio (OR) = 5.20, confidence interval (CI): 1.5-18.3, P = 0.01], older age (OR = 1.03, CI: 1.00-1.07, P = 0.05), and elevated serum lactate level (OR = 1.20, CI: 1.03-1.40, P = 0.02) were independent predictors of death.

CONCLUSION

An NLR ≥ 4.5 may be a useful marker of increased risk of death in patients with IHCA.

Key words: Neutrophil-lymphocyte ratio; In-hospital cardiac arrest; Prognosis; Lactate; Asystole; Ventricular fibrillation; Pulseless electrical alternans; Pulseless ventricular tachycardia

Core tip: Patients who have an in-hospital cardiac arrest (IHCA) event often have poor prognosis and their survival to discharge rates are dismal. Despite advancements in resuscitation, including the use of target temperature management, the prognosis for these patients has not improved over the past 30 years. Markers that are inexpensive and easy to use that may provide some prognostic information after an IHCA event are needed. A neutrophil-lymphocyte ratio greater than 4.5 may be a useful prognostic tool and marker for increased risk of death in patients with IHCA. In addition, older age, elevated serum lactate level were also independent predictors of death.

Citation: Patel VH, Vendittelli P, Garg R, Szpunar S, LaLonde T, Lee J, Rosman H, Mehta RH, Othman H. Neutrophil-lymphocyte ratio: A prognostic tool in patients with in-hospital cardiac arrest. *World J Crit Care Med* 2019; 8(2): 9-17
URL: https://www.wjgnet.com/2220-3141/full/v8/i2/9.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i2.9

INTRODUCTION

In-hospital cardiac arrest (IHCA) events account for 370000 to 750000 events annually in the United States and a number much larger globally[1]. Major advances have been made in resuscitation with the advent of target temperature management, rapid response and code teams nationwide in hospitals based on recommendations of the Joint Commission[2]. The vast majority of patients who achieve sustained return of spontaneous circulation (ROSC) from IHCA, however, die before hospital discharge and their prognosis has not changed over the past 30 years[1].

Survival to discharge is estimated to be about 18%[3], and at one year and three years to be 6.6% and 5.2%[4]. Several clinical factors are of prognostic significance after such an event, including type of initial cardiac rhythm[5,6], age, comorbidities, duration of cardiopulmonary resuscitation, and implementation of target temperature management in appropriate candidates[7]. Post-arrest immune-inflammatory markers including interleukin-6 and high sensitivity C-reactive protein (CRP)[8] as well as markers of neuronal damage such serum neuron-specific enolase concentrations[9] and S-100 protein[10] have also shown some promise as prognostic markers after ROSC.

Many of these biochemical assays are not routinely performed and have to be specifically ordered at a specialized laboratory, adding cost and time delay in receiving the results. These delays preclude their value in the routine care of these sick patients.

Studies of routinely available lab measures have demonstrated that high blood glucose[11], low potassium[12], high platelet count[13] and high lactate[14] levels are all associated with poor prognosis in patients with cardiac arrest. Recently, a high neutrophil-lymphocyte ratio (NLR) has emerged as a marker of poor prognosis for several cardiovascular and non-cardiovascular conditions[15-21]. While the therapies available, demographics of patients and survival rates are different with in and out of hospital cardiac arrest, a NLR > 6 was found to be associated with mortality independent of epinephrine administration[22] in patients with out of hospital cardiac arrest. The degree of abnormalities *i.e.*, elevated glucose, low potassium, high platelet count and high NLR are all directly proportional to the acuteness and the severity of stress during IHCA driven by high catecholamine levels, whereas NLR values were also affected by inflammation. We chose to study the prognostic relevance of high NLR in IHCA patients beyond other routinely available laboratory measures and evaluate whether adrenergic drive or inflammation was the more important underlying mechanism associated with in-hospital death in these patients.

MATERIALS AND METHODS

Patients and setting

The study was carried out after obtaining approval from the IRB at Ascension St John Hospital, Detroit, Michigan. We performed retrospective chart review of patients ages 18 years or older at our institution who had sustained ROSC after an IHCA event (Jan 2015 to December 2015). We defined an IHCA event by the Utstein's criteria as the lack of a cardiac mechanical activity as confirmed by unresponsiveness, absence of a detectable pulse and apnea in patients with a pulse at time of admission[23]. Patients were excluded if they had an out-of-hospital cardiac arrest (n = 102), was a "do not resuscitate" status prior to event (n = 8), or had missing information (n = 18).

Measurements

Data on demographics, medical history, physical examination, laboratory and imaging findings, initial cardiac rhythm, treatment, adverse events and outcomes were collected using retrospective chart review and entered into Excel™ database. Complete blood count with differential and other laboratory information collected during 24 h of the IHCA event were recorded. If there were multiple values of the same laboratory measure during first 24 h, only the first value of these measures *i.e.*, closest to IHCA event was entered into the dataset and used for this analysis.

Statistical methods

We compared the characteristics of patients who died versus those who survived after ROSC following IHCA. Variables are presented as mean with standard deviation or median with range or interquartile range (IQR) for continuous variables and as counts and percentages for categorical variables. Univariable analysis was doing using Student's t-test, the Mann-Whitney U test (for non-normally distributed variables) and the chi-squared test. Multivariable analysis was performed using logistic regression model to adjust for baseline confounders and identify independent predictors of in-hospital mortality. Analyses were performed using SPSS (IBM, Armonk, NY, United States), version 25 and a P value of < 0.05 was considered to be statistically significant.

RESULTS

Characteristics of the study population

Patients who achieved ROSC after IHCA and later died were more likely to be older and/or had pulseless electrical activity or asystole as the initial recorded rhythm (Table 1). Similarly, lower blood pH and higher serum potassium and higher serum lactate levels were associated with in-hospital death in these patients whereas no relationship was observed for serum glucose level and platelet count. The median NLR was higher in non-survivors [8.94 (IQR): 5.1-18.9] compared with survivors [4.94 (IQR: 3.4-12.7), P = 0.001].

Logistic regression analysis

Table 1 Overall characteristics of the survivors and non-survivors of in hospital cardiac arrest event

	Survivor	Non survivor	*P* value[a]
Age (yr)[1]	61.6 ± 17.0	68.5 ± 15.6	0.01
Male	34.2 % (27)	65.8% (52)	0.9
Female	35.1% (26)	64.9% (48)	
Baseline laboratory values			
Potassium (mmol/L)[1]	4.3 ± 1.1	4.6 ± 1.1	0.05
Serum lactate (mmol/L)[1]	5.0 ± 3.7	8.6 ± 7.0	0.001
Glucose (mg/dL)[1]	171 ± 86	184 ± 114	0.5
Platelet (thousand/cu mm)[1]	217 ± 122	201 ± 121	0.47
pH[1]	7.3 ± 0.15	7.2 ± 0.2	0.03
Initial cardiac rhythm			
Pulseless electrical activity	33.7% (34)	66.3% (67)	0.49
Ventricular fibrillation	54.5% (6)	45.5% (5)	
Pulseless ventricular tachycardia	50% (3)	50% (3)	
Asystole	34.8% (8)	65.2% (15)	

[a]*P* value for global difference.
[1]mean ± SD.

An NLR cut-off of 4.55 derived from receiver operating characteristic analysis (area under the curve = 0.66), provided 73% positive predictive value, 82% sensitivity and 42% specificity for predicting in-hospital death after ROSC following IHCA, (Figure 1). In hospital mortality was higher in patients with NLR ≥ 4.55 compared with those with NLR < 4.55 (82% *vs* 45%, $P = 0.02$) (Figure 2). From multivariable logistic regression, an NLR ≥ 4.55 [odds ratio (OR) = 5.2, CI: 1.5-18.3, $P = 0.01$], older age (OR = 1.03, CI: 1.00-1.07, $P = 0.05$), and an elevated serum lactate level (OR = 1.2, CI: 1.03-1.4, $P = 0.02$) as independent predictors of death (Table 2). Type of cardiac rhythm, pH and potassium did not remain significant predictors.

DISCUSSION

Our study shows that patients with ROSC after IHCA had very high mortality with two-thirds of these patients dying before hospital discharge. In-hospital mortality was significantly higher in patients with older age, initial rhythm that showed pulseless electrical activity or asystole and those with abnormal routinely performed laboratory markers such as NLR ≥ 4.55, increased potassium, elevated lactate and lower blood pH. After adjustment for other risk factors, multivariate analysis identified NLR ≥ 4.55, lower blood pH and older age as independent risk factors for mortality. Markers associated with acute stress during IHCA such as glucose, potassium and platelet level were less useful predictors of mortality compared to non-inflammatory markers such as serum lactate level that reflected the end-result of the metabolic derangement.

The range of sensitivity and specificity of neuron specific enolase with a cutoff level of 33 mg/L as a biomarker for worse neurologic injury after cardiac arrest is reported to be 72%-80% and 84%-100% respectively[24]. The false positive rate of neuron specific enolase is 0%-23%. Similarly the reported range of sensitivity and specificity of S-100 with a cutoff range of 0.2-1.5 mg/L as an adverse marker of neurologic injury after cardiac arrest is 72%-80% and 85%-100% respectively with a 0%-16% false positive rate[24]. Timing of measurement as well a target temperature management or lack of has been shown to have an effect on the sensitivity and specificity of neuron specific enolase and S-100 as biomarkers[25]. For example, in hypothermic patients at 24 h S-100 had a specificity of 100% and sensitivity of 30% compared to 100% and 59% respectively in normothermic patients. At 48 h, the specificity and sensitivity of S-100 in hypothermic patients was 96% and 22% respectively compared to 100% and 88% in normothermic patients[25]. In our study, we found that NLR measured within 24 h of IHCA of greater than or equal to 4.5 has a 82% sensitivity, 42% specificity and a 73% positive predictive value to be a marker of mortality. While it should be noted that a NLR ≥ 4.55 is not specific for absence of mortality with many false positives, the association of high sensitivity and positive predictive value with modest specificity

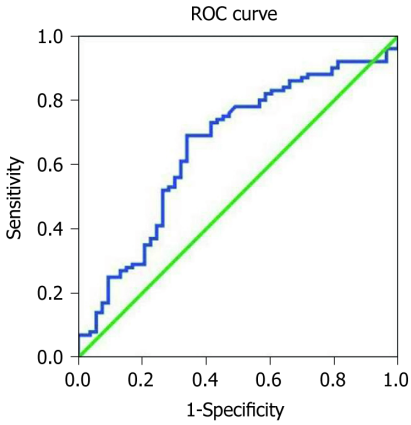


Figure 1 Receiver operating characteristic curve of neutrophil-lymphocyte ratio in in-hospital cardiac arrest showing the true positive rate plotted against the false positive rate. The area under the curve value was 0.66 and cut off point of the neutrophil-lymphocyte ratio was determined to be 4.55 with a 73% positive predictive value, sensitivity of 82% and specificity of 42%. ROC: Receiver operating characteristic.

correlate well with the literature showing similar findings in other clinical conditions. Recently, a study on out of hospital cardiac arrest and targeted temperature management showed NLR cut off value of 6 at 72 h after ROSC was achieved with a sensitivity and specificity of 89% and 47% respectively[26].

Inflammatory and non-inflammatory markers are associated with poor prognosis among patients with out-of-hospital cardiac arrest and other cardiovascular and non-cardiovascular conditions. Inflammatory markers including NLR have been studied in multiple cardiac and non-cardiac diseases recently[15-21]. Elevated white blood counts are associated with a higher risk of death among patients with acute myocardial infarction[23]. Recently, a high NLR, available as a part of routine laboratory tests has been shown to be marker associated with poor prognosis among patients with several conditions including acute coronary syndromes[15], venous thromboembolism[16], atrial fibrillation[17], certain types of cancers[18], severe aortic stenosis[19], heart failure[20] and sepsis[21]. Similarly, elevations of other immune-inflammatory markers including interleukin-6 and high sensitivity CRP[8] have also shown some promise as prognostic markers after ROSC. Our study extends the paradigm of the prognostic significance of NLR seen in other cardiovascular conditions to patients with ROSC after IHCA.

Other laboratory non-inflammatory markers such as high blood glucose[11], low potassium[12], high platelet count[13], and high lactate[14] levels as well as markers of neuronal damage such serum neuron-specific enolase concentrations[9] and S-100 protein[10] have also shown to be potentially associated with adverse prognosis in patients with cardiac arrest. With the exception of high lactate, we did not find any independent association of other routinely available laboratory values (blood glucose, serum potassium or platelet count) with in-hospital mortality in patients with ROSC after IHCA.

Two underlying mechanisms that have been postulated to explain the association of various laboratory values and outcomes are stress-induced stimulation of intrinsic adrenergic sympathetic nerves and propagation of the inflammatory cascade. Severe adrenergic stress during IHCA driven by high catecholamine levels elevates blood glucose, platelet count and NLR while depressing serum potassium. In contrast, NLR values also increase in the inflammatory response to IHCA. Our finding of independent correlation of NLR but not of other routinely available laboratory tests may suggest a more important mechanistic role of inflammation than adrenergic sympathetic activation. This hypothesis, however, and whether targeting inflammation following ROSC leads to improved mortality remains to be further confirmed in future studies.

Finally, the association of lactate level with mortality after cardiac arrest and ROSC warrants further discussion. Lactic acid is produced in tissues and organs during periods of hypoperfusion and ischemia[27]. In addition, lactic acid hepatic clearance is impaired in cases of shock liver often a common accompaniment of cardiac arrest. Epinephrine injections inherently used during resuscitation also have been shown to elevate lactic acid[28]. Thus, lactic acid elevation following a cardiac arrest is the end-result of the above underlying mechanisms and higher levels of lactic acid are expected with longer duration of resuscitation and hypoperfusion in cardiac arrest and ROSC[29]. It is not difficult, therefore, to envision why the initial lactic acid level in patients with IHCA and ROSC predicted an increased risk of death.

Table 2 Predictors of mortality in multiple logistic regression analysis

Variable	Odds ratio	95%CI	*P* value[a]
Age	1.03	1.0-1.07	0.05
Pulseless electrical activity[1]	0.22	0.04-1.2	0.08
Ventricular fibrillation[1]	0.85	0.06-11.4	0.90
Ventricular tachycardia[1]	0.14	0.004-4.3	0.26
NLR > 4.55	5.2	1.5-18.3	0.01
pH	1.8	0.05-68.6	0.76
Lactate	1.2	1.03-1.4	0.02
Potassium	1.6	0.85-3.1	0.15

[a]*P* value for global difference.
[1]As compared to asystole.
CI: Confidence interval.

Our study should be viewed in light of its limitations. This study is a single center retrospective study with modest number of cases and thus subject to missing and incomplete information and our findings should be considered as hypothesis-generating. We did not evaluate the prognostic significance of other biomarkers *i.e.*, CRP, various cytokines, serum neuron-specific enolase concentrations and S-100 protein. Most of these values, however, are not routinely collected and/or have to be sent to specialized laboratories for testing, precluding their value in contemporary practice.

In conclusion, in patients with ROSC after IHCA, in-hospital mortality was high. Our data showed that NLR may be a useful marker of increased risk of in-hospital death in these patients, and thus has potential to improve clinical decision making and family's understanding of risk of in-hospital death after IHCA. Further study in a large cohort of patients with ROSC after IHCA is needed to confirm our findings and to evaluate if targeting inflammation may help improve mortality in these patients.

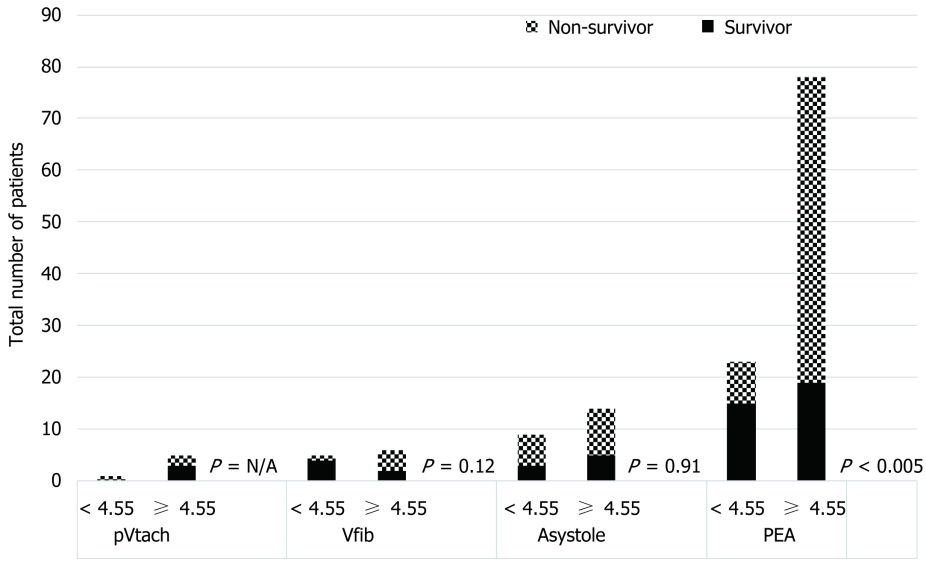


Figure 2 Initial cardiac rhythm and neutrophil lymphocyte ratio in survivors (solid black) and non-survivors (checker-board) of in-hospital cardiac arrest alongside with *P*-values for interaction. pVtach: Pulseless ventricular tachycardia; Vfib: Ventricular fibrillation; PEA: Pulseless electrical alternans.

ARTICLE HIGHLIGHTS

Research background

Mortality and morbidity after having an in hospital cardiac arrest (IHCA) event are high. Despite the advent of therapeutic modalities such as target temperature management and increased access to rapid response and code blue teams, the survival rates after IHCA are dismal. Markers of poor survival after IHCA have been evaluated and include S-100 and serum neuron-specific enolase concentrations. However, this and many other markers are often analyzed at specialized laboratories and may have a time delay in response. Their routine use is therefore limited.

Research motivation

The main motivation for the study was to evaluate whether neutrophil-lymphocyte ratio (NLR), an easy to obtain marker can be used to gain prognostic information after IHCA patients achieve return of spontaneous circulation (ROSC). Previously, NLR has been evaluated as a marker of poor prognosis for several cardiovascular and non-cardiovascular conditions. Interestingly, a high NLR in patients with out of hospital cardiac arrest (OHCA) has been shown to have increased mortality. It is essential to investigate whether NLR provides any prognostic information in IHCA patients as they are often sicker, older and have poor survival compared to patients with OHCA.

Research objectives

The main objective was to determine the value of an elevated NLR in predicting survival to discharge in patients with IHCA. Furthermore, we evaluated whether a high adrenergic drive or inflammation may be associated with the mechanism associated with IHCA. As a result, we looked at the initial cardiac rhythm and other laboratory values such as potassium, lactate, glucose and platelet level as this may be evaluated in future research as therapeutic targets for improving survival after IHCA.

Research methods

A retrospective chart review was conducted at our institution of all patients over 18 years of age who has sustained ROSC after IHCA events. Medical records were reviewed for demographics, history and physical examination, laboratory and imaging findings as well as initial cardiac rhythm and outcomes were collected. Of note, the laboratory data was collected during 24 h of the IHCA being recorded.

Research results

The main finding out this study was that a NLR cut-off of 4.55 derived from receiver operating characteristic analysis (area under the curve = 0.66), provided 73% positive predictive value, 82% sensitivity, 42% specificity predicting in-hospital death. Multivariable logistic regression analysis yielded an NLR ≥ 4.55 [odds ratio (OR) = 5.2, confidence interval (CI): 1.5-18.3, P = 0.01], older age (OR = 1.03, CI: 1.00-1.07, P = 0.05), and an elevated serum lactate level (OR = 1.2, CI: 1.03-1.4, P = 0.02) as independent predictors of death. Older individuals, or those with pulseless electrical activity and/or asystole as the initial cardiac rhythm were more likely to have died from IHCA despite achieving ROSC. A limitation of this paper is that it did not evaluate the prognostic significance of other biomarkers such as S-100, serum neuron-specific enolase amongst others compared to NLR. Our study was also a single center retrospective study with modest number

of cases and as results our findings should be considered as hypothesis-generating.

Research conclusions

The new findings of our study are that an increased NLR may be a marker of decreased survival in patients with ROSC after IHCA. NLR may have some utility in improving clinical decision making and family's understanding of risk of death after IHCA. This study proposes that modulating inflammation may improve mortality in patients after an IHCA event.

Research perspectives

The authors suggest using NLR as a tool to further assist in prognosticating patients with ROSC after IHCA. Future investigations may look to compare NLR values and survival before and after currently accepted interventions such as target temperature management or even after modulation of inflammation, a cascade which is less well understood but likely plays a detrimental role in the outcome after IHCA.

REFERENCES

1 **Sandroni C**, Nolan J, Cavallaro F, Antonelli M. In-hospital cardiac arrest: Incidence, prognosis and possible measures to improve survival. *Intensive Care Med* 2007; **33**: 237-245 [PMID: 17019558 DOI: 10.1007/s00134-006-0326-z]

2 **Morrison LJ**, Neumar RW, Zimmerman JL, Link MS, Newby LK, McMullan PW, Hoek TV, Halverson CC, Doering L, Peberdy MA, Edelson DP; American Heart Association Emergency Cardiovascular Care Committee, Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on P. Strategies for improving survival after in-hospital cardiac arrest in the United States: 2013 consensus recommendations: A consensus statement from the American Heart Association. *Circulation* 2013; **127**: 1538-1563 [PMID: 23479672 DOI: 10.1161/CIR.0b013e31828b2770]

3 **Nadkarni VM**, Larkin GL, Peberdy MA, Carey SM, Kaye W, Mancini ME, Nichol G, Lane-Truitt T, Potts J, Ornato JP, Berg RA; National Registry of Cardiopulmonary Resuscitation Investigators. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA* 2006; **295**: 50-57 [PMID: 16391216 DOI: 10.1001/jama.295.1.50]

4 **Booth CM**, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 2004; **291**: 870-879 [PMID: 14970067 DOI: 10.1001/jama.291.7.870]

5 **Garcia S**, Drexel T, Bekwelem W, Raveendran G, Caldwell E, Hodgson L, Wang Q, Adabag S, Mahoney B, Frascone R, Helmer G, Lick C, Conterato M, Baran K, Bart B, Bachour F, Roh S, Panetta C, Stark R, Haugland M, Mooney M, Wesley K, Yannopoulos D. Early Access to the Cardiac Catheterization Laboratory for Patients Resuscitated From Cardiac Arrest Due to a Shockable Rhythm: The Minnesota Resuscitation Consortium Twin Cities Unified Protocol. *J Am Heart Assoc* 2016; **5**: pii: e002670 [PMID: 26744380 DOI: 10.1161/JAHA.115.002670]

6 **Doshi P**, Patel K, Banuelos R, Darger B, Baker S, Chambers KA, Thangam M, Gates K. Effect of Therapeutic Hypothermia on Survival to Hospital Discharge in Out-of-hospital Cardiac Arrest Secondary to Nonshockable Rhythms. *Acad Emerg Med* 2016; **23**: 14-20 [PMID: 26670621 DOI: 10.1111/acem.12847]

7 **Huang Y**, He Q, Yang LJ, Liu GJ, Jones A. Cardiopulmonary resuscitation (CPR) plus delayed defibrillation versus immediate defibrillation for out-of-hospital cardiac arrest. *Cochrane Database Syst Rev* 2014; CD009803 [PMID: 25212112 DOI: 10.1002/14651858.CD009803.pub2]

8 **Samborska-Sablik A**, Sablik Z, Gaszynski W. The role of the immuno-inflammatory response in patients after cardiac arrest. *Arch Med Sci* 2011; **7**: 619-626 [PMID: 22291797 DOI: 10.5114/aoms.2011.24131]

9 **Sulaj M**, Saniova B, Drobna E, Schudichova J. Serum neuron specific enolase and malondialdehyde in patients after out-of-hospital cardiac arrest. *Cell Mol Neurobiol* 2009; **29**: 807-810 [PMID: 19241153 DOI: 10.1007/s10571-009-9361-y]

10 **Hachimi-Idrissi S**, Van der Auwera M, Schiettecatte J, Ebinger G, Michotte Y, Huyghens L. S-100 protein as early predictor of regaining consciousness after out of hospital cardiac arrest. *Resuscitation* 2002; **53**: 251-257 [PMID: 12062839 DOI: 10.1016/s0300-9572(02)00027-8]

11 **Beiser DG**, Carr GE, Edelson DP, Peberdy MA, Hoek TL. Derangements in blood glucose following initial resuscitation from in-hospital cardiac arrest: A report from the national registry of cardiopulmonary resuscitation. *Resuscitation* 2009; **80**: 624-630 [PMID: 19297067 DOI: 10.1016/j.resuscitation.2009.02.011]

12 **Kjeldsen K**. Hypokalemia and sudden cardiac death. *Exp Clin Cardiol* 2010; **15**: e96-e99 [PMID: 21264075 DOI: 10.1093/eurjhf/hfq190]

13 **Chung SP**, Yune HY, Park YS, You JS, Hong JH, Kong T, Park JW, Chung HS, Park I. Usefulness of mean platelet volume as a marker for clinical outcomes after out-of-hospital cardiac arrest: A retrospective cohort study. *J Thromb Haemost* 2016; **14**: 2036-2044 [PMID: 27437641 DOI: 10.1111/jth.13421]

14 **Wang CH**, Huang CH, Chang WT, Tsai MS, Yu PH, Wu YW, Hung KY, Chen WJ. Monitoring of serum lactate level during cardiopulmonary resuscitation in adult in-hospital cardiac arrest. *Crit Care* 2015; **19**: 344 [PMID: 26387668 DOI: 10.1186/s13054-015-1058-7]

15 **Zhou D**, Wan Z, Fan Y, Zhou J, Yuan Z. A combination of the neutrophil-to-lymphocyte ratio and the GRACE risk score better predicts PCI outcomes in Chinese Han patients with acute coronary syndrome. *Anatol J Cardiol* 2015; **15**: 995-1001 [PMID: 26663224 DOI: 10.5152/AnatolJCardiol.2015.6174]

16 **Barker T**, Rogers VE, Henriksen VT, Brown KB, Trawick RH, Momberger NG, Lynn Rasmussen G. Is there a link between the neutrophil-to-lymphocyte ratio and venous thromboembolic events after knee arthroplasty? A pilot study. *J Orthop Traumatol* 2016; **17**: 163-168 [PMID: 26387114 DOI: 10.1007/s10195-015-0378-3]

17 **Saliba W**, Barnett-Griness O, Elias M, Rennert G. Neutrophil to lymphocyte ratio and risk of a first episode of stroke in patients with atrial fibrillation: A cohort study. *J Thromb Haemost* 2015; **13**: 1971-1979 [PMID: 25988740 DOI: 10.1111/jth.13006]

18 **Grenader T**, Waddell T, Peckitt C, Oates J, Starling N, Cunningham D, Bridgewater J. Prognostic value

of neutrophil-to-lymphocyte ratio in advanced oesophago-gastric cancer: Exploratory analysis of the REAL-2 trial. *Ann Oncol* 2016; **27**: 687-692 [PMID: 26787231 DOI: 10.1093/annonc/mdw012]

19 **Avci A**, Elnur A, Göksel A, Serdar F, Servet I, Atilla K, Mustafa TM, Cuneyt T, Yeliz G, Mustafa B, Metin EA. The relationship between neutrophil/lymphocyte ratio and calcific aortic stenosis. *Echocardiography* 2014; **31**: 1031-1035 [PMID: 24528173 DOI: 10.1111/echo.12534]

20 **Benites-Zapata VA**, Hernandez AV, Nagarajan V, Cauthen CA, Starling RC, Tang WH. Usefulness of neutrophil-to-lymphocyte ratio in risk stratification of patients with advanced heart failure. *Am J Cardiol* 2015; **115**: 57-61 [PMID: 25456873 DOI: 10.1016/j.amjcard.2014.10.008]

21 **Terradas R**, Grau S, Blanch J, Riu M, Saballs P, Castells X, Horcajada JP, Knobel H. Eosinophil count and neutrophil-lymphocyte count ratio as prognostic markers in patients with bacteremia: A retrospective cohort study. *PLoS One* 2012; **7**: e42860 [PMID: 22912753 DOI: 10.1371/journal.pone.0042860]

22 **Weiser C**, Schwameis M, Sterz F, Herkner H, Lang IM, Schwarzinger I, Spiel AO. Mortality in patients resuscitated from out-of-hospital cardiac arrest based on automated blood cell count and neutrophil lymphocyte ratio at admission. *Resuscitation* 2017; **116**: 49-55 [PMID: 28476480 DOI: 10.1016/j.resuscitation.2017.05.006]

23 **Jacobs I**, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, Halperin H, Handley A, Herlitz J, Hickey R, Idris A, Kloeck W, Larkin GL, Mancini ME, Mason P, Mears G, Monsieurs K, Montgomery W, Morley P, Nichol G, Nolan J, Okada K, Perlman J, Shuster M, Steen PA, Sterz F, Tibballs J, Timerman S, Truitt T, Zideman D; International Liaison Committee on Resuscitation; American Heart Association; European Resuscitation Council; Australian Resuscitation Council; New Zealand Resuscitation Council; Heart and Stroke Foundation of Canada; InterAmerican Heart Foundation; Resuscitation Councils of Southern Africa; ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update and simplification of the Utstein templates for resuscitation registries: A statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation* 2004; **110**: 3385-3397 [PMID: 15557386 DOI: 10.1161/01.CIR.0000147236.85306.15]

24 **Scolletta S**, Donadello K, Santonocito C, Franchi F, Taccone FS. Biomarkers as predictors of outcome after cardiac arrest. *Expert Rev Clin Pharmacol* 2012; **5**: 687-699 [PMID: 23234326 DOI: 10.1586/ecp.12.64]

25 **Tiainen M**, Roine RO, Pettilä V, Takkunen O. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. *Stroke* 2003; **34**: 2881-2886 [PMID: 14631087 DOI: 10.1161/01.STR.0000103320.90706.35]

26 **Kim HJ**, Park KN, Kim SH, Lee BK, Oh SH, Moon HK, Jeung KW, Choi SP, Cho IS, Youn CS. Association between the neutrophil-to-lymphocyte ratio and neurological outcomes in patients undergoing targeted temperature management after cardiac arrest. *J Crit Care* 2018; **47**: 227-231 [PMID: 30048779 DOI: 10.1016/j.jcrc.2018.07.019]

27 Correction. *Circulation* 2015; **131**: e535 [PMID: 26078378 DOI: 10.1161/CIR.0000000000000219]

28 **Donnino MW**, Miller J, Goyal N, Loomba M, Sankey SS, Dolcourt B, Sherwin R, Otero R, Wira C. Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients. *Resuscitation* 2007; **75**: 229-234 [PMID: 17583412 DOI: 10.1016/j.resuscitation.2007.03.021]

29 **Starodub R**, Abella BS, Grossestreuer AV, Shofer FS, Perman SM, Leary M, Gaieski DF. Association of serum lactate and survival outcomes in patients undergoing therapeutic hypothermia after cardiac arrest. *Resuscitation* 2013; **84**: 1078-1082 [PMID: 23402966 DOI: 10.1016/j.resuscitation.2013.02.001]

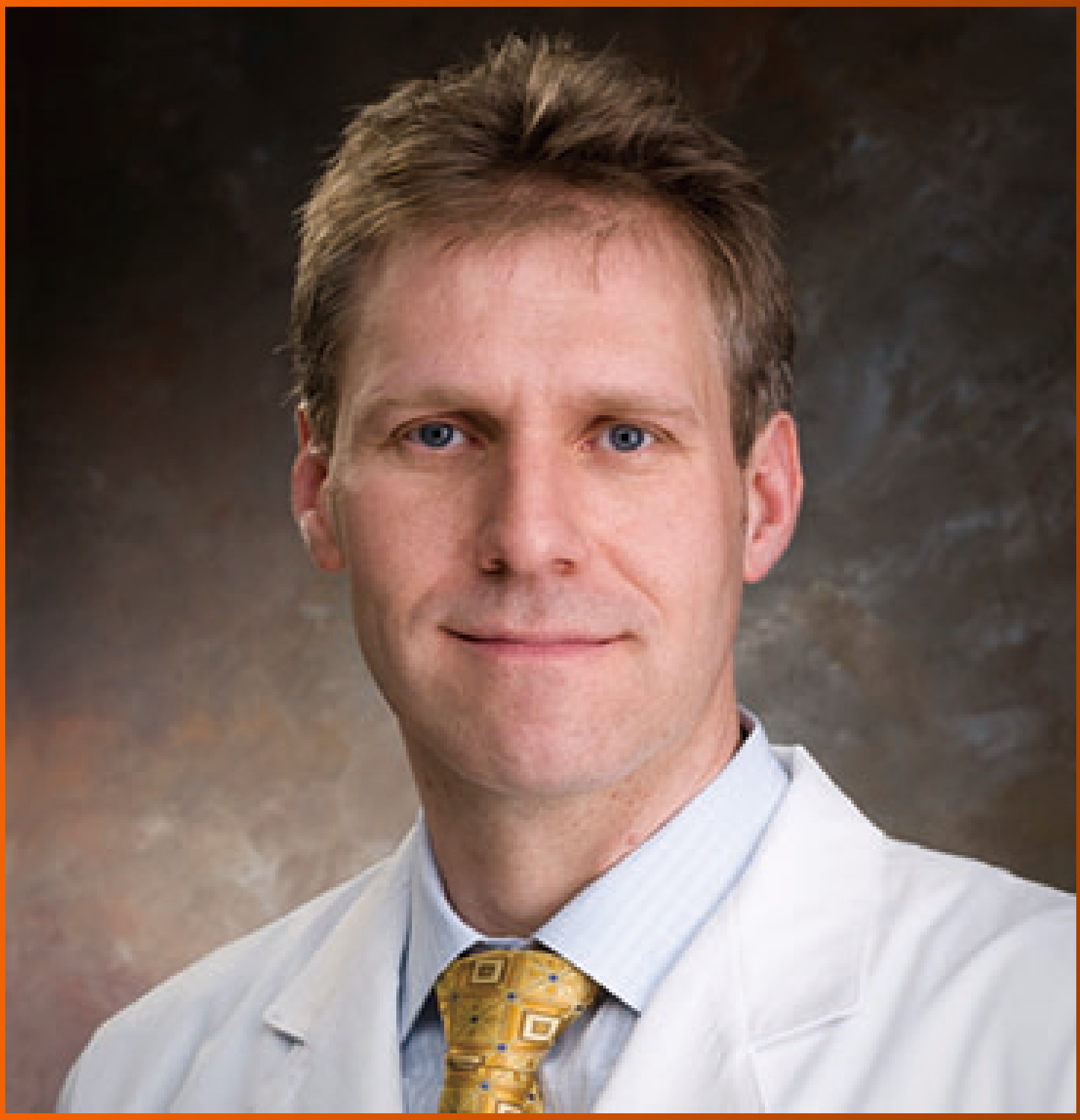
P- Reviewer: Cascella M, Inchauspe AA, Sanfilippo F, Zhao L
S- Editor: Yan JP **L- Editor:** A **E- Editor:** Song H

Published By Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2019 June 12; 8(3): 18-35



Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Irregular Volume 8 Number 3 June 12, 2019

MINIREVIEWS

ORIGINAL ARTICLE

Prospective Study

Contents

World Journal of Critical Care Medicine

Volume 8 Number 3 June 12, 2019

AIMS AND SCOPE

World Journal of Critical Care Medicine (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJCCM* covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, *etc*.

We encourage authors to submit their manuscripts to *WJCCM*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yun-Xiaojian Wu* **Proofing Editorial Office Director:** *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
June 12, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 June 12; 8(3): 18-27

DOI: 10.5492/wjccm.v8.i3.18

ISSN 2220-3141 (online)

MINIREVIEWS

Current controversies and future perspectives on treatment of intensive care unit delirium in adults

Marco Cascella, Marco Fiore, Sebastiano Leone, Domenico Carbone, Raffaela Di Napoli

ORCID number: Marco Cascella (0000-0002-5236-3132); Marco Fiore (0000-0001-7263-0229); Sebastiano Leone (0000-0001-7852-4101); Domenico Carbone (0000-0002-1554-9739); Raffaela Di Napoli (0000-0002-7897-5030).

Author contributions: Cascella M, Fiore M, Leone S, Carbone D and Di Napoli R contributed equally to this manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this manuscript.

Manuscript source: Invited manuscript

Received: February 28, 2019
Peer-review started: March 4, 2019
First decision: April 11, 2019
Revised: April 19, 2019
Accepted: May 3, 2019
Article in press: May 5, 2019
Published online: June 12, 2019

Marco Cascella, Division of Anesthesia and Pain Medicine, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Naples 80049, Italy

Marco Fiore, Department of Women, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples 80138, Italy

Sebastiano Leone, Division of Infectious Diseases, "San Giuseppe Moscati" Hospital, Avellino 83100, Italy

Domenico Carbone, Department of Emergency Medicine, Umberto I Hospital, Nocera Inferiore, Salerno 84014, Italy

Raffaela Di Napoli, Department of Anesthesiology, Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles 1000, Belgium

Corresponding author: Marco Cascella, MD, Professor, Division of Anesthesia and Pain Medicine, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Via Mariano Semmola, 53, Naples 80049, Italy. m.cascella@istitutotumori.na.it
Telephone: +39-81-5903221
Fax: +39-81-5903778

Abstract

Delirium is the most frequent manifestation of acute brain dysfunction in intensive care unit (ICU). Although antipsychotics are widely used to treat this serious complication, recent evidence has emphasized that these agents did not reduce ICU delirium (ICU-D) prevalence and did not improve survival, length of ICU or hospital stay after its occurrence. Of note, no pharmacological strategy to prevent or treat delirium has been identified, so far. In this scenario, new scientific evidences are urgently needed. Investigations on specific ICU-D subgroups, or focused on different clinical settings, and studies on medications other than antipsychotics, such as dexmedetomidine or melatonin, may represent interesting fields of research. In the meantime, because there is some evidence that ICU-D can be effectively prevented, the literature suggests strengthening all the strategies aimed at prevention through no-pharmacological approaches mostly focused on the correction of risk factors. The more appropriate strategy useful to treat established delirium remains the use of antipsychotics managed by choosing the right doses after a careful case-by-case analysis. While the evidence regarding the use of dexmedetomidine is still conflicting and sparse, this drug offers interesting perspectives for both ICU-D prevention and treatment. This paper aims to provide an overview of current pharmacological approaches of

P-Reviewer: Drabek T
S-Editor: Dou Y
L-Editor: A
E-Editor: Wu YXJ

evidence-based medicine practice. The state of the art of the on-going clinical research on the topic and perspectives for future research are also addressed.

Key words: Delirium; Intensive care; Haloperidol; Antipsychotic agents; Major tranquilizers; Cognitive decline; Dexmedetomidine

Core tip: Delirium represents the most common type of acute brain dysfunction in intensive care unit (ICU). Despite no support from rigorous controlled studies, haloperidol and atypical antipsychotics have been for decades the main class of drugs used for its pharmacological management. Recently, large size studies demonstrated that antipsychotics do not significantly shorten the duration of delirium. However, because ICU delirium has multifactorial pathogenesis it is difficult to postulate that a single agent can be useful for all clinical contexts. In this manuscript we want to provide an overview of most recent pharmacological approaches for the ICU delirium treatment.

Citation: Cascella M, Fiore M, Leone S, Carbone D, Di Napoli R. Current controversies and future perspectives on treatment of intensive care unit delirium in adults. *World J Crit Care Med* 2019; 8(3): 18-27
URL: https://www.wjgnet.com/2220-3141/full/v8/i3/18.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i3.18

INTRODUCTION

Delirium is recognised as the most frequent manifestation of acute brain dysfunction in intensive care unit (ICU) as it affects up to 80% patients, especially in the postsurgical or traumatic settings[1]. This complication is associated with increased duration of mechanical ventilation (MV), prolonged ICU and hospital length to stay (LOS), increased rates of self-extubation, refusal of medications, and overall increased hospital costs[2]. Of note, it has been also proved that delirium in ICU (ICU-D) represents an independent predictor for increased mortality[3]. Furthermore, the occurrence of ICU-D and its duration seems to be associated with long-term cognitive impairment in survivors of critical illness[4], probably due to alterations in brain structure and white-matter disruption[5].

Clinically, the two recognized subtypes of delirium are the hyperactive type (often called "ICU psychosis") featuring agitation, hallucinations, restlessness, and the hypoactive delirium (also referred as "quiet delirium" or "acute encephalopathy") characterized by apathy, decreased responsiveness, slowed motor function, withdrawn attitude, lethargy, and drowsiness. Patients may also exhibit a fluctuation between the hypoactive and hyperactive types (mixed delirium) (Table 1)[6]. In terms of clinical relevance, hyperactive delirium has generally a low prevalence whereas the hypoactive form is very often underestimated and is associated with a worse prognosis.

Based on these premises, appropriate management of ICU-D through careful prophylaxis, early detection and treatment, is mandatory for improving patient's outcome. However, this target still remains an unmet need. While no-pharmacological interventions focused on the early recognition and correction of risk factors seems to be the more appropriate strategy to prevent delirium[7], there are numerous controversies concerning pharmacological prophylaxis and treatment of established delirium. Of note, to date there are no United States Food and Drug Administration-approved pharmacologic therapies for ICU-D prevention or treatment. In this complex scenario, this paper aims to offer an overview of current pharmacological approaches and results from evidence based-medicine (EBM) analysis. The state of the art of the clinical research on the topic and perspectives for future research are also addressed.

CURRENT PHARMACOLOGICAL APPROACHES AND CONTROVERSIES

Table 1 Features and pharmacological management of delirium in intensive care unit

Delirium subtypes	Notes
Hypoactive (24.5%-43.5%)[6]: Apathy, decreased responsiveness, slowed motor function, withdrawn attitude, lethargy, and drowsiness	Poor response to antipsychotics
Hyperactive (1.6%-23%)[6]: Agitation, hallucinations, restlessness	May respond to antipsychotics
Mixed (52.5%)[6]: Fluctuation of hypoactive and hyperactive features	Requires a careful assessment over the time
Prevention (Drugs)	
Haloperidol	Poor efficacy on ICU-D prevention and related clinical outcomes (*e.g.*, mortality). Not recommended[15]
Atypical antipsychotics	Poor efficacy. Not recommended[15]
Dexmedetomidine	Although not recommended[15], low doses (*e.g.*, 0.1 μg/kg per hour) may reduce ICU-D occurrence
Treatment (Drugs)	
Haloperidol	Useful: 2-10 mg (IV every 6 h), but recommended for not routinely using (especially in hyperactive form)[15]
Atypical antipsychotics	Olanzapine (IM 5-10 mg; max: 30 mg/d), risperidone (0.5-8 mg), quetiapine (orally 50 mg; max 400 mg/d), and ziprasidone (IM 10 mg; max: 40 mg/d)[1]. Starting regimens may need to be higher than maintenance doses; Recommended for not routinely using[15]
Dexmedetomidine	Useful, but recommended (with low quality evidence) in adults under MV, especially when hyperactive manifestations preclude weaning[15]
Short-acting benzodiazepines	Useful in patient experiencing alcohol or sedative withdrawal, or for delirium resulting from seizures; Lorazepam: IM and IV forms; no active metabolites (preferred); Midazolam: IM and IV forms; has active metabolites
Drug side effects	
Haloperidol	Insomnia, EPSs[2] and agitation are the most common side effects. Dose dependent changes of EPSs. Cardiotoxicity occurs at doses > 2 mg IV
Atypical antipsychotics	EPSs at high doses. Olanzapine and quetiapine may lead to excessive sedation, ziprasidone is more associated with QTc prolongation
Dexmedetomidine	Bradycardia, and hypotension. Hypertension
Benzodiazepines	Delirogenic effect

[1]Compared to haloperidol, their efficacy is similar, and with less extrapyramidal side effects;
[2]EPSs management: dose-escalation; anticholinergic; dopamine agonist; beta blockers or even benzodiazepines for akathisia. ICU-D: Intensive care unit delirium; IV: Intravenous; IM: Intramuscular; MV: Mechanical ventilation; EPSs: Extrapyramidal symptoms; QTc: Corrected QT interval.

About pharmacological interventions (Table 1), despite no support from rigorous randomized controlled trials (RCTs), haloperidol and, subsequently, atypical antipsychotics have been for decades the main class of drugs used for the acute treatment of ICU-D. Haloperidol is a dopamine (D2) receptor antagonist used in 75%-80% of ICU-D cases[8]. Depending on the severity of the delirium its dose may range from 2 to 10 mg (intravenous every 6 h). Common side effects of haloperidol include agitation, drowsiness, insomnia, headache, restlessness, anxiety, and mood changes. Severe side effects are extrapyramidal symptoms (EPSs) including subacute parkinsonism featuring dystonic reactions or akathisia (*i.e.*, the subjective inner restlessness and feeling to need to move), cardiotoxicity [*e.g.*, corrected QT interval (QTc) prolongation, torsade de pointes, hypotension], and neuroleptic malignant syndrome (NMS). This latter condition represents a rare but serious complication characterized by rigidity, fever, and autonomic dysfunctions (*e.g.*, tachycardia). Among all these complications, insomnia, EPSs, and agitation are the most common side effects. Concerning cardiotoxicity, it usually occurs at high doses, whereas a dosage of 2 mg haloperidol can be safely administered[9].

Despite its wide use, several controversies regard the efficacy of haloperidol for both prevention and treatment of ICU-D. In critically ill patients, two large size (RCTs), the Hope-ICU and the REDUCE studies, showed that haloperidol administration was of limited efficacy on ICU-D prevention[10] and compared with placebo did not improve survival at 28 d in patients with a high risk of delirium[11]. Although there have been a number of criticisms levelled at the REDUCE's study mainly concerning design[12] and drug regimens used[13], it seems that this investigation offers more certainties than doubts. Furthermore, it has been demonstrated that low-dose haloperidol did not impact delirium duration and severity even when the antipsychotic was combined with other strategies such as reduced exposure to anticholinergic medications, or the benzodiazepines (BZDs)

use[14]. Thus, a recent guideline suggests that clinicians should not use antipsychotics, either typical and atypical, to prevent delirium in adult ICU patients[15].

Olanzapine, risperidone, quetiapine, and ziprasidone are drugs included among the atypical antipsychotics class. These drugs, also indicated as second-generation antipsychotics (SGAs) are prescribed in 35%-40% of patients with ICU-D. Functionally, they have a variety of effects on the dopaminergic, cholinergic, glutamatergic, and serotoninergic (5-HT2A) systems. Because SGAs have a higher ratio of 5-HT2 to D2 blockade, they induce a low incidence of EPSs. Interestingly, they may decrease neurotoxicity and improve cognitive function[16]. Compared to haloperidol, the efficacy of SGAs for delirium treatment is similar, although their use was found associated with less EPSs, and lower risk of tardive dyskinesia, or NMS[7]. However, olanzapine and quetiapine may lead to excessive sedation due to their strong antagonism at H1 receptors, whereas ziprasidone is more associated with QTc prolongation[17]. Recent data from the MIND-USA RCT, conducted on a large size of patients (n = 1183), demonstrated that compared with placebo haloperidol (maximum dose, 20 mg daily) or ziprasidone (maximum dose, 40 mg daily) did not significantly shorten the duration of delirium or coma. Furthermore, there were no significant differences on other endpoints including mortality (after 30 and 90 d), and duration of MV, or in the ICU and hospital LOS[18]. Previously, two RCTs designed to evaluate the efficacy of SGAs on ICU-D offered contradictory results[19,20]. Again, the sample sizes were too small to extrapolate significant data on clinical outcomes (*e.g.*, mortality, or LOS) to be useful for EBM analysis. In one study (n = 36), Devlin *et al*[19] administered quetiapine by increasing its doses every 24 h added to as-needed haloperidol, and obtained good results in terms of faster ICU-D resolution, whereas there was no significant occurrence of side effects compared to placebo (P = 1.0). On the contrary, in the other study (n = 101), the authors found no significant differences with haloperidol, or ziprasidone, compared to placebo on the duration of ICU-D and MV[20]. In summary, although the routinely use of haloperidol and SGAs have been not recommended, the short-term use of haloperidol or a SGASs may be helpful, especially in case of hyperactive delirium characterized by excessive agitation[15]. In case of lack of response to haloperidol/SGAs, other pharmacological strategies could be evaluated in order to avoid serious dose-related side effects.

Short-acting BDZs, such as midazolam and lorazepam, are often used for sedation in ICU. Because, their delirogenic effect especially after continuous infusion[21] has been well recognized[22], these drugs are particularly administered for managing delirium only in patient experiencing alcohol withdrawal[23] whereas there is no evidence to support their use in the treatment of other types of delirium[24].

Dexmedetomidine is an alpha-2-adrenergic agonist with sedative, analgesic, and anxiolytic properties. Several investigations demonstrated that this agent may reduce the use of other sedatives and the duration of MV. Furthermore, it could be able to promote natural sleep without respiratory depression by inhibiting noradrenergic neurons in the locus coeruleus and, in turn, by inducing rapid eye movement sleep (REM) and non-REM I-III sleep states[25]. Prophylactic low-dose dexmedetomidine (0.1 μg/kg/h; given only the first postoperative day) significantly decreases the occurrence of delirium (from 23% to 9%) during the first 7 d after non-cardiac surgery. Moreover, there was a reduction in sedative and narcotics agents administration[26]. Other controlled investigations demonstrated that this alpha-2 agonist medication reduced the incidence and duration of ICU-D when compared with lorazepam[27] or midazolam[28] in patients under MV, although with a higher occurrence of bradycardia. About side effects, the administration of dexmedetomidine may induce bradycardia, and hypotension through inhibition of sympathetic activity in the periphery. Moreover, it may lead to withdrawal symptoms if abruptly discontinued, whereas limited data are available on circulatory insufficiency and mortality[29]. Despite this limitation, a recent guideline recommends - with low quality evidence - the use of dexmedetomidine in the pharmacological management of ICU-D in adults under MV, especially when hyperactive manifestations preclude weaning[15].

According to the theory of cholinergic deficit in delirium, van Eijk *et al*[30] tested the cholinesterase inhibitor rivastigmine. Because the intervention did not decrease duration of delirium and, in turn, increased mortality, the RCT was prematurely terminated. The explanation for this negative finding was that plasma cholinesterase activity is impaired in ICU patients[31], especially in those with sepsis[32]. However, according to Opdam *et al*[33] this agent should receive a second chance.

Multiple mechanisms of hippocampal and extra-hippocampal dysfunction due to neuroinflammation are involved in the pathogenesis of delirium[34]. Thus, based on anti-inflammatory properties of statins, Page *et al*[35] tested simvastatin in the prevention and treatment of delirium. The results, however, were not encouraging as duration of delirium was not shortened and high creatine kinase concentrations were registered after the statin administration.

Melatonin is a hormone released by the pineal gland with a key role in sleep and circadian rhythm regulation[36]. In ICU patients, it has been proved a significant alteration in the sleep patterns and these findings are associated with decreased melatonin production and, in turn, with delirium occurrence[37]. A retrospective analysis demonstrated that the exogenous administration of melatonin for at least 48 hours was associated with a significant reduction in development of ICU-D[38]. Previously, the administration of melatonin (5 mg preoperatively) has been found to decrease incidence of postoperative delirium (POD)[39]. Ramelteon is a melatonin receptor agonist prescribed for insomnia due to difficulty with sleep onset. In a RCT this medication (given 8 mg/d every night for 7 d) was associated with a decreased incidence of delirium[40].

EVIDENCE BASED MEDICINE FINDINGS ON PHARMACOLOGICAL PREVENTIVE AND THERAPEUTIC STRATEGIES

In non-ICU patients, a recent Cochrane analysis found that there is poor evidence about the efficacy of typical or SGAs on the duration of delirium, length of hospital stay, discharge time, or health-related quality of life (HRQoL)[41]. In the setting of POD, although based on small studies of limited scope, another Cochrane research showed that low dose haloperidol (< 3.0 mg/d) may be effective in decreasing the degree and duration of delirium whereas compared to the SGAs higher doses haloperidol were associated with a greater incidence of side effects[42]. In contrast with previous EBM analysis that found that prophylactic use of haloperidol, or dexmedetomidine, may be useful for reducing the prevalence of ICU-D[43], a recent EBM research highlighted and confirmed the poor results demonstrated through the Hope-ICU and REDUCE investigations[44]. In summary, evidence suggests that there is no benefit from prophylactic treatment with haloperidol, or SGAs, against the development of ICU-D.

Concerning ICU-D treatment, the authors of a recent systematic overview of reviews and meta-analyses failed to identify, through their methodology, any EBM study assessing any pharmacological agents[45]. This lack concerns also dexmedetomidine and confirmed results from the previous analysis. For instance, Chen *et al*[46] found no evidence on the prophylactic and therapeutic role of this medication against ICU-D and its clinical outcome when compared with BZDs or propofol. On the contrary, other meta-analysis indicated that dexmedetomidine may reduce delirium and duration of MV in patients after cardiac surgery when compared with propofol[47], or in patients undergoing non-invasive ventilation in no-cardiac ICU[48]. According to Maagaard *et al*[49], the evidence regarding the use of dexmedetomidine in the treatment of ICU-D is conflicting and sparse. As the authors designed an exhaustive protocol for a systematic review, their results could give us valuable information on the real effectiveness of the drug on delirium management[49]. Finally, there is more uncertainty on the efficacy of anticholinesterase inhibitors as a systematic review found that these drugs offer no benefit in terms of prophylaxis, or treatment of diagnosed delirium[50]. Selected evidence-based research on pharmacological management of ICU-D is summarized in Table 2.

ON-GOING TRIALS

Several RCTs focused on pharmacological approaches for prevention and/or treatment of ICU-D are on-going. One study was designed to test haloperidol (2.5 mg haloperidol × 3 daily intravenously with additional doses to a maximum of 20 mg/daily) in a large number of ICU patients with delirium (NCT03392376). Another investigation (NCT02216266) regards the use of physostigmine (24 mg + 25 min a 0.04 mg/kg intravenously) after elective, or emergency, heart surgery. Of note, for assessing the efficacy of their treatment the authors are evaluating changes in the spontaneous EEG and auditory evoked potentials in patients with ICU-D and agitation. Researchers from the Hôpitaux de Paris are evaluating the effect of melatonin *vs* placebo. Through enteral route, low (0.3 mg/d) or high (3 mg/d) doses of the medication will be administered up to Day-14 in patients under MV (NCT03524937). Melatonin is under investigation in another RCT enrolling elderly non-ventilated patients (NCT03013790). Again, a phase II triple blind RCT comparing two doses of melatonin (0.5 mg and 2.0 mg) are currently assessing the feasibility to subsequently design a full-scale RCT (NCT02615340).

Table 2 Selected evidence-based research on pharmacological management of delirium in intensive care unit

Ref.	Analysis	Findings
Burry *et al*[41]	Cochrane analysis	In non-ICU patients there is a poor evidence about the efficacy of typical, or SGAs, on the duration of delirium, discharge time, or HRQoL
Lonergan *et al*[42]	Cochrane analysis	Low dose haloperidol may be effective against POD, although with greater incidence of side effects when compared to the SGAs; Limitation: analysis based on small studies of limited scope
Serafim *et al*[43]	Systematic review	Prophylactic use of haloperidol, may be useful for reducing the prevalence of ICU-D
Herling *et al*[44]	Cochrane analysis	No difference proved between haloperidol and placebo for preventing ICU-D
Tao *et al*[53]	Meta-analysis	Administration of dexamethasone was associated with a reduction in delirium after on-pump cardiac surgery; Limitation: studies at a high risk of bias
Barbateskovic *et al*[45]	Systematic overview of reviews and meta-analyses	Pharmacological strategies for prevention or management of ICU-D is poor, or sparse
Chen *et al*[46]	Cochrane analysis	No evidence on the preventive and therapeutic role of dexmedetomidine against ICU-D and its outcome
Liu *et al*[47]	Meta-analysis	Dexmedetomidine may reduce delirium and duration of MV in patients after cardiac surgery when compared with propofol
Pasin *et al*[48]	Meta-analysis	Dexmedetomidine may reduce delirium also in patients undergoing non-invasive ventilation
Tampi *et al*[50]	Systematic review	Anticholinesterase inhibitors have no benefit against ICU-D prevention, or treatment
Lonergan *et al*[24]	Cochrane analysis	There is no evidence to support the use of BDZs in the treatment of non-alcohol withdrawal related delirium

ICU: Intensive care unit; SGAs: Second generation antipsychotics; LOS: Length of stay; HRQoL: Health-related quality of life; POD: Postoperative delirium; MV: Mechanical ventilation; BDZs: Benzodiazepines.

Based on their protocol adopted for pain control, sedation, and delirium in ICU patients (PAD protocol: Propofol or dexmedetomidine)[51], researcher from the Duke University are evaluating its feasibility versus midazolam in post cardiac surgery patients under MV (NCT02903407). Apart from the Duke's study, because dexmedetomidine represents an interesting perspective, other RCTs on this drug are on-going. In these studies, dexmedetomidine is used at low dosage continuously (NCT03172897), or during the night of surgery in the ICU unit (NCT03624595). Dexmedetomidine is also investigated compared to propofol in specific delirium types (hyperactive or mixed type) (NCT02807467), in the setting of sepsis (NCT01739933), and with the purpose to reduce incidence and severity of delirium by restoring sleep, in not intubated patients (NCT02856594).

Despite BDZs are commonly used for discomfort, anxiety, agitation, and alcohol withdrawal syndrome in the ICU, their use may induce the so-called BDZ-associated hypoactive delirium. Researchers are testing the hypothesis that the continuous infusion of flumazenil may be able to reverse this hypoactive ICU-D type (NCT02899156).

PERSPECTIVES

In the lack of effective pharmacological strategies for the prevention and management of ICU-D, new scientific evidence is urgently needed. Further large size trials on antipsychotics should be designed, should be conducted in order to evaluate preventive pharmacological strategies. These investigations must necessarily focus on a cohort of patients recognized as at higher risk. For instance, in a no-controlled investigation conducted on high-risk patients, van den Boogaard *et al*[52] found that prophylactic treatment with haloperidol (3 mg/d) was very effective. Pharmacological prophylactic agents other than antipsychotics should be investigated. For instance, because a meta-analysis suggested that the perioperative use of dexa-

methasone may prevent POD after on-pump cardiac surgery, studies on non-cardiac ICU patients could be encouraged[53].

Concerning delirium therapy, investigation on different clinical settings (*e.g.*, postsurgical, or sepsis), or focused on sedated or non-sedated patients receiving assessment before and after sedative interruption, could represent an interesting perspective. Moreover, the clinical practice suggests that the hyperactive delirium type seems to respond to antipsychotics whereas the hypoactive form is usually refractory to this therapy. Indeed, because delirium has multifactorial etiology and a complex pathophysiology involving neuroinflammation, microglia activation, surgical stress response (in postsurgical patients), and neurotoxic effects due to systemic infection[54], it is difficult to suppose that a single drug can be useful for all forms of delirium. Thus, the typology of delirium should be better typed and specific RCTs should be designed on specific ICU-D subgroups or by targeting specific symptoms such as anxiety or apathy.

Different outcomes such as delirium duration, ICU length of stay, mortality, duration of MV as well as the correlation between the severity of delirium and these clinical outcomes must be better highlighted. The issue of safety endpoints included excessive sedation and drug-related side effects could be exceeded through studies designed with defined drug regimens.

In addition, clinical studies on medications other than antipsychotics as a potential alternative or adjunct treatment could offer useful data. For instance, it seems that melatonin, and melatonin agonists (*e.g.*, L-tryptophan, and ramelteon) may offer some benefit, although clinical data are inconclusive[55]. Positive results from studies on valproic acid[56], or suvorexant[57], a potent and selective orexin receptor antagonist, should encourage further attempts focused on these interesting substances. More research should be also conducted on dexmedetomidine in order to investigate its overall safety profile, and efficacy in different clinical settings. Finally, systematic reviews with low risk of bias, or addressing serious adverse events, and clinical outcomes such as those related to the HRQoL and cognitive function are urgently warranted.

CONCLUSION

Despite the huge number of clinical investigations conducted on the topic, to date results from EBM analysis highlighted that there are no effective pharmacological strategies in both prevention and management of established ICU-D. Thus, for these purposes no-pharmacological approaches must be preferred. The identification of specific risk factors and their prompt correction is certainly a winning strategy; however, given the significant clinical impact of this complication, it is necessary to offer clinicians effective and safe therapeutic opportunities. Results from several on-going RCTs could provide useful information. Furthermore, a careful analysis of the unsatisfactory results obtained from previous research is necessary to identify possible lines of research.

REFERENCES

1 **Pandharipande P**, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA, Dittus R, Ely EW. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma* 2008; **65**: 34-41 [PMID: 18580517 DOI: 10.1097/TA.0b013e31814b2c4d]

2 **Vasilevskis EE**, Chandrasekhar R, Holtze CH, Graves J, Speroff T, Girard TD, Patel MB, Hughes CG, Cao A, Pandharipande PP, Ely EW. The Cost of ICU Delirium and Coma in the Intensive Care Unit Patient. *Med Care* 2018; **56**: 890-897 [PMID: 30179988 DOI: 10.1097/MLR.0000000000000975]

3 **Lin SM**, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, Fang YF, Shieh MH, Kuo HP. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med* 2004; **32**: 2254-2259 [PMID: 15640638 DOI: 10.1097/01.CCM.0000145587.16421.BB]

4 **Girard TD**, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, Gordon SM, Canonico AE, Dittus RS, Bernard GR, Ely EW. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med* 2010; **38**: 1513-1520 [PMID: 20473145 DOI: 10.1097/CCM.0b013e3181e47be1]

5 **Morandi A**, Rogers BP, Gunther ML, Merkle K, Pandharipande P, Girard TD, Jackson JC, Thompson J, Shintani AK, Geevarghese S, Miller RR, Canonico A, Cannistraci CJ, Gore JC, Ely EW, Hopkins RO; VISIONS Investigation, VISualizing Icu SurvivOrs Neuroradiological Sequelae. The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study*. *Crit Care Med* 2012; **40**: 2182-2189 [PMID: 22584766 DOI: 10.1097/CCM.0b013e318250acdc]

6 **Collet MO**, Caballero J, Sonneville R, Bozza FA, Nydahl P, Schandl A, Wøien H, Citerio G, van den Boogaard M, Hästbacka J, Haenggi M, Colpaert K, Rose L, Barbateskovic M, Lange T, Jensen A, Krog MB, Egerod I, Nibro HL, Wetterslev J, Perner A; AID-ICU cohort study co-authors. Prevalence and risk factors related to haloperidol use for delirium in adult intensive care patients: the multinational AID-ICU

inception cohort study. *Intensive Care Med* 2018; **44**: 1081-1089 [PMID: 29767323 DOI: 10.1007/s00134-018-5204-y]

7 **Arumugam S**, El-Menyar A, Al-Hassani A, Strandvik G, Asim M, Mekkodithal A, Mudali I, Al-Thani H. Delirium in the Intensive Care Unit. *J Emerg Trauma Shock* 2017; **10**: 37-46 [PMID: 28243012 DOI: 10.4103/0974-2700.199520]

8 **Patel RP**, Gambrell M, Speroff T, Scott TA, Pun BT, Okahashi J, Strength C, Pandharipande P, Girard TD, Burgess H, Dittus RS, Bernard GR, Ely EW. Delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals. *Crit Care Med* 2009; **37**: 825-832 [PMID: 19237884 DOI: 10.1097/CCM.0b013e31819b8608]

9 **Meyer-Massetti C**, Cheng CM, Sharpe BA, Meier CR, Guglielmo BJ. The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond? *J Hosp Med* 2010; **5**: E8-16 [PMID: 20394022 DOI: 10.1002/jhm.691]

10 **Page VJ**, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, Jackson J, Perkins GD, McAuley DF. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2013; **1**: 515-523 [PMID: 24461612 DOI: 10.1016/S2213-2600(13)70166-8]

11 **van den Boogaard M**, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, Pretorius D, de Koning J, Simons KS, Dennesen PJW, Van der Voort PHJ, Houterman S, van der Hoeven JG, Pickkers P; REDUCE Study Investigators, van der Woude MCE, Besselink A, Hofstra LS, Spronk PE, van den Bergh W, Donker DW, Fuchs M, Karakus A, Koeman M, van Duijnhoven M, Hannink G. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium: The REDUCE Randomized Clinical Trial. *JAMA* 2018; **319**: 680-690 [PMID: 29466591 DOI: 10.1001/jama.2018.0160]

12 **Torbic H**, Duggal A. Prophylactic Haloperidol for Critically Ill Adults. *JAMA* 2018; **320**: 303-304 [PMID: 30027243 DOI: 10.1001/jama.2018.6045]

13 **Strik JJMH**, Schieveld JNM. Prophylactic Haloperidol for Critically Ill Adults. *JAMA* 2018; **320**: 303 [PMID: 30027242 DOI: 10.1001/jama.2018.6041]

14 **Khan BA**, Perkins AJ, Campbell NL, Gao S, Farber MO, Wang S, Khan SH, Zarzaur BL, Boustani MA. Pharmacological Management of Delirium in the Intensive Care Unit: A Randomized Pragmatic Clinical Trial. *J Am Geriatr Soc* 2019; **67**: 1057-1065 [PMID: 30681720 DOI: 10.1111/jgs.15781]

15 **Devlin JW**, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018; **46**: e825-e873 [PMID: 30113379 DOI: 10.1097/CCM.0000000000003299]

16 **Meltzer HY**. What's atypical about atypical antipsychotic drugs? *Curr Opin Pharmacol* 2004; **4**: 53-57 [PMID: 15018839 DOI: 10.1016/j.coph.2003.09.010]

17 **Mo Y**, Yam FK. Rational Use of Second-Generation Antipsychotics for the Treatment of ICU Delirium. *J Pharm Pract* 2017; **30**: 121-129 [PMID: 26033792 DOI: 10.1177/0897190015585763]

18 **Girard TD**, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, Douglas IS, Malhotra A, Owens RL, Feinstein DJ, Khan B, Pisani MA, Hyzy RC, Schmidt GA, Schweickert WD, Hite RD, Bowton DL, Masica AL, Thompson JL, Chandrasekhar R, Pun BT, Strength C, Boehm LM, Jackson JC, Pandharipande PP, Brummel NE, Hughes CG, Patel MB, Stollings JL, Bernard GR, Dittus RS, Ely EW; MIND-USA Investigators. Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness. *N Engl J Med* 2018; **379**: 2506-2516 [PMID: 30346242 DOI: 10.1056/NEJMoa1808217]

19 **Devlin JW**, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, Robbins T, Garpestad E. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med* 2010; **38**: 419-427 [PMID: 19915454 DOI: 10.1097/CCM.0b013e3181b9e302]

20 **Girard TD**, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, Pun BT, Thompson JL, Shintani AK, Meltzer HY, Bernard GR, Dittus RS, Ely EW; MIND Trial Investigators. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. *Crit Care Med* 2010; **38**: 428-437 [PMID: 20095068 DOI: 10.1097/CCM.0b013e3181c58715]

21 **Zaal IJ**, Devlin JW, Hazelbag M, Klein Klouwenberg PM, van der Kooi AW, Ong DS, Cremer OL, Groenwold RH, Slooter AJ. Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Med* 2015; **41**: 2130-2137 [PMID: 26404392 DOI: 10.1007/s00134-015-4063-z]

22 **Pandharipande P**, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006; **104**: 21-26 [PMID: 16394685 DOI: 10.1097/00000542-200601000-00005]

23 **Amato L**, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. *Cochrane Database Syst Rev* 2010; CD005063 [PMID: 20238336 DOI: 10.1002/14651858.CD005063.pub3]

24 **Lonergan E**, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. *Cochrane Database Syst Rev* 2009; CD006379 [PMID: 19821364 DOI: 10.1002/14651858.CD006379.pub3]

25 **Nelson S**, Muzyk AJ, Bucklin MH, Brudney S, Gagliardi JP. Defining the Role of Dexmedetomidine in the Prevention of Delirium in the Intensive Care Unit. *Biomed Res Int* 2015; **2015**: 635737 [PMID: 26576429 DOI: 10.1155/2015/635737]

26 **Su X**, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, Zhu X, Zhu SN, Maze M, Ma D. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016; **388**: 1893-1902 [PMID: 27542303 DOI: 10.1016/S0140-6736(16)30580-3]

27 **Pandharipande PP**, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; **298**: 2644-2653 [PMID: 18073360 DOI: 10.1001/jama.298.22.2644]

28 **Riker RR**, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a

randomized trial. *JAMA* 2009; **301**: 489-499 [PMID: 19188334 DOI: 10.1001/jama.2009.56]
29 **Flükiger J**, Hollinger A, Speich B, Meier V, Tontsch J, Zehnder T, Siegemund M. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. *Ann Intensive Care* 2018; **8**: 92 [PMID: 30238227 DOI: 10.1186/s13613-018-0437-z]
30 **van Eijk MM**, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, Spronk PE, van Gool WA, van der Mast RC, Kesecioglu J, Slooter AJ. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet* 2010; **376**: 1829-1837 [PMID: 21056464 DOI: 10.1016/S0140-6736(10)61855-7]
31 **al-Kassab AS**, Vijayakumar E. Profile of serum cholinesterase in systemic sepsis syndrome (septic shock) in intensive care unit patients. *Eur J Clin Chem Clin Biochem* 1995; **33**: 11-14 [PMID: 7756436 DOI: 10.1515/cclm.1995.33.1.11]
32 **van Gool WA**, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet* 2010; **375**: 773-775 [PMID: 20189029 DOI: 10.1016/S0140-6736(09)61158-2]
33 **Opdam FL**, Oleksik AM, Westendorp RG. Cholinesterase inhibitor treatment in patients with delirium. *Lancet* 2011; **377**: 900-1; author reply 901 [PMID: 21397759 DOI: 10.1016/S0140-6736(11)60345-0]
34 **Cascella M**, Bimonte S. The role of general anesthetics and the mechanisms of hippocampal and extra-hippocampal dysfunctions in the genesis of postoperative cognitive dysfunction. *Neural Regen Res* 2017; **12**: 1780-1785 [PMID: 29239315 DOI: 10.4103/1673-5374.219032]
35 **Page VJ**, Casarin A, Ely EW, Zhao XB, McDowell C, Murphy L, McAuley DF. Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2017; **5**: 727-737 [PMID: 28734823 DOI: 10.1016/S2213-2600(17)30234-5]
36 **Chowdhury I**, Sengupta A, Maitra SK. Melatonin: fifty years of scientific journey from the discovery in bovine pineal gland to delineation of functions in human. *Indian J Biochem Biophys* 2008; **45**: 289-304 [PMID: 19069840]
37 **Oldham MA**, Lee HB, Desan PH. Circadian Rhythm Disruption in the Critically Ill: An Opportunity for Improving Outcomes. *Crit Care Med* 2016; **44**: 207-217 [PMID: 26308428 DOI: 10.1097/CCM.0000000000001282]
38 **Baumgartner L**, Lam K, Lai J, Barnett M, Thompson A, Gross K, Morris A. Effectiveness of Melatonin for the Prevention of Intensive Care Unit Delirium. *Pharmacotherapy* 2019; **39**: 280-287 [PMID: 30663785 DOI: 10.1002/phar.2222]
39 **Sultan SS**. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. *Saudi J Anaesth* 2010; **4**: 169-173 [PMID: 21189854 DOI: 10.4103/1658-354X.71132]
40 **Hatta K**, Kishi Y, Wada K, Takeuchi T, Odawara T, Usui C, Nakamura H; DELIRIA-J Group. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. *JAMA Psychiatry* 2014; **71**: 397-403 [PMID: 24554232 DOI: 10.1001/jamapsychiatry.2013.3320]
41 **Burry L**, Mehta S, Perreault MM, Luxenberg JS, Siddiqi N, Hutton B, Fergusson DA, Bell C, Rose L. Antipsychotics for treatment of delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2018; **6**: CD005594 [PMID: 29920656 DOI: 10.1002/14651858.CD005594.pub3]
42 **Lonergan E**, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. *Cochrane Database Syst Rev* 2007; CD005594 [PMID: 17443602 DOI: 10.1002/14651858.CD005594.pub2]
43 **Serafim RB**, Bozza FA, Soares M, do Brasil PE, Tura BR, Ely EW, Salluh JI. Pharmacologic prevention and treatment of delirium in intensive care patients: A systematic review. *J Crit Care* 2015; **30**: 799-807 [PMID: 25957498 DOI: 10.1016/j.jcrc.2015.04.005]
44 **Herling SF**, Greve IE, Vasilevskis EE, Egerod I, Bekker Mortensen C, Møller AM, Svenningsen H, Thomsen T. Interventions for preventing intensive care unit delirium in adults. *Cochrane Database Syst Rev* 2018; **11**: CD009783 [PMID: 30484283 DOI: 10.1002/14651858.CD009783.pub2]
45 **Barbateskovic M**, Krauss SR, Collet MO, Larsen LK, Jakobsen JC, Perner A, Wetterslev J. Pharmacological interventions for prevention and management of delirium in intensive care patients: a systematic overview of reviews and meta-analyses. *BMJ Open* 2019; **9**: e024562 [PMID: 30782910 DOI: 10.1136/bmjopen-2018-024562]
46 **Chen K**, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. *Cochrane Database Syst Rev* 2015; **1**: CD010269 [PMID: 25879090 DOI: 10.1002/14651858.CD010269.pub2]
47 **Liu X**, Xie G, Zhang K, Song S, Song F, Jin Y, Fang X. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: A meta-analysis with trial sequential analysis of randomized controlled trials. *J Crit Care* 2017; **38**: 190-196 [PMID: 27936404 DOI: 10.1016/j.jcrc.2016.10.026]
48 **Pasin L**, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, Isella F, Zangrillo A. Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically Ill patients: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth* 2014; **28**: 1459-1466 [PMID: 25034724 DOI: 10.1053/j.jvca.2014.03.010]
49 **Maagaard M**, Barbateskovic M, Perner A, Jakobsen JC, Wetterslev J. Dexmedetomidine for the management of delirium in critically ill patients-A protocol for a systematic review. *Acta Anaesthesiol Scand* 2019; **63**: 549-557 [PMID: 30701537 DOI: 10.1111/aas.13329]
50 **Tampi RR**, Tampi DJ, Ghori AK. Acetylcholinesterase Inhibitors for Delirium in Older Adults. *Am J Alzheimers Dis Other Demen* 2016; **31**: 305-310 [PMID: 26646113 DOI: 10.1177/1533317515619034]
51 **Barr J**, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41**: 263-306 [PMID: 23269131 DOI: 10.1097/CCM.0b013e3182783b72]
52 **van den Boogaard M**, Schoonhoven L, van Achterberg T, van der Hoeven JG, Pickkers P. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. *Crit Care* 2013; **17**: R9 [PMID: 23327295 DOI: 10.1186/cc11933]
53 **Tao R**, Wang XW, Pang LJ, Cheng J, Wang YM, Gao GQ, Liu Y, Wang C. Pharmacologic prevention of postoperative delirium after on-pump cardiac surgery: A meta-analysis of randomized trials. *Medicine (Baltimore)* 2018; **97**: e12771 [PMID: 30412068 DOI: 10.1097/MD.0000000000012771]
54 **Cascella M**, Muzio MR, Bimonte S, Cuomo A, Jakobsson JG. Postoperative delirium and postoperative

cognitive dysfunction: updates in pathophysiology, potential translational approaches to clinical practice and further research perspectives. *Minerva Anestesiol* 2018; **84**: 246-260 [PMID: 28984099 DOI: 10.23736/S0375-9393.17.12146-2]

55 **Walker CK**, Gales MA. Melatonin Receptor Agonists for Delirium Prevention. *Ann Pharmacother* 2017; **51**: 72-78 [PMID: 27539735 DOI: 10.1177/1060028016665863]

56 **Sher Y**, Miller Cramer AC, Ament A, Lolak S, Maldonado JR. Valproic Acid for Treatment of Hyperactive or Mixed Delirium: Rationale and Literature Review. *Psychosomatics* 2015; **56**: 615-625 [PMID: 26674479 DOI: 10.1016/j.psym.2015.09.008]

57 **Hatta K**, Kishi Y, Wada K, Takeuchi T, Ito S, Kurata A, Murakami K, Sugita M, Usui C, Nakamura H; DELIRIA-J Group. Preventive Effects of Suvorexant on Delirium: A Randomized Placebo-Controlled Trial. *J Clin Psychiatry* 2017; **78**: e970-e979 [PMID: 28767209 DOI: 10.4088/JCP.16m11194]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 June 12; 8(3): 28-35

DOI: 10.5492/wjccm.v8.i3.28

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Prospective Study

Implementation of a nurse-led protocol for early extubation after cardiac surgery: A pilot study

Giovanni Serena, Carlos Corredor, Nick Fletcher, Filippo Sanfilippo

ORCID number: Giovanni Serena (0000-0001-7986-1150); Carlos Corredor (0000-0003-4984-2244); Nick Fletcher (0000-0002-1110-6287); Filippo Sanfilippo (0000-0001-5144-0776).

Author contributions: Sanfilippo F designed the research and proposed the clinical audit; Serena G, Sanfilippo F, Fletcher N designed the protocol; Sanfilippo F, Serena G, Corredor C and Fletcher N collected and analysed the data; Sanfilippo F, Corredor C wrote the paper; Fletcher N reviewed the paper.

Institutional review board statement: As part of a clinical audit, this study received a waiver from the institutional review board.

Clinical trial registration statement: This audit has not been registered as a clinical trial.

Informed consent statement: Informed consent was not required, as data were collected as part of a clinical audit.

Conflict-of-interest statement: Authors declared no conflict-of-interest.

Data sharing statement: Authors will provide full data declared in this manuscript on request.

Giovanni Serena, Carlos Corredor, Nick Fletcher, Filippo Sanfilippo, Cardiothoracic Intensive Care Unit, Intensive Care Directorate – St Georges Healthcare NHS Foundation Trust, London SW170QT, United Kingdom

Corresponding author: Filippo Sanfilippo, MD, PhD, EDIC, Consultant Anaesthetist, Cardiothoracic Intensive Care Unit, Intensive Care Directorate – St Georges Healthcare NHS Foundation Trust, Blackshaw Rd, London SW170QT, United Kingdom. filipposanfi@yahoo.it
Telephone: +44-20-87251504
Fax: +44-20-87252180

Abstract

BACKGROUND

Protocols for nurse-led extubation are as safe as a physician-guided weaning in general intensive care unit (ICU). Early extubation is a cornerstone of fast-track cardiac surgery, and it has been mainly implemented in post-anaesthesia care units. Introducing a nurse-led extubation protocol may lead to reduced extubation time.

AIM

To investigate results of the implementation of a nurse-led protocol for early extubation after elective cardiac surgery, aiming at higher extubation rates by the third postoperative hour.

METHODS

A single centre prospective study in an 18-bed, consultant-led Cardiothoracic ICU, with a 1:1 nurse-to-patient ratio. During a 3-wk period, the protocol was implemented with: (1) Structured teaching sessions at nurse handover and at bed-space (all staff received teaching, over 90% were exposed at least twice; (2) Email; and (3) Laminated sheets at bed-space. We compared "standard practice" and "intervention" periods before and after the protocol implementation, measuring extubation rates at several time-points from the third until the 24th postoperative hour.

RESULTS

Of 122 cardiac surgery patients admitted to ICU, 13 were excluded as early weaning was considered unsafe. Therefore, 109 patients were included, 54 in the standard and 55 in the intervention period. Types of surgical interventions and baseline left ventricular function were similar between groups. From the third to the 12th post-operative hour, the intervention group displayed a higher

Manuscript source: Unsolicited manuscript

Received: February 14, 2019
Peer-review started: February 15, 2019
First decision: March 14, 2019
Revised: March 31, 2019
Accepted: May 21, 2019
Article in press: May 22, 2019
Published online: June 12, 2019

P-Reviewer: Drabek T
S-Editor: Wang JL
L-Editor: Filipodia
E-Editor: Wu YXJ

proportion of patients extubated compared to the standard group. However, results were significant only at the sixth hour (58% *vs* 37%, $P = 0.04$), and not different at the third hour (13% *vs* 6%, $P = 0.33$). From the 12th post-operative hour time-point onward, extubation rates became almost identical between groups (83% in standard *vs* 83% in intervention period).

CONCLUSION
The implementation of a nurse-led protocol for early extubation after cardiac surgery in ICU may gradually lead to higher rates of early extubation.

Key words: Fast-track; Extubation protocol; Intensive care; Mechanical ventilation; Implementation strategies

Core tip: Fast-track is emerging in cardiac surgery, and early extubation is a cornerstone for fast-track. Nurse-led extubation protocols may be introduced in clinical practice with different teaching techniques, aiming for early extubation.

Citation: Serena G, Corredor C, Fletcher N, Sanfilippo F. Implementation of a nurse-led protocol for early extubation after cardiac surgery: A pilot study. *World J Crit Care Med* 2019; 8(3): 28-35
URL: https://www.wjgnet.com/2220-3141/full/v8/i3/28.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i3.28

INTRODUCTION

Close monitoring of patients is required during the early postoperative period after cardiac surgery, particularly the first few hours, in order to identify and treat potentially life-threatening complications such as bleeding and cardiovascular instability. Traditionally, patients are managed in the intensive care unit (ICU) during the initial perioperative period. Nonetheless, the evolution of surgical perfusion techniques and anaesthetic management have allowed the successful implementation of fast-track care protocols after cardiac surgery. Patients with lower levels of complexity can be safely managed in post-anaesthesia care units (PACUs) with a decreased time to extubation, shorter ICU and hospital length of stay (LOS), and possible cost reduction[1-3]. These results have been confirmed by a Cochrane meta-analysis, which found no difference in complication rates, and outcomes between conventional care *vs* fast-track approach in low and moderate risk cardiac surgery patients. Moreover, the fast-track approach shortened time to extubation and LOS in ICU compared to conventional care[4]. Early extubation is a cornerstone for fast-track cardiac care and is associated with shorter duration of mechanical ventilation (MV), decreased ICU and hospital LOS, and fewer postoperative respiratory complications[5]. Conversely, prolonged MV in ICU is associated with higher incidence of pulmonary complications, increased ICU and hospital LOS and associated cost in both general ICU[6] and in the post-cardiac surgery populations[2,7,8].

In the general ICU setting, Kollef *et al*[9] showed that a nurse-led extubation protocol was as safe as physician-guided extubation, showing similar complications and mortality rates, significantly reducing MV time and possibly being effective in cost reduction. In the cardiac surgery setting, the largest amount of studies evaluating the safety and advantages of early extubation are based in the PACU, where staff are usually more experienced in rapid extubation than ICU personnel, and often have a higher physician-to-patient ratio.

Early extubation following cardiac surgery can be also used as a performance indicator in cardiac surgical centres[10]. Achieving safe early extubation depends on many contributing factors comprising the pre, intra and postoperative periods. Early extubation also relies on the successful coordination of efforts from multiple disciplines, *i.e.*, nursing, surgery, anaesthesia and critical care.

In our study, we aimed to evaluate the results of the implementation of a nurse-led protocol for early extubation after cardiac surgery in ICU as part of a quality improvement initiative. Research Ethics committee authorization and informed consent were not required to perform this study.

MATERIALS AND METHODS

This was a single centre prospective study in an 18-bed Cardiothoracic ICU across an 11-week period (11.08.2014 – 21.12.2014). Our Cardiothoracic ICU is a closed critical care consultant-led ICU admitting patients after cardiac, thoracic and vascular procedures. During the period of study, the Cardiothoracic ICU was staffed with a team of two consultants from 8:00 to 18:00 and one consultant during the night hours with junior doctor support. Patients mechanically ventilated after cardiac surgery received nursing care in a one-to-one ratio.

In the two years preceding this study, almost 1000 cardiac surgical cases per year were performed at our institution with an average of 80% being admitted to the Cardiothoracic ICU. The remaining 20% was managed in the fast-track PACU. In this study, we aimed to evaluate the results of the introduction of a nurse-led protocol for early extubation after cardiac surgery. Before the implementation of the nurse-led protocol, patients after cardiac surgery were extubated according to the decision of the treating physician. A simplified nurse-led protocol for extubation after cardiac surgery was introduced as part of a quality improvement initiative. A small steering group wrote a draft of the nurse-led protocol, which was reviewed, modified and approved by all of the Cardiothoracic ICU consultants and senior nurses. The final version of the protocol is shown in Figure 1. The protocol did not involve any changes in the anaesthetic or surgical intraoperative management.

The study was divided into two periods of eight weeks each. The "standard practice" period, 11/08/2014 to 05/10/2014 and the "intervention" period, 27/10/2014 to 21/12/2014 (Figure 2). We anticipated approximately 100 patients per period. The overall data collection included the following time-points: admission, 1st - 2nd - 3rd - 4th - 5th - 6th - 9th - 12th – 15th - 18th - 24th postoperative hour. Data were collected in a pre-defined sheet by the bed-space nurse and entered into spread-sheet software (Microsoft Office Excel 2011). Patients admitted to the ICU were included in the nurse led protocol, unless a consultant anaesthetist/intensivist or cardiac surgeon stated it would have not been safe to extubate the patient early, based on both premorbid status and/or intraoperative course. Therefore, for this pilot study, we followed a pragmatic approach for the inclusion of patients in the nurse-led extubation pathway.

Implementation strategy

The two study periods were separated by a three-week period (06/10/2014 – 26/10/2014) dedicated to teaching the new protocol to all nursing and medical staff using short small group sessions held by the members of the steering group. Additionally, we delivered one to one bed-side teaching to the nursing staff. An attendance form was kept to ensure that all staff received frontal teaching. This resulted in over 90% of the staff exposed to this teaching at least twice. The protocol was disseminated *via* email to the entire staff, and laminated sheets containing the protocol were printed and distributed at each bed-space with additional copies available in the staff room.

Characteristics of the new protocol

As shown in Figure 1, the new protocol set a target of extubation from operating theatre arrival by the third postoperative hour, if conditions specified by the protocol were met. The bedside nurse was in charge of implementing the protocol from arrival with setting of pre-specified parameters for titration of sedation and analgesia. Mechanical ventilation settings following a "lung protective strategy" were also outlined in the protocol. Within one hour from arrival, the bedside nurse confirmed the absence of several exclusion criteria (excessive bleeding and/or tamponade, metabolic and hemodynamic derangements, hypoxia and or hypercarbia, hypothermia) against a checklist, before decreasing sedation levels and attempting to start pressure support ventilation mode. From the second postoperative hour, or whenever criteria for extubation were met, nurses were asked to wean sedation and mechanical ventilation in order to extubate by the third postoperative hour, after confirming the clinical decision with the senior nurse in charge or with the doctor on duty. Bedside nurses informed the senior nurse in charge and/or the doctor on duty in case of clinical issues or uncertainty.

Outcomes

The primary outcome of our study was that a proportion of patients extubated at different pre-defined time-points (from the third until the 12th postoperative hour). Secondary outcomes were re-intubation rates within 12 hours from extubation and adherence to a lung protective ventilation strategy. Lung protective was defined as a tidal volume of 6-8 mL/kg ideal body weight.

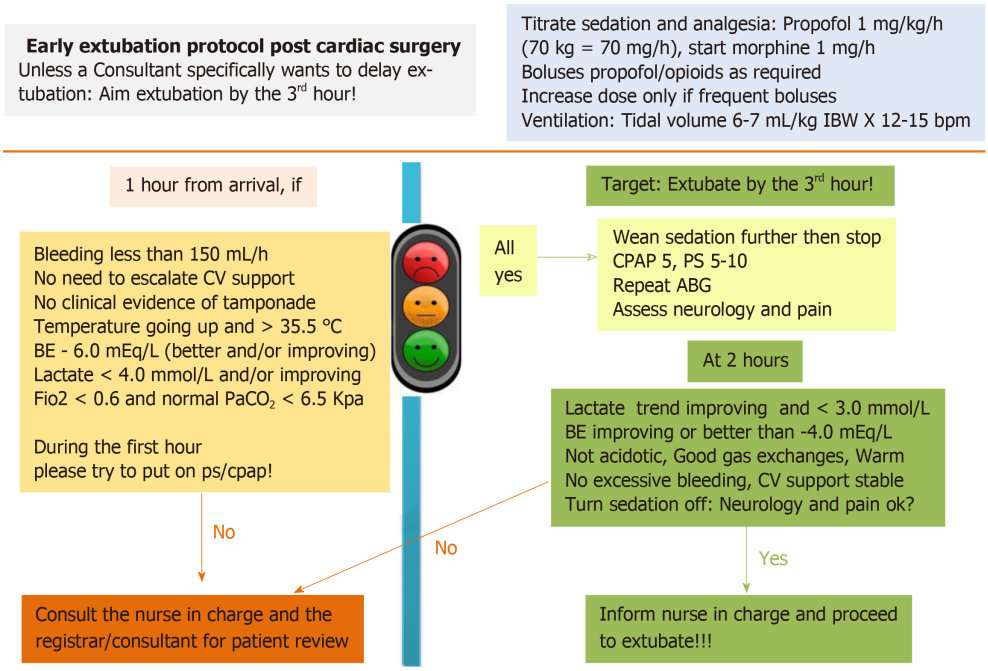


Figure 1 Protocol for the management of patients after cardiac surgery. ABG: Arterial blood gas; BE: Base excess; CPAP: Continuous positive airway pressure; CV: Cardiovascular; IBW: Ideal body weight; PS: Pressure support.

Statistical analysis

Formal sample size calculation was not performed in this study, but assumption on the length of each period was made based on average number of cardiac surgery intervention admitted to the Cardiothoracic ICU.

The Kolmogorov-Smirnoff test, histograms and normal quartile plots were examined to test for the normality assumption of continuous variables. Continuous variables are presented as mean (SD) with 95% confidence interval (95%CI) or median [(interquartile range) (IQR)] and categorical variables as number and percentage (%). A Wilcoxon signed rank test was then used to detected differences among pairs of samples. Categorical variables were compared through the Chi-square test with Yates correction. All tests were two-sided, and a result of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM® SPSS® Statistics 17 for Windows.

RESULTS

During the two study periods, a total of 122 postoperative cardiac surgical patients were admitted to the cardiothoracic ICU, 60 in the standard practice and 62 during the intervention period. Thirteen patients (six in the standard practice period and seven in the intervention period) were excluded from the early extubation protocol at the discretion of the attending consultant due to complex surgery, comorbidities or intraoperative issues. Therefore, data from a total of 109 patients were collected, 54 in the standard practice and 55 in the intervention period.

Patients in the "standard period", as compared to the "intervention period", had similar height (168.3 ± 9.7 cm *vs* 170.8 ± 8.8 cm respectively, $P = 0.11$) and age (66.5 ± 11.7 *vs* 65.7 ± 10.9, respectively, $P = 0.74$) and body weight (76.8 ± 13.4 kg *vs* 82.3 ± 14.8 kg, respectively, $P = 0.07$). In both periods, male patients represented 76% of the population ($P = 0.96$).

The types of interventions were similar between groups. The two most common surgical intervention were isolated elective coronary artery surgery ($n = 31/54$, 57% of all surgeries during the "standard period" *vs* $n = 27/55$, 49% in the "intervention period", $P = 0.50$) and coronary surgery associated to aortic valve replacement ($n = 7/54$, 13% "standard period" *vs* $n = 5/55$, 9% "intervention period", $P = 0.73$). The groups were also comparable with regards to their baseline LV function (Table 1).

Extubation rates

Extubation rates did not differ between the two study groups at the third post-operative hour. However, from the third to the 12th post-operative hour, the inter-

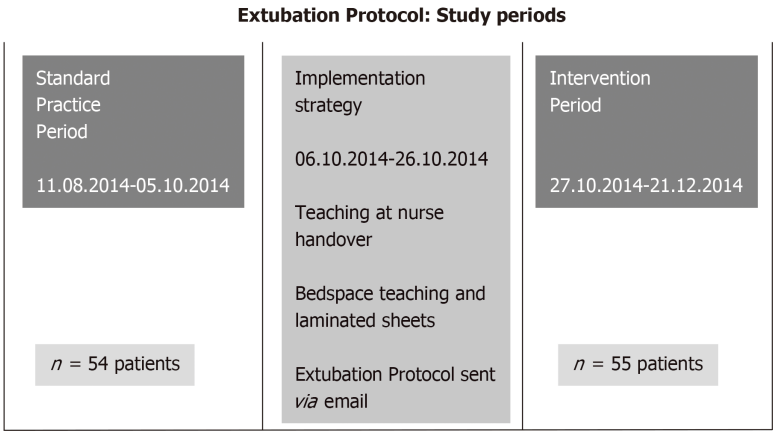


Figure 2 Study periods. Three study periods were identified: "standard practice", "implementation" and "intervention". The duration of each period is indicated in the figure.

vention group displayed a higher proportion of patients extubated compared to the standard group. The difference was only statistically significant at the sixth postoperative hour (37% in the standard *vs* 58% in the intervention period, $P = 0.04$). A non-significant trend towards higher extubation rates in the intervention period was found from the fourth until the ninth postoperative hour (fourth hour: $P = 0.12$; 5th h: $P = 0.13$; ninth hour: $P = 0.10$). From the 12th post-operative hour time-point onward, extubation rates became almost identical between the groups (Figure 3). Only one patient in the standard group and two patients in the intervention group were re-intubated within 12 h after extubation. All cases were due to respiratory failure, and the difference between periods was not statistically significant ($P = 0.99$).

Lung protection

Patients were ventilated with similar positive end-expiratory pressure (PEEP) levels throughout the postoperative period between groups. More than 99% of PEEP values recorded were 5 cmH_2O or above in both groups. There was an acceptable degree of adherence to the indication regarding the TV, with less than 7% of patients in both groups ventilated with 8 mL/kg or higher, and in most cases, such TV were achieved in pressure support ventilation mode.

DISCUSSION

Early extubation is a cornerstone in fast-track care protocols after cardiac surgery, and it has been repeatedly investigated in dedicated PACU settings. Our study found that early extubation following the introduction of a nurse-led protocol can be implemented in a cardiovascular ICU setting, possibly resulting in a greater number of early extubations.

The early extubation project constitutes the initial stages of a quality cycle aimed to streamline and standardize patient flow in our cardiovascular ICU to improve patient outcomes. We observed statistically significantly higher rates of extubation in the intervention group at the sixth postoperative hour ($P = 0.04$). Although non-significant, we saw also a trend towards higher extubation rates from the fourth until the ninth postoperative hour. We believe that our study was underpowered to detect significant differences in extubation rates between the study groups. Indeed, there was a lower-than-expected number of patients included in the study due to unplanned reduction in our case-load. Therefore, it remains speculative that collecting a higher number of cases would have resulted in an earlier and larger separation of the extubation rate curves. From the 12th postoperative hour, the curves of patients extubated did not differ between the two investigated periods, likely because patients mechanically ventilated beyond this stage were not suitable for early extubation and that the reduced number of cases had no impact after the 12th postoperative hour. We found similar compliance with TV and PEEP levels compatible with a lung protective strategy in both groups, which probably reflects the widespread practice of lung protective ventilation in modern ICUs.

We acknowledge that our protocol failed to boost the target set by our protocol of increasing extubation rates as early as two hours after cardiac surgery. This is not unexpected, since adopting a new and faster protocol may take time. Resistance to

Table 1 Distribution of left ventricular function between the pre- and post-implementation of extubation protocol

	Before the implementation of extubation protocol (*n* of patients)	After the implementation of extubation protocol (*n* of patients)
Normal LV function	41	40
Mild-to-moderate LV impairment	11	14
Severe LV impairment	2	1
Total	54	55

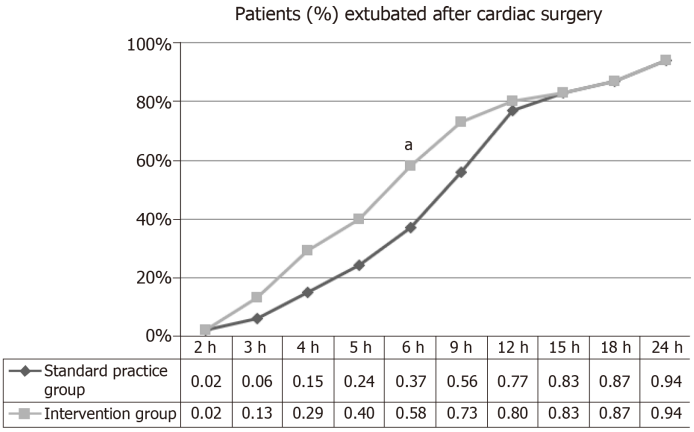
LV: Left ventricular.

sudden changes in clinical practice is not uncommon. Nevertheless, studies in other scenarios have shown that improvements in clinical practice can be obtained when new interventions are introduced using a continuous education program leading to improving outcomes in critically ill patients[11]. The need for a learning curve based on experience is likely, and this should be taken into account as well. Moreover, the lower-than-expected number of cases included in our study probably reduced staff exposure to the new strategy on early extubation, which in turn may have slowed the learning curve process. We believe our strategy for implementing the new protocol was well-designed and had the advantage of making the personnel more comfortable with the new approach.

Extubation remains a challenging perioperative stage with a higher number of perioperative respiratory complications occurring at the extubation rather than during the intubation process (12.6% *vs* 4.6%)[12]. Furthermore, extubation may expose fragile cardiac patients to significant shifts in intrathoracic pressures, which can lead to a number of cardiac complications such as pulmonary oedema due to left ventricular dysfunction. Therefore, safe extubation demands a systematic approach, especially in the setting of complex surgery in patients with significant comorbidities. Early extubation of patients after cardiac surgery involves multiple tasks, such as appropriate sedation and analgesia titration, frequent neurological assessment, continuous evaluation of haemodynamic stability, progressive respiratory weaning, careful temperature control and assessment of bleeding. Our protocol covered all of the aspects mentioned above. We believe that these tasks can be satisfactorily accomplished by trained and motivated nurses, with the back-up support of experienced medical staff. In the general ICU, a large study showed that a nurse-led extubation protocol had similar complications and mortality rates than physician-guided extubation and significantly reduced MV time, possibly having positive effects on cost saving[9].

Our study has the value of investigating the implementation of a structured nurse-led protocol for early extubation after cardiac surgery in a Cardiothoracic ICU with a 1:1 nurse-to-patient ratio for ventilated patients. However, in the cardiac surgery setting, the largest amount of studies evaluating safety and advantages of early extubation are based in the PACU, where staff have more experience in extubation than the ICU personnel. Moreover, PACU usually has a higher consultant-to-patient ratio compared to ICU. For instance, Probst *et al*[13] recently compared post-cardiac surgery management in PACU *vs* cardiac ICU and found a significant shorter extubation time and a higher rate of extubation within the first six postoperative hours in hemodynamically stable, normo-thermic, non-bleeding patients admitted to PACU as compared to a similar group of patients admitted to ICU. Moreover, PACU patients had shorter LOS before step-down and less arrhythmic complication, with no difference in other complication rates. When looking at such results, it is worthwhile noting some of the structural differences between PACU and ICU in this study: (1) 3-bed PACU *vs* 21-bed ICU; (2) Dedicated post-cardiac surgery PACU *vs* mixed ICU; and (3) 1:3 consultant-to-patient ratio in PACU and 1:12 in ICU. Considering these structural differences together with the usually higher airway skills of PACU staff, the observed differences are not surprising.

The most important limitation of our study is the lower than expected number of cases collected in the study period. We were able to analyse data from only 105 patients rather than the estimated target of 200. A second limitation is the lack of standardisation of anaesthetic management that likely influenced the neurological appropriateness for extubation. A third limitation of this study is that safety could not be fully evaluated with such small numbers; although only three patients were re-intubated after extubation, this is not an infrequent event after cardiac surgery, and larger numbers are required to fully evaluate the safety of early extubation in Cardiothoracic ICU after cardiac surgery. Finally, protocols implementing nurse-led



	2 h	3 h	4 h	5 h	6 h	9 h	12 h	15 h	18 h	24 h
Standard practice group	0.02	0.06	0.15	0.24	0.37	0.56	0.77	0.83	0.87	0.94
Intervention group	0.02	0.13	0.29	0.40	0.58	0.73	0.80	0.83	0.87	0.94

Figure 3 Rates of patients extubated at different time-points. The analysis starts at the third postoperative hour. Standard practice group is shown in black colour (series 1) and intervention group in grey (series 2). [a]*P* < 0.05, standard practice group *vs* intervention group.

extubation should take into account the staff skills and knowledge. Our results should be interpreted, considering that in the United Kingdom, there is a very high level of training and continuous re-training for nurses. Other countries and Healthcare Systems with lower resources may struggle in providing such level of training and therefore the practice of nurse-led extubation after cardiac surgery may not be practical.

The study covered the data acquisition, pattern analysis, interpretation and change in action stages necessary to initiate a quality cycle[14]. Our intention is to complete the quality cycle by acquiring further data for a larger cohort of patients and periodical evaluation of outcomes.

In conclusion, we implemented a nurse-led protocol for early extubation in the Cardiothoracic ICU with structured teaching and training. Although the extubation rates were similar by the third postoperative hour, a higher rate of patients in the intervention group was extubated by the sixth postoperative hour. We did not have enough data to establish the safety of our early extubation protocol.

ARTICLE HIGHLIGHTS

Research background

Nurse led-extubation is safe in the general intensive care unit (ICU) setting, but data in field of cardiac surgery are scarce and limited to post-anaesthesia care units.

Research motivation

Nurse-led extubation protocols may help in shortening postoperative mechanical ventilation, thus expediting patient recovery after cardiac surgery.

Research objectives

To evaluate the results of the implementation of a nurse-led extubation protocol.

Research methods

In a single centre prospective study during a 3-wk period, we implemented a nurse-led extubation protocol in patients admitted after cardiac surgery. The protocol was implemented with structured teaching sessions at nurse handover, teaching at bed-space, information provided *via* email and apposition of laminated sheets with the protocol at each bed-space. We performed a comparison of before and after protocol implementation ("standard practice" and "intervention" periods, respectively), measuring extubation rates at several time-points from the third until the 24th postoperative hour.

Research results

We included 109 patients, 54 in the standard and 55 in the intervention period. Although the intervention group displayed a higher proportion of patients extubated from the third to the 12th post-operative hour compared to the standard group, results were significant only at the sixth hour (58% *vs* 37%, $P = 0.04$) and not different at the third hour (13% *vs* 6%, $P = 0.33$). After the 12th post-operative hour time-point onward, extubation rates become almost identical between groups.

Research conclusions

The implementation of a nurse-led protocol for early extubation after cardiac surgery in the cardiac ICU may gradually lead to higher rates of early extubation.

Research perspectives

The present study adds information regarding a growing body of literature of fast-track extubation and identifies a nurse-led protocol as a possible intervention that shortens the length of mechanical ventilation in patients recovering after cardiac surgery. The study findings should be interpreted in the context of the level of training and the nurse-to-patient ratio.

REFERENCES

1 **Cheng DC**. Fast track cardiac surgery pathways: early extubation, process of care, and cost containment. *Anesthesiology* 1998; **88**: 1429-1433 [PMID: 9637632 DOI: 10.1097/00000542-199806000-00002]

2 **Cheng DC**, Karski J, Peniston C, Asokumar B, Raveendran G, Carroll J, Nierenberg H, Roger S, Mickle D, Tong J, Zelovitsky J, David T, Sandler A. Morbidity outcome in early vs conventional tracheal extubation after coronary artery bypass grafting: a prospective randomized controlled trial. *J Thorac Cardiovasc Surg* 1996; **112**: 755-764 [PMID: 8800165 DOI: 10.1016/S0022-5223(96)70062-4]

3 **Cheng DC**, Wall C, Djaiani G, Peragallo RA, Carroll J, Li C, Naylor D. Randomized assessment of resource use in fast-track cardiac surgery 1-year after hospital discharge. *Anesthesiology* 2003; **98**: 651-657 [PMID: 12606909 DOI: 10.1097/00000542-200303000-00013]

4 **Zhu F**, Lee A, Chee YE. Fast-track cardiac care for adult cardiac surgical patients. *Cochrane Database Syst Rev* 2012; **10**: CD003587 [PMID: 23076899 DOI: 10.1002/14651858.CD003587.pub2]

5 **Meade MO**, Guyatt G, Butler R, Elms B, Hand L, Ingram A, Griffith L. Trials comparing early vs late extubation following cardiovascular surgery. *Chest* 2001; **120**: 445S-453S [PMID: 11742964 DOI: 10.1378/chest.120.6_suppl.445S]

6 **Safdar N**, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med* 2005; **33**: 2184-2193 [PMID: 16215368 DOI: 10.1097/01.CCM.0000181731.53912.D9]

7 **Cheng DC**. Pro: early extubation after cardiac surgery decreases intensive care unit stay and cost. *J Cardiothorac Vasc Anesth* 1995; **9**: 460-464 [PMID: 7579120 DOI: 10.1016/S1053-0770(05)80105-3]

8 **Cheng DC**, Karski J, Peniston C, Raveendran G, Asokumar B, Carroll J, David T, Sandler A. Early tracheal extubation after coronary artery bypass graft surgery reduces costs and improves resource use. A prospective, randomized, controlled trial. *Anesthesiology* 1996; **85**: 1300-1310 [PMID: 8968177 DOI: 10.1097/00000542-199612000-00011]

9 **Kollef MH**, Shapiro SD, Silver P, St John RE, Prentice D, Sauer S, Ahrens TS, Shannon W, Baker-Clinkscale D. A randomized, controlled trial of protocol-directed vs physician-directed weaning from mechanical ventilation. *Crit Care Med* 1997; **25**: 567-574 [PMID: 9142019 DOI: 10.1097/00003246-199704000-00004]

10 **Lobdell K**, Camp S, Stamou S, Swanson R, Reames M, Madjarov J, Stiegel R, Skipper E, Geller R, Velardo B, Mishra A, Robicsek F. Quality improvement in cardiac critical care. *HSR Proc Intensive Care Cardiovasc Anesth* 2009; **1**: 16-20 [PMID: 23439222]

11 **Pellis T**, Sanfilippo F, Roncarati A, Dibenedetto F, Franceschino E, Lovisa D, Magagnin L, Mercante WP, Mione V. A 4-year implementation strategy of aggressive post-resuscitation care and temperature management after cardiac arrest. *Resuscitation* 2014; **85**: 1251-1256 [PMID: 24892264 DOI: 10.1016/j.resuscitation.2014.05.019]

12 **Asai T**, Koga K, Vaughan RS. Respiratory complications associated with tracheal intubation and extubation. *Br J Anaesth* 1998; **80**: 767-775 [PMID: 9771306 DOI: 10.1093/bja/80.6.767]

13 **Probst S**, Cech C, Haentschel D, Scholz M, Ender J. A specialized post anaesthetic care unit improves fast-track management in cardiac surgery: a prospective randomized trial. *Crit Care* 2014; **18**: 468 [PMID: 25123092 DOI: 10.1186/s13054-014-0468-2]

14 **Donabedian A**. Evaluating the quality of medical care. 1966. *Milbank Q* 2005; **83**: 691-729 [PMID: 16279964 DOI: 10.1111/j.1468-0009.2005.00397.x]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2019 July 31; 8(4): 36-58

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Irregular Volume 8 Number 4 July 31, 2019

REVIEW

MINIREVIEWS

Contents

World Journal of Critical Care Medicine

Volume 8 Number 4 July 31, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Tomas Drabek, MD, PhD, Associate Professor, Department of Anesthesiology, University of Pittsburgh, Pittsburgh, PA 15213, United States

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, infection and anti-infection treatment, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, severe infection, and shock and multiple organ dysfunction syndrome.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yun-Xiaojian Wu*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

EDITORIAL OFFICE
Jia-Ping Yan, Director

PUBLICATION DATE
July 31, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 July 31; 8(4): 36-48

DOI: 10.5492/wjccm.v8.i4.36

ISSN 2220-3141 (online)

REVIEW

One approach to circulation and blood flow in the critical care unit

Camilo Pena-Hernandez, Kenneth Nugent

ORCID number: Camilo Pena-Hernandez (0000-0002-5149-0930); Kenneth Nugent (0000-0003-2781-4816).

Author contributions: Pena-Hernandez C and Nugent K contributed equally to this work.

Conflict-of-interest statement: Authors declare no conflict of interest for this article.

Manuscript source: Unsolicited manuscript

Received: March 7, 2019
Peer-review started: March 11, 2019
First decision: April 16, 2019
Revised: May 14, 2019
Accepted: June 12, 2019
Article in press: June 12, 2019
Published online: July 31, 2019

P-Reviewer: Aurilio C, Willms DC, Yeh YC
S-Editor: Wang JL
L-Editor: A
E-Editor: Liu JH

Camilo Pena-Hernandez, Department of Internal Medicine, Division of Nephrology and Hypertension, Texas Tech University Health Sciences Center, Lubbock, TX 79430, United States

Kenneth Nugent, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Texas Tech University Health Sciences Center, Lubbock, TX 79430, United States

Corresponding author: Camilo Pena-Hernandez, MD, Assistant Professor, Department of Internal Medicine, Division of Nephrology and Hypertension, Texas Tech University Health Sciences Center, 3601 4th Street STOP 9410, Lubbock, TX 79430, United States.
camilo.pena@ttushc.edu
Telephone: +1-210-5511524
Fax: +1-806-7433143

Abstract

Evaluating and managing circulatory failure is one of the most challenging tasks for medical practitioners involved in critical care medicine. Understanding the applicability of some of the basic but, at the same time, complex physiological processes occurring during a state of illness is sometimes neglected and/or presented to the practitioners as point-of-care protocols to follow. Furthermore, managing hemodynamic shock has shown us that the human body is designed to fight to sustain life and that the compensatory mechanisms within organ systems are extraordinary. In this review article, we have created a minimalistic guide to the clinical information relevant when assessing critically ill patients with failing circulation. Measures such as organ blood flow, circulating volume, and hemodynamic biomarkers of shock are described. In addition, we will describe historical scientific events that led to some of our current medical practices and its validation for clinical decision making, and we present clinical advice for patient care and medical training.

Key words: Shock; Volume status; Fluid; Vasopressors; Mean systemic pressure; Pulse pressure; Plethysmography variability index

Core tip: In this review, we depict the historical understanding of circulation and blood flow physiology. Also, by characterizing the different approaches to circulatory failure, we attempt to provide a simplified tool for education and one summarized clinical guideline for management in the critical care unit.

Citation: Pena-Hernandez C, Nugent K. One approach to circulation and blood flow in the critical care unit. *World J Crit Care Med* 2019; 8(4): 36-48
URL: https://www.wjgnet.com/2220-3141/full/v8/i4/36.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i4.36

INTRODUCTION

In the era of evidence-based medicine and quality measures, shock has become a synonym for critically ill patients. Shock has a significant effect on morbidity, mortality, and costs; septic shock has been associated with 40%-80% of all sepsis-related deaths in the hospital and has increased hospital costs to more than $3000 per day for these patients[1]. The management of patients with shock remains a challenge for clinicians and subspecialists involved in their care. Not only is circulatory failure common in the hospital and intensive care unit (ICU) setting (to the point that administrative efforts by the hospitals are now made to protocolize management), but it is also such a common problem that physicians sometimes focus more on symptomatic stepwise approaches than on understanding the disease process to determine the best treatment.

In this review we will discuss the pathophysiology of shock, the assessment of volume status, and approaches to management.

DEFINITIONS AND PATHOPHYSIOLOGY

Shock

For the medical practitioner in charge of the ICU, shock is the clinical manifestation of inadequate blood flow and circulatory failure[2]. Some define it as insufficient oxygen delivery; the problem with this definition is that there are overlapping diseases of the respiratory tract associated with hypoxemia, which cause inadequate tissue oxygenation but not necessarily a state of shock.

Hypotension

Blood pressure determines the blood flow distribution but does not define the state of shock or the adequacy of circulation. Manual blood pressure readings are an appropriate way to determine blood pressure, but an arterial line continues to be the best practice when more accurate readings are needed, even though arterial lines are invasive, painful, and difficult in patients with vascular disease and have a variety of complications.

To understand circulatory failure, it is paramount to recognize that blood pressure and flow are uncoupled physiological processes. From basic physiology, we know that in the range of acceptable blood pressures and normal circulation, all vital organs (including the brain and kidneys) have a wide array of blood flow patterns that are completely disengaged from blood pressure; thus, clinicians will be incapable of making any assumptions about organ flow and cardiac output based on blood pressure alone (Figures 1 and 2, Table 1)[3,4].

Regulation of blood flow

In basic science classes, we learn about the physiology of cardiovascular circulation based on the idea that organ blood flow is similar to electric voltage and currents; consequently, we have adapted Ohm's principle of conduction for a better understanding of the cardiovascular system: Voltage (V) = electric current (I) x resistance (R). Replacement with hemodynamic parameters results in mean arterial pressure (MAP) – right atrial pressure (PRA) = cardiac output (CO) x systemic vascular resistance (SVR): MAP – PRA = CO x SVR.

For explaining the theoretical bases of hemodynamics and flow, this equation is adequate. The clinical application of this equation fails since it neglects the fact that humans have baroreceptors and reflex responses to changes in pressure. Therefore, when CO decreases, there is an instantaneous vasoconstrictor response to maintain equilibrium within the system, thereby maintaining a normal blood pressure. Understanding this concept is imperative, since patients may become overtly hypertensive with low cardiac output or uncalibrated/dysfunctional baroreceptors[5,6].

The sicker the patients become, the more difficult it is for the cardiovascular system to increase the SVR to maintain balance; when the ability to increase the SVR is

Table 1 Types of shock and relationship with blood pressure and cardiac output

	Blood pressure	Cardiac output
Hypovolemic	?	↓
Cardiogenic	?	↓
Obstructive	?	↓
Distributive	↓ (Most of the time)	?

?: May be high, normal, or low.

exhausted, patients develop hypotension. Conversely, when patients present with a vasodilated state (*e.g.*, septic shock), they will attempt to increase the CO to preserve an adequate MAP, and as the blood pressure continues to drop, they may reach a point at which the ability to increase the CO is surpassed, following which they become overtly hypotensive. These ideas indicate that low blood pressure is a late and insensitive indicator of inadequate circulation[7]. Furthermore, this concept applies when you are describing cardiogenic shock[8], sepsis[9], cardiac tamponade[10], or traumatic shock[11]. For example, an ICU patient with class 3 hypovolemic shock (Table 2) exemplifies the fact that 40% of the blood volume needs to be lost before the blood pressure decreases.

Understanding this concept will afford a clinical advantage when assessing the patient as one will know that hypoperfusion may be the result of a low SVR, a low CO, or a high SVR in the setting of a critically depressed CO. As a result, planning medical care and prognosis based solely on blood pressure may not work. In 2013, Lehman *et al*[12] reported interesting data related to the clinical applications of these concepts and observed that only when the MAP dropped below 70 mmHg did the risk for acute kidney injury and/or mortality increase.

Adequacy of circulation and venous oxygenation

For more than 20 years, critical care medicine has been trying to assess the adequacy of circulation. There are overwhelming data and information on mixed venous oxygen saturation (SvO_2), lactic acid, and clinical signs and symptoms, such as mental status and urine output.

We should start with an understanding of adequate oxygen (O_2) delivery and consumption to assess SvO_2. A healthy individual deliver approximately 1,000 ml/min of oxygen to peripheral tissues, and the tissues extract nearly 25% of the oxygen [extraction ratio (ER)]. In low-oxygen delivery states, such as low CO, anemia, or hypoxia, there is an increase in the extraction of oxygen that continues until the low O_2 state is either corrected or surpasses the capacities of the tissues to extract O_2 (approximately 60%–70% ER). At this point, any further decline in O_2 delivery will cause an abrupt decline in O_2 consumption, with deterioration of the clinical condition (Figure 3, Table 3). As a result, assessing SvO_2 provides a quantitative method of assuring that patients do not encounter the critical points of O_2 consumption and extraction. With a better understanding of oxygen physiology in ICU patients, the concepts of venous oxygen saturation in central venous catheters ($ScvO_2$) *vs* mixed venous oxygen saturation in pulmonary artery catheters (SvO_2) were developed. The conclusion from regression analysis and determination coefficients (R^2) was that there is no significant difference between the two assessment tools with R = 0.945, SvO_2 = 1.16 ($ScvO_2$)$^{0.96}$[9,13]. In clinical practice, this translates to two different procedures with different risks, costs, and complications but with similar medical utility.

Early goal-directed therapy

Because of the similar findings and the lesser risk associated with the insertion of a central venous catheter compared to a pulmonary artery catheter, $ScvO_2$ became an important measurement in the original "early goal-directed therapy (EGDT) in the treatment of sepsis and septic shock"[9] (Figure 4). With the implementation of the EGDT across the board as a standard of care for sepsis and septic shock, it was found that the clinical validity for $ScvO_2$*vs* SvO_2 performed well for sepsis and septic shock (R = 0.88 – R = 0.89, $P < 0.001$)[14,15], but not as well for cardiac surgery patients (R = 0.72, $P < 0.001$ – $ScvO_2$ most reliable > 70%)[16]. Therefore, for patients with significant cardiac disease/cardiac surgery, $ScvO_2$ and SvO_2 are not interchangeable for medical decision making.

A series of clinical trials concerning EGDT and clinical outcomes have been performed through the years. The ProCESS trial published in 2014 compared the EGDT *vs* an alternative protocol *vs* usual care. There was no difference in 60-d (P =

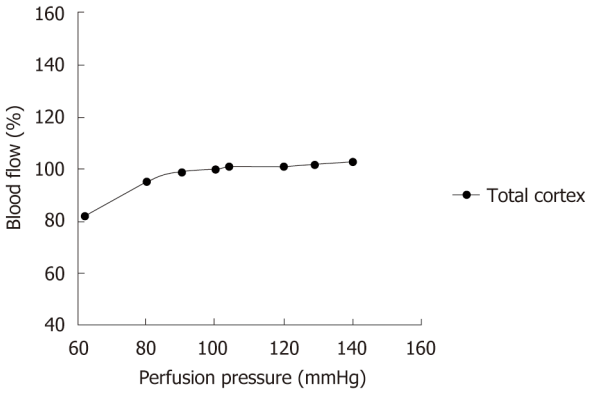


Figure 1 Renal autoregulation. Total renal blood flow over a range of perfusion pressure. Adapted from[61].

0.52) or 1-year mortality (P = 0.92)[17]. Similar findings were published in 2015 in a trial by Mouncey *et al*[18], in which 1200 patients were randomized to EGDT *vs* usual care, with no difference in mortality outcomes (P = 0.63).

Lactate

Lactic acid measurement has become an important method for the assessment of critically ill patients while avoiding the cumbersome process of obtaining central venous oxygen saturation. Some of the initial algorithms for the use of lactate measurements in the ICU involved combining the measurements with $ScvO_2$, to provide a stepwise approach for guiding the resuscitation of patients with circulatory failure: If lactate > 3.0 meq/L, then the $ScvO_2$ should be checked, and if it is not more than 3.0 meq/L, then there is no need to check the $ScvO_2$[19]. However, when serum lactic acid was compared to $ScvO_2$ as the goal for resuscitation of patients with sepsis and septic shock, there was no difference in outcome[20]. Considering these outcomes, there has been a shift in clinical practice from using central venous oxygen saturation to lactate in patients with sepsis and septic shock (*i.e.*, for patients without major cardiovascular disease).

Circulating volume/volume status

What is the volume status in the ICU patient? We do not know. A more definite answer is "nobody knows". However, to better understand, assess, and manage volume in critically ill patients, we need to first recognize what we do know about circulating volume and the fact that physical examination, regardless of many years of training and experience, is neither sensitive nor specific[21].

In the 1950s, Guyton *et al*[22]'s experiments with the Frank and Starling models of cardiac physiology gave rise to some interesting concepts regarding circulation and blood flow. One of his conclusions regarding venous return (VR) physiology is that when the PRA and the mean systemic filling pressure (PMS) are equal, there will be no return of blood to the heart: VR = (PMS – PRA)/resistance to the venous return (RVR).

Furthermore, Guyton *et al*[23]'s model established that PRA is not an indicator of circulating volume but a marker of pressure exerted by the venous system for the return of blood to the heart; thus, the lower the PRA, the higher the venous return[23] (Figure 5). With his description, we understood the importance of the PMS as the driving force for the return of blood volume back to the heart and one of the most useful parameters for assessing the actual circulating volume status[24].

Central venous pressure and capillary wedge pressure

With the understanding of the mechanistic aspect of circulatory physiology described with the Starling curve (Figure 6) and the notion of venous return by Guyton's model, it is possible to extrapolate the central venous pressure (CVP) as a product of the interaction between the venous system and cardiac function. Under those circumstances, the clinical inference from the CVP measured in patients is that, regardless of the number, it is lower than the mean systemic venous pressure (Figure 7).

Although the bedside utility of CVP alone for predicting volume responsiveness and medical decision making is not ideal, it is, however, a measurement available for the evaluation of critically ill patients with circulatory failure. The CVP alone in the ICU does not correlate with either the circulating volume status (R = 0.27)[25] or the clinical response to volume/fluid administration[26]. Similarly, the estimated left atrial pressure by pulmonary capillary wedge pressure (PCWP) via the more invasive

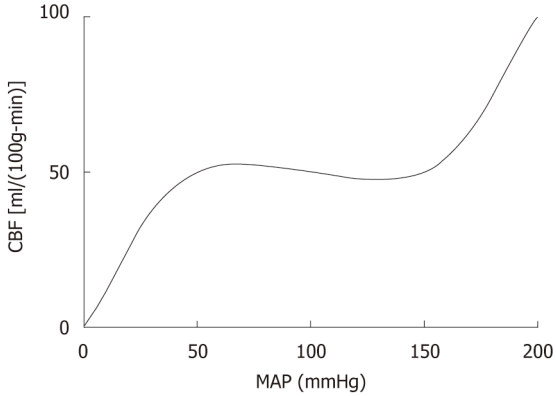


Figure 2 Cerebral autoregulation. Blood flow over a range of perfusion pressures. Reproduced from[4] with permission of the Society of Photo Optical Instrumentation Engineers (SPIE)

pulmonary artery catheterization (Swan-Ganz catheter) was once considered to be one of the most reliable methods to assess the ventricular preload and circulating volume. This method was one of the characteristic features of critical care medicine, but has been shown to underperform in the clinical setting in predicting responsiveness to intravascular volume administration[27].

Peripheral vs central venous pressure

As an available tool, the CVP continues to be widely used alone or in combination with other parameters to enable an educated guess about the venous system volume status. An alternative and less invasive method, which provides an equivalent physiological estimation of the volume status, is the peripheral venous pressure (PVP). The PVP is a tool that is inadequately and seldom used, is less invasive, requires the same transducer/equipment as the CVP, and has similar results. Any patent peripheral intravenous access (for flushing and drawing) may be used for measuring PVP. One does need to adjust the value of PVP by subtracting 2 mmHg. Thus, PVP = CVP + 2 or PVP – 2 = CVP[28]. The PVP not only is useful but also has been validated in many clinical scenarios in humans and animals (R = 0.97)[29,30]; its validity has been tested and proven in surgical patients (for surgical scenarios such as brain, abdominal, and cardiac surgery), in ICU patients, and in pediatric patients[28,31,32].

ASSESSMENT OF THE PATIENT WITH CIRCULATORY FAILURE

Once the basic concepts of blood flow and circulating volume are understood for a critically ill patient with circulatory failure, the next step is to determine if the patient responds to volume expansion. The most physiologically correct method to determine this is by measuring the mean systemic pressure (PMS). Currently, we do not have a validated clinical tool to measure the PMS in the hospital. However, there is research in the Netherlands with noninvasive devices to quantify the PMS and predict volume responsiveness, which may entirely change our methods of approaching and managing shock and volume administration[33].

Mean systemic pressure, systolic pressure variation, and pulse pressure variation

Since we do not currently have a way to measure PMS in our patients, what has been done through the years for assessing the circulating volume status and volume administration is to measure indices, such as the systolic pressure variation (SPV) and pulse pressure variation (PPV) in mechanically ventilated patients with circulatory failure[34] (Figure 8). The idea behind using these volumetric indicators (SPV and PPV) comes from the expected fluctuation of the Frank-Starling curve with mechanical ventilation and the minimal variability in the systolic and pulse pressures on the flat portion of the Starling curve. However, as volume depletion develops, the venous return decreases, and the system shifts towards the steep portion of the Starling curve, resulting in an increase in the variability in systolic pressure and pulse pressure. The implication is that the higher the PPV and SPV, the greater the expected response to volume administration, and this provides a guide for volume resuscitation[35].

The correlation between PPV/SPV and respiratory changes has been widely

Table 2 Hypovolemic shock categories

	I	II	III	IV
Blood loss (mL)	Up to 750	750-1500	1500-2000	> 2000
% of blood loss	Up to 15	15-30	30-40	> 40
Blood pressure	Normal	Normal	Decreased	Decreased
Mentation	Preserved	Anxious	Confused	Lethargic

Summary as described by the American College of Surgeons in The Advanced Trauma Life Support training program.

validated as a means to predict volume responsiveness in different scenarios, with sensitivities and specificities of 94% and 96%, respectively. For septic shock, the correlation (R = 0.85) is higher than the PCWP and PRA (R = 0.5 for both RAP and PCWP)[35]. It also performs well after cardiac surgery compared with the CVP and PCWP (PPV/SPV: R = 0.8, CVP/PCWP: R = 0.5)[36,37]. The two most important clinical scenarios in which PPV/SPV are known to fail are right ventricular failure (*e.g.*, right ventricular infarction, cardiomyopathy, and pulmonary hypertension) and obstructive shock (*e.g.*, tension pneumothorax, abdominal compartment syndrome, and cardiac tamponade)[35,38].

However, what if the patient is not mechanically ventilated, is spontaneously breathing, does not have a regular heart rate or on adequate tidal volume—can PPV and SPV still be used? The answer is yes, they can. The requirement for specific ventilatory parameters has been challenged, and both PPV and SPV tests work well in patients breathing spontaneously, with an AUC (area under the curve) of more than 0.8 for both. However, it is important to be cautious when using PPV/SPV with spontaneously breathing patients due to the varying reliability and results with changes in breathing patterns[39,40]. Similarly, the need for arterial catheter insertion to measure the changes in PPV/SPV has been questioned, and plethysmographic waveform changes by pulse oximetry make it possible to calculate the plethysmography variability index (PVI). Subsequently, validated with comparable results as the more invasive PPV/SPV, the PVI can detect circulatory volume changes as low as 4%. Measurements with blood pressure require > 30% reduction in circulatory volume for hypotension to be present. A PVI of more than 17% will correlate with volume responsiveness. Furthermore, the PPV will change in parallel to the PVI (R = 0.85, $P < 0.001$), making it an excellent tool for evaluating patients with circulatory failure[41,42].

Cardiac output

Interestingly, in the acute care setting when the patient has developed circulatory failure, knowing and calculating the current blood flow is not as essential as understanding and assessing the consequences of appropriate blood flow, such as mental status, urine output, lactic acid level, and even central venous oxygen saturation. Moreover, pulse pressure (PP) is one of the more reliable correlates of low cardiac output (Table 4) since the aorta functions as a left ventricular counterpulsation balloon pump, stretching during systole and contracting during diastole while maintaining the mean arterial pressure with changes in flow, but the PP will vary with the amount of volume per stroke. This translates to a scenario in which the more that the stroke volume decreases, the more that the PP will decrease, giving enough information for medical decision making in the ICU. However, if the need is to know and quantify the cardiac output, then there are numerous devices available in hospitals to do so.

In summary, before adding more accessories to measure cardiac output, we recommend going back to your previous answers when assessing the patient. If your biological markers (*e.g.*, urine output, mental status) and your surrogates of blood flow (*e.g.*, lactate, central venous saturation) are within normal limits, then the cardiac output should not be the major concern. On the other hand, if the available bedside tools fail to support your clinical assessment about the cardiac output, we recommend more physiological substitutes for blood flow and stroke volume, such as the PP to make inferences and medical decisions.

VOLUME MANAGEMENT IN A NUTSHELL

The "silver lining" of restoring adequate circulation is the balance between

Table 3 Conditions that affect the venous oxygen saturation measurement

Condition	SvO_2 change
Anemia (Hemoglobin < 8)	↓
Low cardiac output	↓
Agitation	↓
Sepsis	↑
States of hypoxia	↓
Anesthesia (↓ O_2 utilization)	↑

Normal SvO_2: 60%-80%.

reestablishing tissue perfusion with the appropriate/physiological distribution of blood flow by improving circulatory volume and avoiding iatrogenic volume excess. In the event of hypovolemic failure (regardless of the state of shock), the treatment is to replace the volume. Needless to say, hemorrhagic shock necessitates blood transfusion.

The classic example of the most common type of shock seen in the ICU is a septic shock patient who has not felt well before admission, not eating or drinking, and who developed a low volume state from lack of water (dehydration) and solutes (nutrition). This is in addition to the associated loss of fluid from increased capillary permeability, which is part of the septic process, and this loss of extra volume from the intravascular space into the interstitium leads to a state of relative hypovolemia superimposed on actual hypovolemia. Additionally, septic shock also induces maladaptive venous vasodilation, which decreases the circulatory blood flow return to the heart even after adequate fluid replacement[43]. It may also cause cardiac dysfunction and vasomotor paralysis to the point that patients need inotropes and sometimes corticosteroids[2].

Protocols for optimal preload optimization and volume administration have been used in the clinical setting to improve outcomes (as previously discussed in the section: "Definitions and Pathophysiology"), but no benefit in survival or prevention of developing new organ failure has been achieved using protocolized fluid therapies. If anything, when comparing the fluid administration for patients receiving a lower total amount of fluid per usual care against the protocols, there may, in fact, be an association with renal dysfunction and the need for dialysis (P = 0.04) with the protocolized fluid therapies[17,44].

Type of fluid

The type and composition of fluid given do seem to matter. Recently published, the Isotonic Solutions and Major Adverse Renal Events Trial concluded that the use of balanced crystalloid solutions is overall better than the use of saline solutions, with less adverse kidney events (P = 0.04) and lower 30-d mortality (P = 0.02)[45]. Normal saline (0.9% NaCl) is the most commonly administered solution in our hospital and around the world[46]. Some of the problems associated with chloride-rich solutions include the development of hyperchloremic acidosis with an increase in morbidity and mortality outcomes[47-50]. On the other hand, the Saline vs Plasma-Lyte for ICU fluid Therapy trial did not show any difference in outcomes between the two solutions studied (P = 0.85), although it is important to mention that these patients received, on average, a total of less than 2 liters of either solution throughout the whole study. Additionally, this amount of fluid may not be enough compared with the fluid quantities used for resuscitation and maintenance for ICU patients with circulatory failure[51]. One clinical scenario in which normal saline should be the principal solution to use is in patients with intravascular volume depletion, metabolic alkalosis, and hypochloremic hyponatremia (*e.g.*, over diuresis).

Hydroxyethyl starch is known to be nephrotoxic and is not used currently in the United States for fluid resuscitation (it was never used that much before either)[52]. Other colloids, such as albumin and gelatins, remain valuable tools when used appropriately (Table 5). However, no significant clinical benefit from using colloids instead of crystalloids for volume resuscitation has been demonstrated[53,54].

Vasopressors and corticosteroids

Several different classes of vasopressors, including inotropic agents, are widely available and used in the treatment of shock for primarily inducing vasoconstriction, increasing mean arterial pressures, and optimizing blood flow and tissue perfusion.

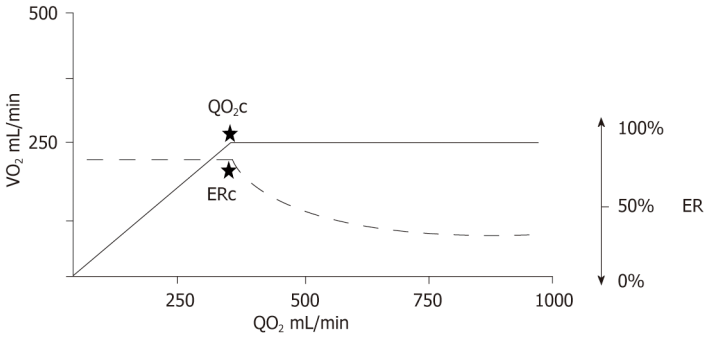


Figure 3 Relationship between oxygen delivery and venous oxygenation/oxygen consumption. VO_2: Oxygen consumption; QO_2: Oxygen flow delivery; ER: Extraction ratio; ERc: Critical point of extraction; QO_2c: Critical point of delivery.

The three main categories that divide vasopressors are catecholamines (*e.g.*, epinephrine, norepinephrine, dopamine), non-adrenergic drugs (*e.g.*, vasopressin, angiotensin II), and other adrenergic agonists (*e.g.*, phenylephrine, midodrine, dobutamine).

Despite the fact that there is no difference in survival between norepinephrine and dopamine as the first-line agent for the treatment of shock (P = 0.07), there are significantly more adverse events related to arrhythmias (atrial fibrillation, ventricular tachycardia, ventricular fibrillation) with dopamine, and for this reason, its use has declined significantly over the years[55]. Although phenylephrine has not been tested against norepinephrine and continues to be widely available, there have been observational data reported after the 2011 shortage of norepinephrine in the United States which showed increased in-hospital mortality when phenylephrine is used as first line agent[56].

Vasopressin performs as well as norepinephrine and is a useful medication for second-line therapy if needed[57]. The new vasopressor being used more frequently in the ICU is angiotensin II. The Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3) trial demonstrated that it works well for vasodilatory/high output shock, has a great safety profile, and has minimal side effects. It is an excellent second-line therapy currently and will be so the near future, with appropriate concerns about price and availability[58]. Corticosteroid use in septic shock has been debated throughout the years and is recommended for refractory shock per Surviving Sepsis guidelines. These drugs do not have any other proven benefit in this clinical setting[59,60].

In summary, we recommend avoiding dopamine as a first line drug due to the severity of side effects and possibility of harm. We continue to use norepinephrine as the first line agent, but vasopressin is also an option for either first or second drug choice. If available, angiotensin II will work well as second line vasopressor; it is possible that phenylephrine may lead to worse outcomes if used as first line therapy.

CONCLUSION

Accuracy in diagnosis with selection of the right tool for assessment and not simply symptomatic treatment must be a strategic element in the care provided to patients with circulatory failure. Understanding physiological concepts is vital. More importantly, learning and practicing medicine based only on protocols and flowcharts will always exclude an important portion of the science. The careful understanding and management of circulation must be part of daily clinical practice. Changing dogmas in medicine generates apprehension as the illusion of knowledge and expertise becomes vulnerable, but we as health care providers should continue evolving for the benefit of our patients.

Intravenous fluid solutions are more similar to drugs than is acknowledged and therefore need to be used with care and precision. The composition of the fluid does matter, but only if the patient is alive. When administering intravascular fluids, targets such as the restoration of intravascular volume should have more impact on medical decisions than urine output or blood pressure. Extravasation of water and solutes can occur, and for this reason, we need to be mindful that not every patient in a hospital bed needs a fluid bolus.

Table 4 Correlates of low cardiac output

	Low CO	High CO
Blood pressure	↓	↓
Heart rate	↑	↑
Systemic vascular resistance	↑	↓
CO	↓	↑
Pulse pressure	↓	↑

CO: Cardiac output.

Table 5 Crystalloid *vs* colloid solutions

Crystalloid	Colloid
Lower price	Expensive
Believed to be safer	Some toxic (hydroxyethyl starch)
Higher amount needed for resuscitation	Less required
Slower action	Faster action
Moves out the intravascular space faster	Remains in circulation longer

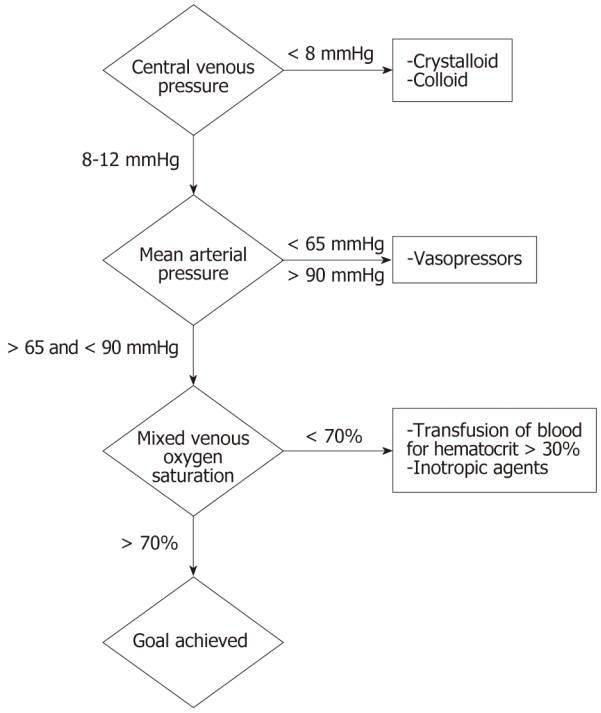


Figure 4 Protocol for early goal-directed therapy. Adapted from[9].

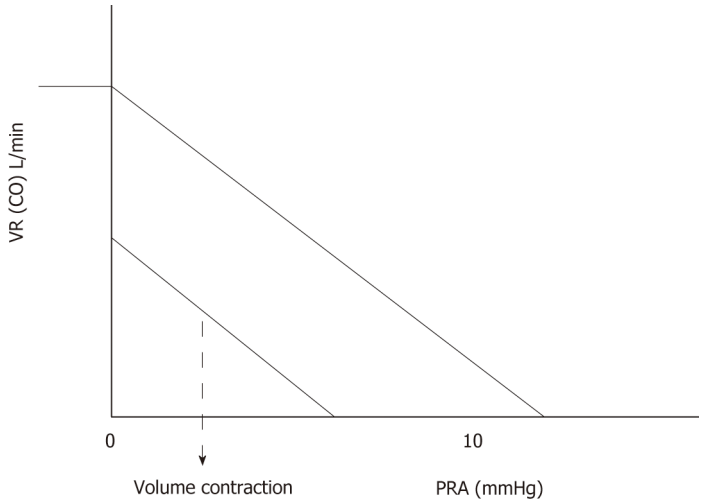


Figure 5 Guyton's model of venous return and cardiac output in relation to the right atrial pressure. Adapted from[62].

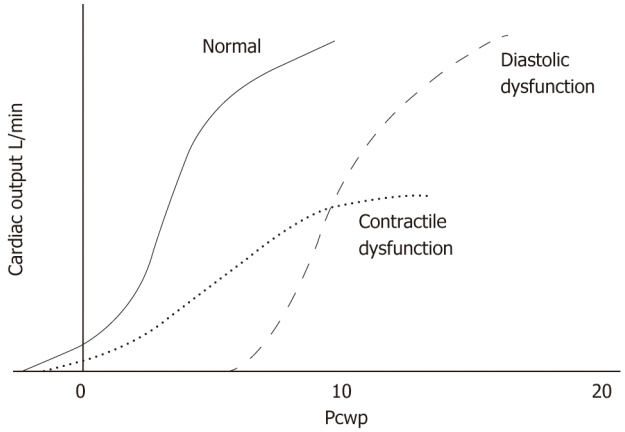


Figure 6 Frank-Starling curves representing normal contractility, diastolic dysfunction, and contractile dysfunction. Pcwp: Pulmonary capillary wedge pressure. Adapted from[63].

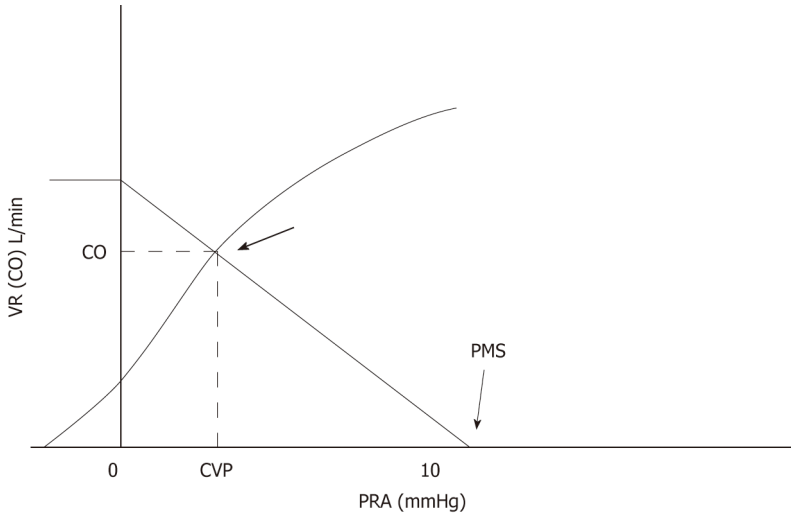


Figure 7 Modified cardiac function curve representing the central venous pressure measured in the clinical setting by superimposing Guyton's model of venous return and Frank-Starling contractility curve. CO: Cardiac output; CVP: Central venous pressure; PRA: Right atrial pressure; VR: Venous return; PMS: Mean systemic filling pressure. Adapted from[62].

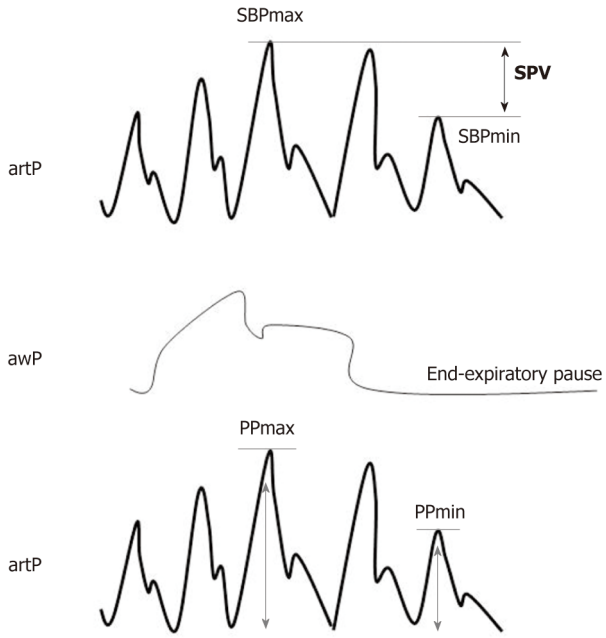


Figure 8 Description of the systolic pressure variation and pulse pressure variation during mechanical ventilation. SPV: Systolic pressure variation; PPV: Pulse pressure variation; artP: Arterial pressure; awP: Airway pressure; SBP: Systolic pressure. PP = 100 x (PPmax – PPmin) / [(PPmax + PPmin)/2].

REFERENCES

1 **Paoli CJ**, Reynolds MA, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. *Crit Care Med* 2018; **46**: 1889-1897 [PMID: 30048332 DOI: 10.1097/CCM.0000000000003342]

2 **Vincent JL**, De Backer D. Circulatory shock. *N Engl J Med* 2013; **369**: 1726-1734 [PMID: 24171518 DOI: 10.1056/NEJMra1208943]

3 **Navar LG**, Inscho EW, Majid SA, Imig JD, Harrison-Bernard LM, Mitchell KD. Paracrine regulation of the renal microcirculation. *Physiol Rev* 1996; **76**: 425-536 [PMID: 8618962 DOI: 10.1152/physrev.1996.76.2.425]

4 **Fantini S**, Sassaroli A, Tgavalekos KT, Kornbluth J. Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods. *Neurophotonics* 2016; **3**: 031411 [PMID: 27403447 DOI: 10.1117/1.NPh.3.3.031411]

5 **Wallbach M**, Zürbig P, Dihazi H, Müller GA, Wachter R, Beige J, Koziolek MJ, Mischak H. Kidney protective effects of baroreflex activation therapy in patients with resistant hypertension. *J Clin Hypertens (Greenwich)* 2018; **20**: 1519-1526 [PMID: 30203514 DOI: 10.1111/jch.13365]

6 **Wallbach M**, Koziolek MJ. Baroreceptors in the carotid and hypertension-systematic review and meta-analysis of the effects of baroreflex activation therapy on blood pressure. *Nephrol Dial Transplant* 2018; **33**: 1485-1493 [PMID: 29136223 DOI: 10.1093/ndt/gfx279]

7 **Graham CA**, Parke TR. Critical care in the emergency department: shock and circulatory support. *Emerg Med J* 2005; **22**: 17-21 [PMID: 15611535 DOI: 10.1136/emj.2003.012450]

8 **Ander DS**, Jaggi M, Rivers E, Rady MY, Levine TB, Levine AB, Masura J, Gryzbowski M. Undetected cardiogenic shock in patients with congestive heart failure presenting to the emergency department. *Am J Cardiol* 1998; **82**: 888-891 [PMID: 9781972 DOI: 10.1016/S0002-9149(98)00497-4]

9 **Rivers E**, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368-1377 [PMID: 11794169 DOI: 10.1056/NEJMoa010307]

10 **Reddy PS**, Curtiss EI, O'Toole JD, Shaver JA. Cardiac tamponade: hemodynamic observations in man. *Circulation* 1978; **58**: 265-272 [PMID: 668074 DOI: 10.1161/01.CIR.58.2.265]

11 **Wo CC**, Shoemaker WC, Appel PL, Bishop MH, Kram HB, Hardin E. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. *Crit Care Med* 1993; **21**: 218-223 [PMID: 8428472 DOI: 10.1097/00003246-199302000-00012]

12 **Lehman LW**, Saeed M, Talmor D, Mark R, Malhotra A. Methods of blood pressure measurement in the ICU. *Crit Care Med* 2013; **41**: 34-40 [PMID: 23269127 DOI: 10.1097/CCM.0b013e318265ea46]

13 **Ladakis C**, Myrianthefs P, Karabinis A, Karatzas G, Dosios T, Fildissis G, Gogas J, Baltopoulos G. Central venous and mixed venous oxygen saturation in critically ill patients. *Respiration* 2001; **68**: 279-285 [PMID: 11416249 DOI: 10.1159/000050511]

14 **Chawla LS**, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M. Lack of equivalence between central and mixed venous oxygen saturation. *Chest* 2004; **126**: 1891-1896 [PMID: 15596689 DOI: 10.1378/chest.126.6.1891]

15 **Varpula M**, Karlsson S, Ruokonen E, Pettilä V. Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock. *Intensive Care Med* 2006; **32**: 1336-1343 [PMID: 16826387 DOI: 10.1007/s00134-006-0270-y]

16 **Sander M**, Spies CD, Foer A, Weymann L, Braun J, Volk T, Grubitzsch H, von Heymann C. Agreement of central venous saturation and mixed venous saturation in cardiac surgery patients. *Intensive Care Med*

2007; **33**: 1719-1725 [PMID: 17525841 DOI: 10.1007/s00134-007-0684-1]
17 **ProCESS Investigators**; Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; **370**: 1683-1693 [PMID: 24635773 DOI: 10.1056/NEJMoa1401602]
18 **Mouncey PR**, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, Coats TJ, Singer M, Young JD, Rowan KM; ProMISe Trial Investigators. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; **372**: 1301-1311 [PMID: 25776532 DOI: 10.1056/NEJMoa1500896]
19 **Jansen TC**, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, Willemsen SP, Bakker J; LACTATE study group. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 2010; **182**: 752-761 [PMID: 20463176 DOI: 10.1164/rccm.200912-1918OC]
20 **Jones AE**, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010; **303**: 739-746 [PMID: 20179283 DOI: 10.1001/jama.2010.158]
21 **Hiemstra B**, Eck RJ, Keus F, van der Horst ICC. Clinical examination for diagnosing circulatory shock. *Curr Opin Crit Care* 2017; **23**: 293-301 [PMID: 28570301 DOI: 10.1097/MCC.0000000000000420]
22 **Guyton AC**, Lindsey AW, Kaufmann BN. Effect of mean circulatory filling pressure and other peripheral circulatory factors on cardiac output. *Am J Physiol* 1955; **180**: 463-468 [PMID: 14376522 DOI: 10.1152/ajplegacy.1955.180.3.463]
23 **Guyton AC**, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 1957; **189**: 609-615 [PMID: 13458395 DOI: 10.1152/ajplegacy.1957.189.3.609]
24 **Maas JJ**, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; **37**: 912-918 [PMID: 19237896 DOI: 10.1097/CCM.0b013e3181961481]
25 **Marik PE**, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 2008; **134**: 172-178 [PMID: 18628220 DOI: 10.1378/chest.07-2331]
26 **Osman D**, Ridel C, Ray P, Monnet X, Anguel N, Richard C, Teboul JL. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007; **35**: 64-68 [PMID: 17080001 DOI: 10.1097/01.CCM.0000249851.94101.4F]
27 **Kumar A**, Anel R, Bunnell E, Habet K, Zanotti S, Marshall S, Neumann A, Ali A, Cheang M, Kavinsky C, Parrillo JE. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med* 2004; **32**: 691-699 [PMID: 15090949 DOI: 10.1097/01.CCM.0000114996.68110.C9]
28 **Munis JR**, Bhatia S, Lozada LJ. Peripheral venous pressure as a hemodynamic variable in neurosurgical patients. *Anesth Analg* 2001; **92**: 172-179 [PMID: 11133622 DOI: 10.1097/00000539-200101000-00033]
29 **Hadimioglu N**, Ertug Z, Yegin A, Sanli S, Gurkan A, Demirbas A. Correlation of peripheral venous pressure and central venous pressure in kidney recipients. *Transplant Proc* 2006; **38**: 440-442 [PMID: 16549142 DOI: 10.1016/j.transproceed.2005.12.057]
30 **Chow RS**, Kass PH, Haskins SC. Evaluation of peripheral and central venous pressure in awake dogs and cats. *Am J Vet Res* 2006; **67**: 1987-1991 [PMID: 17144798 DOI: 10.2460/ajvr.67.12.1987]
31 **Baty L**, Russo P, Tobias JD. Measurement of central venous pressure from a peripheral intravenous catheter following cardiopulmonary bypass in infants and children with congenital heart disease. *J Intensive Care Med* 2008; **23**: 136-142 [PMID: 18372352 DOI: 10.1177/0885066607305861]
32 **Choi SJ**, Gwak MS, Ko JS, Kim GS, Kim TH, Ahn H, Kim JA, Yang M, Lee S, Kim M. Can peripheral venous pressure be an alternative to central venous pressure during right hepatectomy in living donors? *Liver Transpl* 2007; **13**: 1414-1421 [PMID: 17902127 DOI: 10.1002/lt.21255]
33 **Maas JJ**, Pinsky MR, Aarts LP, Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. *Anesth Analg* 2012; **115**: 880-887 [PMID: 22763909 DOI: 10.1213/ANE.0b013e31825fb01d]
34 **Michard F**. Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 2005; **103**: 419-28; quiz 449-5 [PMID: 16052125 DOI: 10.1097/00000542-200508000-00026]
35 **Magder S**. Clinical usefulness of respiratory variations in arterial pressure. *Am J Respir Crit Care Med* 2004; **169**: 151-155 [PMID: 14718237 DOI: 10.1164/rccm.200211-1360CC]
36 **Hofer CK**, Müller SM, Furrer L, Klaghofer R, Genoni M, Zollinger A. Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. *Chest* 2005; **128**: 848-854 [PMID: 16100177 DOI: 10.1378/chest.128.2.848]
37 **Preisman S**, Kogan S, Berkenstadt H, Perel A. Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the Respiratory Systolic Variation Test and static preload indicators. *Br J Anaesth* 2005; **95**: 746-755 [PMID: 16286349 DOI: 10.1093/bja/aei262]
38 **Wyler von Ballmoos M**, Takala J, Roeck M, Porta F, Tueller D, Ganter CC, Schröder R, Bracht H, Baenziger B, Jakob SM. Pulse-pressure variation and hemodynamic response in patients with elevated pulmonary artery pressure: a clinical study. *Crit Care* 2010; **14**: R111 [PMID: 20540730 DOI: 10.1186/cc9060]
39 **Zöllei E**, Bertalan V, Németh A, Csábi P, László I, Kaszaki J, Rudas L. Non-invasive detection of hypovolemia or fluid responsiveness in spontaneously breathing subjects. *BMC Anesthesiol* 2013; **13**: 40 [PMID: 24188480 DOI: 10.1186/1471-2253-13-40]
40 **Hong DM**, Lee JM, Seo JH, Min JJ, Jeon Y, Bahk JH. Pulse pressure variation to predict fluid responsiveness in spontaneously breathing patients: tidal vs. forced inspiratory breathing. *Anaesthesia* 2014; **69**: 717-722 [PMID: 24773446 DOI: 10.1111/anae.12678]
41 **Pizov R**, Eden A, Bystritski D, Kalina E, Tamir A, Gelman S. Arterial and plethysmographic waveform analysis in anesthetized patients with hypovolemia. *Anesthesiology* 2010; **113**: 83-91 [PMID: 20526193 DOI: 10.1097/ALN.0b013e3181da839f]
42 **Loupec T**, Nanadoumgar H, Frasca D, Petitpas F, Laksiri L, Baudouin D, Debaene B, Dahyot-Fizelier C, Mimoz O. Pleth variability index predicts fluid responsiveness in critically ill patients. *Crit Care Med* 2011; **39**: 294-299 [PMID: 21057311 DOI: 10.1097/CCM.0b013e3181ffde1c]
43 **Siddall E**, Khatri M, Radhakrishnan J. Capillary leak syndrome: etiologies, pathophysiology, and

management. *Kidney Int* 2017; **92**: 37-46 [PMID: 28318633 DOI: 10.1016/j.kint.2016.11.029]
44 **Kellum JA**, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, Yealy DM, Huang DT, Angus DC; ProCESS and ProGReSS-AKI Investigators. The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock. *Am J Respir Crit Care Med* 2016; **193**: 281-287 [PMID: 26398704 DOI: 10.1164/rccm.201505-0995OC]
45 **Semler MW**, Self WH, Rice TW. Balanced Crystalloids versus Saline in Critically Ill Adults. *N Engl J Med* 2018; **378**: 1951 [PMID: 29768150 DOI: 10.1056/NEJMc1804294]
46 **Finfer S**, Liu B, Taylor C, Bellomo R, Billot L, Cook D, Du B, McArthur C, Myburgh J; SAFE TRIPS Investigators. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care* 2010; **14**: R185 [PMID: 20950434 DOI: 10.1186/cc9293]
47 **Yunos NM**, Kim IB, Bellomo R, Bailey M, Ho L, Story D, Gutteridge GA, Hart GK. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med* 2011; **39**: 2419-2424 [PMID: 21705897 DOI: 10.1097/CCM.0b013e31822571e5]
48 **Kellum JA**, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. *Chest* 2006; **130**: 962-967 [PMID: 17035425 DOI: 10.1378/chest.130.4.962]
49 **Shaw AD**, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg* 2012; **255**: 821-829 [PMID: 22470070 DOI: 10.1097/SLA.0b013e31825074f5]
50 **Raghunathan K**, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, Setoguchi S, Beadles C, Lindenauer PK. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis*. *Crit Care Med* 2014; **42**: 1585-1591 [PMID: 24674927 DOI: 10.1097/CCM.0000000000000305]
51 **Young P**, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A, Reddy S, Bellomo R; SPLIT Investigators, ANZICS CTG. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. *JAMA* 2015; **314**: 1701-1710 [PMID: 26444692 DOI: 10.1001/jama.2015.12334]
52 **Perner A**, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J; 6S Trial Group; Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; **367**: 124-134 [PMID: 22738085 DOI: 10.1056/NEJMoa1204242]
53 **Finfer S**, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350**: 2247-2256 [PMID: 15163774 DOI: 10.1056/NEJMoa040232]
54 **Annane D**, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, Preiser JC, Outin H, Troché G, Charpentier C, Trouillet JL, Kimmoun A, Forceville X, Darmon M, Lesur O, Reignier J, Abroug F, Berger P, Clec'h C, Cousson J, Thibault L, Chevret S; CRISTAL Investigators. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA* 2013; **310**: 1809-1817 [PMID: 24108515 DOI: 10.1001/jama.2013.280502]
55 **De Backer D**, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; **362**: 779-789 [PMID: 20200382 DOI: 10.1056/NEJMoa0907118]
56 **Vail E**, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H. Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock. *JAMA* 2017; **317**: 1433-1442 [PMID: 28322415 DOI: 10.1001/jama.2017.2841]
57 **Russell JA**, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; **358**: 877-887 [PMID: 18305265 DOI: 10.1056/NEJMoa067373]
58 **Khanna A**, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, Busse LW, Altaweel L, Albertson TE, Mackey C, McCurdy MT, Boldt DW, Chock S, Young PJ, Krell K, Wunderink RG, Ostermann M, Murugan R, Gong MN, Panwar R, Hästbacka J, Favory R, Venkatesh B, Thompson BT, Bellomo R, Jensen J, Kroll S, Chawla LS, Tidmarsh GF, Deane AM; ATHOS-3 Investigators. Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med* 2017; **377**: 419-430 [PMID: 28528561 DOI: 10.1056/NEJMoa1704154]
59 **Rhodes A**, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017; **43**: 304-377 [PMID: 28101605 DOI: 10.1007/s00134-017-4683-6]
60 **Sprung CL**, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; **358**: 111-124 [PMID: 18184957 DOI: 10.1056/NEJMoa071366]
61 **Mattson DL**, Lu S, Roman RJ, Cowley AW. Relationship between renal perfusion pressure and blood flow in different regions of the kidney. *Am J Physiol* 1993; **264**: R578-583 [PMID: 8457011 DOI: 10.1152/ajpregu.1993.264.3.R578]
62 **Guyton AC**. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; **35**: 123-129 [PMID: 14356924 DOI: 10.1152/physrev.1955.35.1.123]
63 **Koeppen BM**, Stanton BA, Koeppen BM, Stanton BA. Integrated Control of The Cardiovascular System. Koeppen BM, Stanton BA. *Berne and Levy Physiology*. Amsterdam: Elsevier 2017;

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 July 31; 8(4): 49-58

DOI: 10.5492/wjccm.v8.i4.49

ISSN 2220-3141 (online)

MINIREVIEWS

Independent lung ventilation: Implementation strategies and review of literature

Sheri Berg, Edward A Bittner, Lorenzo Berra, Robert M Kacmarek, Abraham Sonny

ORCID number: Sheri Berg (0000-0001-6932-1775); Edward A Bittner (0000-0002-0159-2373); Lorenzo Berra (0000-0003-2702-2093); Robert M Kacmarek (0000-0002-3833-380X); Abraham Sonny (0000-0002-2101-9849).

Author contributions: Berg S and Kacmarek RM performed the case and edited the manuscript; Bittner EA and Sonny A wrote and edited the manuscript; Berra L was involved in reviewing and editing the manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Manuscript source: Unsolicited manuscript

Received: March 14, 2019
Peer-review started: March 15, 2019
First decision: June 6, 2019
Revised: June 21, 2019

Sheri Berg, Edward A Bittner, Lorenzo Berra, Abraham Sonny, Division of Critical Care, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA 02114, United States

Robert M Kacmarek, Department of Respiratory Care, Massachusetts General Hospital, Boston, MA 02114, United States

Corresponding author: Abraham Sonny, MD, Assistant Professor, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, 55 Fruit Street, GRB 444, Boston, MA 02114, United States. asonny@mgh.harvard.edu
Telephone: +1-617-7269379

Abstract

Independent lung ventilation, though infrequently used in the critical care setting, has been reported as a rescue strategy for patients in respiratory failure resulting from severe unilateral lung pathology. This involves isolating and ventilating the right and left lung differently, using separate ventilators. Here, we describe our experience with independent lung ventilation in a patient with unilateral diffuse alveolar hemorrhage, who presented with severe hypoxemic respiratory failure despite maximal ventilatory support. Conventional ventilation in this scenario leads to preferential distribution of tidal volume to the non-diseased lung causing over distension and inadvertent volume trauma. Since each lung has a different compliance and respiratory mechanics, instituting separate ventilation strategies to each lung could potentially minimize lung injury. Based on review of literature, we provide a detailed description of indications and procedures for establishing independent lung ventilation, and also provide an algorithm for management and weaning a patient from independent lung ventilation.

Key words: Unilateral lung injury; Unilateral pneumonia; Double lumen tube; Differential lung ventilation; Acute lung injury; Ventilator induced lung injury

Core tip: Severe unilateral lung disease presents a unique scenario where the diseased lung has very poor compliance, while the non-diseased lung remains normally compliant. In these patients, conventional positive pressure ventilation causes preferential distribution of tidal volume to the non-diseased lung causing its

Accepted: July 17, 2019
Article in press: July 17, 2019
Published online: July 31, 2019

P-Reviewer: Nacak M, Nardo MD
S-Editor: Ma YJ
L-Editor: A
E-Editor: Wu YXJ

overdistension and inadvertent volutrauma. Placement of a double lumen endotracheal tube and providing independent lung ventilation, with a ventilator for each lung, can potentially minimize lung injury. This will allow institution of lung protective ventilation strategies to each lung, individualized based on their respective compliances.

Citation: Berg S, Bittner EA, Berra L, Kacmarek RM, Sonny A. Independent lung ventilation: Implementation strategies and review of literature. *World J Crit Care Med* 2019; 8(4): 49-58
URL: https://www.wjgnet.com/2220-3141/full/v8/i4/49.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i4.49

INTRODUCTION

Independent lung ventilation (ILV), though infrequently used in the critical care setting, has been reported by various authors as a rescue strategy for patients with unilateral lung pathology. These are mostly confined to case reports or small case series, but span a variety of patient populations, including medical[1-3], surgical[4-6], pediatric[7-10], and trauma[3,11]. ILV involves anatomical as well as physiological separation of each lung into separate units, and the success of implementation depends on the experience of the critical care team with ILV. Outside of a critical care setting anatomical separation of the lung is routinely performed in thoracic surgical operating rooms to either facilitate lung surgeries or to improve surgical exposure during other intrathoracic procedures. The complexity and lack of experience of many providers with ILV makes it an underutilized ventilation strategy in the intensive care unit (ICU). Here, we describe the use of ILV for management of respiratory failure in a patient with unilateral diffuse alveolar hemorrhage. We then critically review available literature on the use of ILV and provide a detailed description of indications and procedures for establishing ILV and provide an algorithm for management and weaning a patient from ILV.

CASE

Recently, we cared for a 63-year-old man who presented to our surgical ICU with hypoxemic respiratory failure. His medical history was notable for hepatitis C, atrial fibrillation, myelodysplasia treated with allogenic stem cell transplantation complicated by graft *vs* host disease and persistent thrombocytopenia. His chest X-ray showing complete white out of the right lung. Though aspiration, and unilateral pneumonia were important differentials, unilateral diffuse alveolar hemorrhage was the most likely etiology in the setting of his severe thrombocytopenia. Severe hypoxemia persisted (P/F about 60) despite tracheal intubation and mechanical ventilation. X-ray continued to show complete white out of right lung, and suggested over inflation of the left lung. With continued worsening of hypoxemia, we decided to place a double lumen tube, and independent lung ventilation was initiated as a rescue measure. Independent lung ventilation lead to improvement in oxygenation, and allowed titration of ventilation parameters independently for each lung based on their best compliance. Once his unilateral lung pathology improved substantially, he was transitioned back to a single lumen endotracheal tube and conventional ventilation was resumed. He was eventually weaned and extubated after 10 d of mechanical ventilation.

DISCUSSION

Independent lung ventilation requires anatomical and physiological separation of the lungs. Anatomical separation involves physical isolation of one lung from the other, while physiological separation refers to ventilating the two lungs independently as separate units. The focus of this article is on physiological separation of lungs, specifically, indications as well as ventilation and weaning strategies in patients receiving ILV. Techniques for anatomical separation is well described elsewhere[12-14].

The indications for ILV in a critical care setting may be broadly classified into two types based on the need for anatomical separation alone *vs* need for physiological separation of the lungs (Table 1). Anatomical separation is typically sought for

conditions which require lung isolation to prevent cross contamination of the healthy lung by harmful material contained within the diseased lung. Physiological separation of lung is instituted for refractory respiratory failure resulting from unilateral lung disease, causing marked differences in pulmonary mechanics between right and left lung. For instance, in the presence of a poorly compliant diseased lung, such as in our case, conventional positive pressure ventilation would result in preferential over distension of the non-diseased lung potentially causing volutrauma to the non-diseased lung[15]. In addition, over distention of the non-diseased lung could result in diversion of pulmonary blood flow to the diseased lung thereby worsening shunt and hypoxemia[16]. Institution of an independent ventilation strategy for each lung may prevent volume trauma to the non-diseased lung, reduce shunting and allow for alveolar recruitment in the diseased lung.

The most commonly reported indications for ILV include differential lung injury due to unilateral pneumonia[1,3,7,17], large air leak from bronchopleural fistula[6,18], pulmonary hemorrhage[6,19], and pulmonary contusion[3,11,20]. ILV has been reported to be useful in patients who develop primary graft dysfunction following single lung transplantation, resulting in a poorly compliant graft lung and a native lung with markedly different lung mechanics[5,21]. However, the data on single lung transplantation is from one center, and additional factors such as role of early extracorporeal membrane oxygenation (ECMO), and effect of double lumen tube (DLT) on bronchial anastomotic healing needs to be considered.

When to perform lung isolation?

The severity of unilateral lung disease where one should consider ILV is unclear. Most reports have instituted ILV as a rescue strategy after conventional ventilation failed to maintain adequate oxygenation or ventilation. It can be argued that early institution of ILV may be more beneficial in reducing ventilator induced lung injury superimposed on the existing lung injury especially in the non-diseased injured lung. This is especially important with accumulating evidence favoring use of low tidal volumes during positive pressure ventilation of normal healthy lungs[22]. It is conceivable that by reducing lung injury and decreasing shunt, the use of ILV might decrease the need for utilizing more invasive strategies like ECMO, associated with a higher risk of complications. Moreover, ECMO is contraindicated in presence of thrombocytopenia (as in our patient), disseminated intravascular coagulation, or recent tPA use. In addition, ECMO requires a dedicated team and advanced institutional capabilities, which might not be available in resource poor locations. Thus, ILV is likely underutilized and there maybe potential benefit from earlier institution of ILV than typically reported.

Considerations for lung isolation in the intensive care unit

A DLT is most commonly used for lung isolation during thoracic surgery. Similarly, DLT is the most commonly reported method for instituting ILV. DLTs are endotracheal tubes with two lumens and two cuffs (tracheal and bronchial), the tracheal lumen terminating in trachea and the bronchial lumen in either the right or left main stem bronchus (Figure 1). Some others have described using two endotracheal tubes, one for each lung, placed via a tracheostomy[2]. Since the smallest available DLT (26F, outer diameter- 8.7 mm) is recommended for patients between 8 and 10 years of age[23], endotracheal intubation with two single lumen tubes is the only way to achieve ILV in younger pediatric patients[9].

Interruption of ventilation, though momentary, during placement of DLT has potential for significant hypoxemia, especially in a critically ill patient with limited reserve. This risk is especially significant in patients with high levels of ventilator support, or in patients with a difficult airway. Thus, these need to be performed by individuals experienced with airway management, with difficult airway equipment and bronchoscope at the bedside.

Though anatomical separation is confirmed with bronchoscopy, adequate functional separation needs to be established as well. In the past, investigators have assessed functional lung separation by either water bubble or balloon inflation techniques. However, these require temporary interruption of ventilation and might not be a feasible strategy for an ICU patient with limited reserve. Functional separation can be assessed with most modern ventilators by measuring the inspired and expired tidal volumes from each lung. Loss or gain of tidal volume would suggest a leak. However, interpretation may be more difficult in the presence of a bronchopleural fistula.

Management of patients on ILV, outside of ventilation strategies, should be guided by the patient's needs and not influenced by institution of ILV. Though paralysis was thought to be necessary for institution of ILV, use of ILV without paralysis is reported[4]. However, DLT is more stimulating to the airway than a single lumen tube

Table 1 Indications for independent lung ventilation[32]

Massive hemoptysis[6,19]
Pneumonia[1-3,17]
Aspiration
Single lung transplantation with graft dysfunction[5,21]
Bronchopleural fistula[3,6,18]
Lung contusion[3,31]
Copious infected secretions in one lung (*e.g.*, lung abscess)
Unilateral pulmonary edema[4]

and might require more sedation for patient tolerance and comfort.

Complications and limitations

Lung isolation is maintained in the operating room under the constant surveillance of an anesthesia provider experienced in airway and lung isolation. ILV may be safely performed in the ICU with nurses and respiratory therapists properly trained in the care of patients receiving ILV. They should be able to identify and notify a clinician when endotracheal tube dislodgement is suspected. Tube malposition may inadvertently occur during patient movement or during routine change of patient's position[24]. Malposition should be suspected with sudden change in tidal volumes, or an increase in airway pressure. When dislodgement is suspected bronchoscopic assessment should be performed quickly to re-establish appropriate tube position.

DLTs have low volume high pressure cuffs. If not monitored, bronchial cuff pressure may be as high a 50 mmHg with as little as 2 cc of air[25]. The effects of prolonged use of a bronchial cuff on bronchial mucosal blood flow is unknown, since most data is from intraoperative literature where lung isolation only lasts for a few hours. In addition, a critically ill patient might already have a compromised mucosal blood flow, increasing the risk of mucosal ischemia. Ideally, cuff pressure should be maintained at 25 to 30 cm H_2O by an automated continuous pressure cuff controller preventing tracheal mucosa injury and air leak at peak inspiratory pressure. Complications reported to be associated with DLT use include bronchial ischemia and stenosis, bronchial rupture resulting in pneumothorax, pneumo-mediastinum and subcutaneous emphysema[7]. Though the typical duration of ILV reported in literature ranges from 2 to 4 d, some have used it for over two weeks without complications[3,7].

How to achieve physiological separation of lungs?

Physiological separation of lungs requires ability to independently alter ventilator parameters for each lung. This is best achieved using two separate ventilators one for each lung. Historically, a single ventilator had been used to ventilate two lungs, however in most cases each lung requires a different PEEP level. This was accomplished by connecting one ventilator to both limbs of the DLT through a Y-connector. This strategy allows for independent titration of PEEP between the two lungs, by adding a PEEP valve between the Y-connector and the limb of DLT ventilating the lung requiring additional PEEP. This approach is suboptimal as the presence of a PEEP valve in the circuit may impede accurate measurement of airway pressure by the ventilator, and generation of high levels of auto-PEEP might not be detected by the ventilator. In addition, other parameters such as tidal volume, respiratory rate and inspired oxygen concentration cannot be independently altered with this approach. Using a separate ventilator for each lung allows for independent adjustment of ventilator parameters, an essential feature for optimization of patients with ILV.

Synchronous vs asynchronous ventilation

Synchronous *vs* asynchronous ventilation results from the presence or absence of coordination between ventilated breaths provided to each lung. A single ventilator strategy evidently delivers synchronous ventilation. While using two ventilators, the most common strategy for ILV, synchronous ventilation can be accomplished by electronically linking the two ventilators using an external cable. Initiation of ventilation by one ventilator would transmit a signal through the external cable triggering the second ventilator resulting in near simultaneous delivery of a breath by that ventilator. It was thought that asynchronous ILV might result in cardiovascular compromise, from decreased (systemic and pulmonary) venous return as inflation of each lung at different times would result in elevated intrathoracic pressure for a longer duration of time. Subsequently, it has been shown that asynchronous

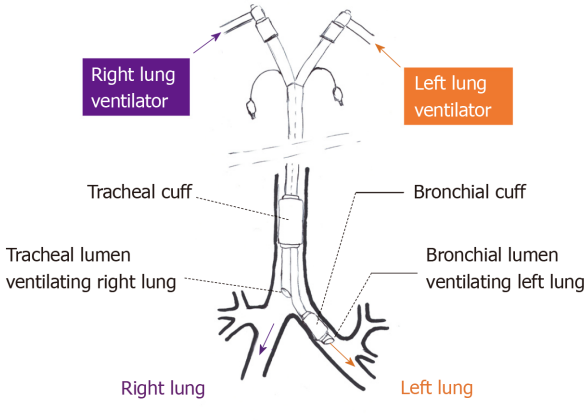


Figure 1 Institution of independent lung ventilation using a left sided- double lumen tube.

ventilation strategies can be instituted without these concerns and is equally well tolerated by patients[17]. Asynchronous ventilation strategy with two ventilators is much less complicated, offer greater flexibility allowing for individual titration of ventilation parameters, and thus is the preferred strategy for ILV.

How to determine the optimal ventilator strategy?

The selection of ventilator strategy for ILV is guided by the underlying pathology of each lung based and on principles of lung protective ventilation. Institution of ILV in patients with different lung compliances can ensure delivery of an appropriate tidal volume to each lung. Most of the literature on ventilation strategies during single lung ventilation comes from thoracic anesthesia literature, but may be extrapolated to ILV. Below we describe some principles for determining optimal ventilator parameters during ILV (Figure 2).

Positive end expiratory pressure: As in conventional ventilation, positive end expiratory pressure (PEEP) in ILV should be determined based on a PEEP titration trial ('best PEEP' trial) to identify the optimal PEEP providing highest lung compliance and adequate oxygenation. Since compliance of the diseased and non-diseased lung are markedly different, the best PEEP for each lung should be determined separately and instituted independently. Certain factors unique to ILV, must be considered while performing a best PEEP trial for each lung. Due to the impairment in gas exchange associated with severe unilateral lung disease, the diseased lung largely functions as a shunt, contributing to hypoxemia. A high PEEP applied to the normal lung may further worsen shunting through the diseased lung, and thereby worsen oxygenation.

The best strategy would be to initially perform a best PEEP trial of the diseased lung. The PEEP trial in the diseased lung should be primarily driven by compliance, since the diseased lung has minimal contribution to gas exchange. The PEEP resulting in the lowest driving pressure or the highest compliance might be chosen as the optimal PEEP in the diseased lung. Subsequently, a best PEEP trial for the non-diseased lung may follow. Determination of best PEEP of the non-diseased lung should also consider chronic underlying pathology such as asthma, emphysema or pulmonary fibrosis. Since increasing PEEP on the non-diseased lung may worsen shunting and hypoxemia, titration of optimal PEEP in the non-diseased should be based on oxygenation and compliance, rather than compliance alone.

Tidal volume, driving pressure and minute ventilation: In patients with lung injury or adult respiratory distress syndrome (ARDS) receiving conventional ventilation, protective lung ventilation involves limiting tidal volume to 4 to 8 cc/kg of predicted body weight (kg PBW), plateau pressures < 28 cmH_20 and driving pressure < 15 cmH_2O. Maintaining a tidal volume lower than 5 cc/ kg PBW and a plateau pressure lower than 28 cmH_2O during one lung ventilation has consistently been associated with decreased lung injury in patients undergoing lung surgeries[26]. These estimates are based on ventilation for a few hours during surgery, as opposed to ILV in ICU which may last days. Also, there is strong evidence on the benefits of low tidal volume ventilation, even when used intraoperatively for a few hours, in patients with normal lungs[22]. Thus a low tidal volume strategy (3 to 5 cc/kg PBW) should be adhered to separately for each lung, including the non-diseased lung, during ILV. The

	Non-diseased lung	Diseased lung		Recovery of diseased lung
PEEP	Perform best PEEP trial after determining the best PEEP of diseased lung Choose best PEEP based on compliance and oxygenation	Initially, perform best PEEP trial of the diseased lung Choose PEEP with lowest driving pressure and highest compliance	WEANING	Titrate PEEP of diseased lung based on change in compliance With recovery, the PEEP would decrease to be equivalent to PEEP of the non-diseased lung
Tidal Volume	Satisfy following criteria □3-5cc/ kg PBW/ lung, driving pr < 15 cm H2O and plateau pr < 28 cm H2O □Total tidal volume 4-6 cc/kg PBW	Minimal contribution by the diseased lung (limited by plateau pr)		Improved compliance will allow delivery of larger tidal volume, improving the contribution of the diseased lung to total tidal volume
FiO_2	Titrate to patient's PaO_2 55-80 mm Hg	Maintain low FiO_2 ~ 40- 60 %		Increase to be equal to non-diseased lung
Mode of ventilation	Assist control ventilation	CPAP or Assist control ventilation		Assist control ventilation

Figure 2 Guide to initial ventilator setting and weaning strategy during independent lung ventilation. PEEP: Positive end expiratory pressure; kg PBW: Kilogram predicted body weight; FiO_2: Fractional inspired oxygen concentration; PaO_2: Partial pressure of arterial oxygen.

tidal volume delivered to the diseased lung may be further limited by need to keep plateau pressure less than 28 cmH_2O and driving pressure < 15 cmH_2O. Since lower driving pressures is known to independently determine survival in ARDS, ability to keep driving pressure below 15 cmH_2O in the diseased lung should primarily drive the delivered tidal volume[27]. This might be best achieved by using a pressure control ventilation strategy in the diseased lung. Overall, it should be ensured that the additive tidal volume delivered to both lungs should not exceed 6-8 cc/kg PBW and that the plateau pressure and driving pressure for each lung is below 28 and 15 cmH_2O, respectively.

During ILV, each lung may have different minute ventilations, tidal volumes and respiratory rates. In the initial period, more benefit would be obtained by titrating the minute ventilation of the non-diseased lung to pCO_2, since it contributes most to ventilation. The ventilation strategy to be instituted for the diseased lung when it is not contributing to ventilation is unclear. There exists some evidence for providing lung rest (very low frequency positive pressure ventilation) and thus decreasing volutrauma, while instituting extracorporeal CO_2 removal in patients with hypercarbic respiratory failure[28,29]. Extrapolating that data to ILV, one may advocate for just providing continuous positive airway pressure to the diseased lung, especially in the presence of a severely diseased lung where the plateau and driving pressure are high. This may especially be considered when the diseased lung is not contributing much to oxygenation or CO_2 clearance. With improvement in compliance of the diseased lung and radiological improvement, ventilation can be resumed in a stepwise manner. One should favor permissive hypercapnia than to choose ventilator settings that contributes to lung injury.

Fractional concentration of inspired oxygen: Inspired oxygen concentration (FiO_2) of the non-diseased lung should be determined based on the systemic oxygenation. The FiO_2 of the non-diseased lung should be titrated to maintain the partial pressure of arterial oxygen between 55 and 80 mmHg and SpO_2 between 88% and 95%. Various considerations exist while choosing FiO_2 for the diseased lung. A lower FiO_2 in the diseased lung may result in poorer oxygenation of the blood circulating through the diseased lung, thereby worsening the impact of shunt. On the other hand, a higher FiO_2 may result in an increased risk for hyperoxic injury to the diseased lung. Also, the higher FiO_2 in the diseased lung might mitigate the hypoxic pulmonary vasoconstriction, thereby worsen shunt through the diseased lung. FiO_2 for the diseased lung should be titrated based on these competing factors. Thus, when the disease severity results in minimal contribution to oxygenation by the diseased lung, an FiO_2 between 40% and 60% might be favorable. This could be further titrated based on its impact on systemic oxygenation. Once the disease severity improves and the diseased lung contributes to oxygenation, the FiO_2 in that lung may be titrated similarly and equally with that of the non-diseased lung, to optimize systemic oxygenation.

Mode of ventilation: Various modes of ventilation have been reported with ILV, based on the underlying pathology and the comfort of the critical care team instituting ILV. These include assist control volume or pressure ventilation, pressure support ventilation, or high frequency oscillatory ventilation. Assist control is the most commonly utilized mode for ILV reported in literature. In a severely diseased low compliant lung which is not contributing significantly to oxygenation or ventilation, continuous positive airway pressure may be utilized initially. Though various studies have shown no mortality benefit with using high frequency oscillatory ventilation in severe ARDS[30], its role when preferentially applied to the diseased lung in ILV is uncertain. As the diseased lung begins to recover, an assist control pressure ventilation targeting driving pressures < 15 cmH_2O might be a useful strategy.

When and how to wean?

Evaluation of the readiness to wean the ventilator requirements should happen regularly and independently for each individual lung. However, ventilator parameters of the diseased lung can only be weaned when its pathological process begins to resolve. An important goal of weaning ventilator support in ILV is continual assessment of lung mechanics of each lung independently, to evaluate feasibility of transitioning to conventional ventilation using a single lumen endotracheal tube and one ventilator.

Though weaning happens separately for each lung during ILV, changing support on one lung may affect the other. The following considerations and principles should be borne in mind while weaning from ILV (Figure 2).

FiO_2: When the diseased lung is not contributing to gas exchange, the FiO_2 of the non-diseased lung may be weaned based on systemic oxygenation. However, as the diseased lung starts recovering and contributes to gas exchange, its FiO_2 may be titrated similarly (and made equal) to that of the non-diseased lung.

PEEP: Weaning PEEP may occur separately for each lung based on the 'best PEEP' calculated for each lung, and principles previously discussed. The goal of PEEP titration is to maintain maximum compliance in each lung and thereby minimizing driving pressures. As the diseased lung recovers, its compliance improves resulting in a reduced level of PEEP, bringing it closer to that of the non-diseased lung.

Tidal volume: If delivery of adequate tidal volume was initially limited in the diseased lung to maintain a lung protective driving pressure (< 15 cmH_2O), improvement in disease process will allow delivery of adequate tidal volume (3- 5 cc/ kg PBW/ lung).

Mode of ventilation: If separate modes of ventilation were used for each lung during ILV, recovery of the diseased lung should allow use of same mode. Assist control ventilation is the preferred mode of ventilation for both lungs, before transitioning to conventional ventilation.

Various measures have been described in the literature to determine the readiness to transition back from ILV to conventional single ventilator ventilation (Table 2). These are primarily based on assessment of improvement in the underlying unilateral lung pathology. The goal is to ensure that restoration of standard single ventilator ventilation would not result in markedly unequal distribution of tidal volumes resulting in volutrauma, or exacerbation of leak in bronchopleual fistula. With resolution of the unilateral lung pathology, lung mechanics, which were initially markedly different between the lungs, will progressively converge. Perhaps the most important parameter to follow would be individual lung compliances. Similar compliance between the two lungs would ensure that tidal volume delivered during conventional ventilation would be comparably distributed to each lung. Some authors have successfully discontinued ILV when the tidal volume and compliance differed between the lungs by less than 100 mL and 20%, respectively[11,31]. Use of capnography for each lung has shown that the diseased lung often has a much lower end tidal carbon dioxide concentration, likely from its minimal contribution to ventilation. Equivalence of end tidal carbon dioxide concentration between the two lungs during ILV could point towards comparable contribution to ventilation by each lung[31]. Other indicators would be radiological improvement and decrease in air leak from the chest tube in patients with unilateral bronchopleural fistula.

Before institution of single ventilator ventilation, its feasibility should be measured by temporarily ventilating each lung with the exact same settings. It is best achieved by ventilating both lungs using assist control pressure ventilation. This allows one to use the same settings (FiO2, PEEP, driving pressure, and minute ventilation) when transitioning to conventional single ventilator ventilation. Maintaining oxygenation should not be the sole criteria for determining feasibility. Presence of markedly different compliances may result in adequate oxygenation, but could result in volutrauma to the healthy lung. Thus, comparable compliance and tidal volume (Table 2) in each lung on the same ventilator settings establishes feasibility for

Table 2 Criteria favoring transitioning from double lumen tube to single lumen tube[11,31]

Near complete or complete resolution of the disease process- clinically or radiologically
Difference in tidal volume between the two lungs < 100 cc
Difference in compliance between the two lungs < 20%
Difference in end tidal carbon dioxide concentration between the two lungs < 20%

switching to single ventilator ventilation. Figure 3 compares tidal volumes and compliance for each lung in our patient, before conventional ventilation was instituted. Continuation of ILV also needs to be weighed against the risks associated with the duration of ILV. The deeper sedation necessary with ILV prevents patient participation in physical therapy, and minimizes patient effort in ventilation causing respiratory muscle atrophy. Longer duration of ILV may also increase the risk of airway mucosal injury from DLT. Moreover, with resolution of underlying pathology, mucus plugging and secretion clearance could become important considerations. Suctioning or bronchoscopic clearance of secretions are difficult through a DLT due to its narrow lumen, but may be more easily accomplished through a single lumen tube. Once single ventilator ventilation is tolerated, the DLT can be exchanged to a single lumen tube and conventional ventilation instituted.

CONCLUSION

Unilateral lung injury presents a markedly different scenario from the heterogeneous lung injury seen with ARDS. ILV is likely the most optimal way to provide lung protective ventilation in patients with severe unilateral lung pathology, thereby avoiding ECMO, which is more invasive and unavailable in resource poor locations. Safe utilization of ILV requires education and a collaborative effort by critical care nurses, respiratory therapists and physicians. With the stepwise clinical flow-chart proposed here, we hope to encourage more utilization of ILV. However, optimal strategies for ventilating the diseased lung and weaning from ILV needs further characterization.

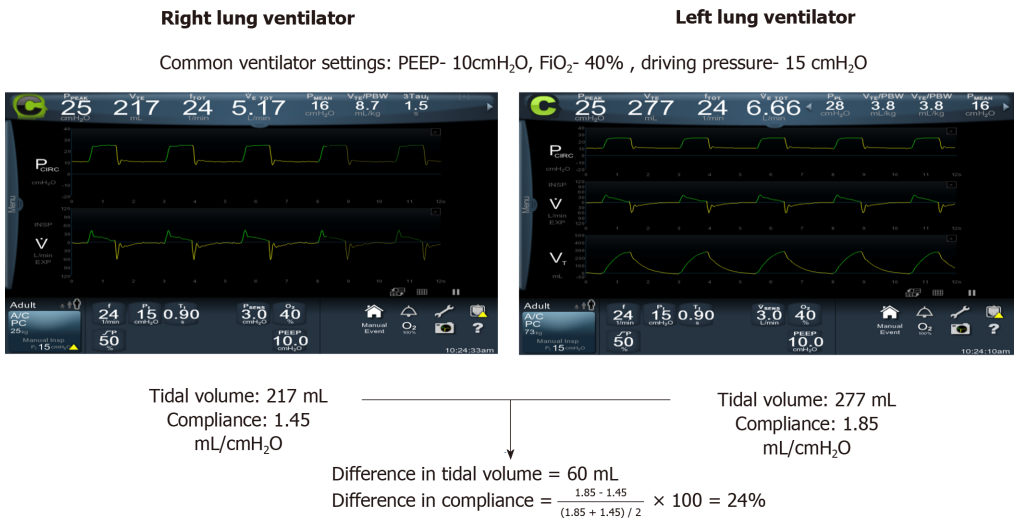


Figure 3 Test to determine readiness for transitioning from independent lung ventilation using double lumen tube to conventional single ventilator ventilation using a single lumen endotracheal tube. The tidal volumes and compliances of right and left lung are compared on identical ventilator settings. PEEP: Positive end expiratory pressure; FiO_2: Fractional inspired oxygen concentration.

REFERENCES

1 **Fujita M**, Tsuruta R, Oda Y, Kaneda K, Miyauchi T, Kasaoka S, Maekawa T. Severe Legionella pneumonia successfully treated by independent lung ventilation with intrapulmonary percussive ventilation. *Respirology* 2008; **13**: 475-477 [PMID: 18399877 DOI: 10.1111/j.1440-1843.2007.01220.x]

2 **Skjeflo GW**, Dybwik K. A new method of securing the airway for differential lung ventilation in intensive care. *Acta Anaesthesiol Scand* 2014; **58**: 463-467 [PMID: 24588330 DOI: 10.1111/aas.12285]

3 **Yamakawa K**, Nakamori Y, Fujimi S, Ogura H, Kuwagata Y, Shimazu T. A novel technique of differential lung ventilation in the critical care setting. *BMC Res Notes* 2011; **4**: 134 [PMID: 21545715 DOI: 10.1186/1756-0500-4-134]

4 **Achar SK**, Chaudhuri S, Krishna H, Sagar M. Re-expansion pulmonary oedema - differential lung ventilation comes to the rescue. *Indian J Anaesth* 2014; **58**: 330-333 [PMID: 25024481 DOI: 10.4103/0019-5049.135051]

5 **Badesch DB**, Zamora MR, Jones S, Campbell DW, Fullerton DA. Independent ventilation and ECMO for severe unilateral pulmonary edema after SLT for primary pulmonary hypertension. *Chest* 1995; **107**: 1766-1770 [PMID: 7781385 DOI: 10.1378/chest.107.6.1766]

6 **Shekar K**, Foot CL, Fraser JF. Independent lung ventilation in the intensive care unit: desperate measure or viable treatment option? *Crit Care Resusc* 2008; **10**: 144-148 [PMID: 18522530]

7 **Graciano AL**, Barton P, Luckett PM, Morriss F, Sommerauer JF, Toro-Figueroa LO. Feasibility of asynchronous independent lung high-frequency oscillatory ventilation in the management of acute hypoxemic respiratory failure: a case report. *Crit Care Med* 2000; **28**: 3075-3077 [PMID: 10966299 DOI: 10.1097/00003246-200008000-00067]

8 **Murkute A**, Angadi U, Jain P, Sharique T, Hegde R. Paediatric pulmonary haemorrhage: Independent lung ventilation as effective strategy in management. *Indian J Crit Care Med* 2014; **18**: 694-696 [PMID: 25316981 DOI: 10.4103/0972-5229.142180]

9 **Di Nardo M**, Perrotta D, Stoppa F, Cecchetti C, Marano M, Pirozzi N. Independent lung ventilation in a newborn with asymmetric acute lung injury due to respiratory syncytial virus: a case report. *J Med Case Rep* 2008; **2**: 212 [PMID: 18565228 DOI: 10.1186/1752-1947-2-212]

10 **Plötz FB**, Hassing MB, Sibarani-Ponsen RD, Markhorst DG. Differentiated HFO and CMV for independent lung ventilation in a pediatric patient. *Intensive Care Med* 2003; **29**: 1855 [PMID: 14534775 DOI: 10.1007/s00134-003-1949-y]

11 **Cinnella G**, Dambrosio M, Brienza N, Bruno F, Brienza A. Compliance and capnography monitoring during independent lung ventilation: report of two cases. *Anesthesiology* 2000; **93**: 275-278 [PMID: 10861174 DOI: 10.1097/00000542-200007000-00043]

12 **Campos JH**. Lung isolation techniques. *Anesthesiol Clin North Am* 2001; **19**: 455-474 [PMID: 11571902 DOI: 10.1017/CBO9780511842306.089]

13 **Campos JH**. Progress in lung separation. *Thorac Surg Clin* 2005; **15**: 71-83 [PMID: 15707347 DOI: 10.1016/j.thorsurg.2004.09.003]

14 **Narayanaswamy M**, McRae K, Slinger P, Dugas G, Kanellakos GW, Roscoe A, Lacroix M. Choosing a lung isolation device for thoracic surgery: a randomized trial of three bronchial blockers versus double-lumen tubes. *Anesth Analg* 2009; **108**: 1097-1101 [PMID: 19299767 DOI: 10.1213/ane.0b013e3181999339]

15 **Siegel JH**, Stoklosa JC, Borg U, Wiles CE, Sganga G, Geisler FH, Belzberg H, Wedel S, Blevins S, Goh KC. Quantification of asymmetric lung pathophysiology as a guide to the use of simultaneous independent lung ventilation in posttraumatic and septic adult respiratory distress syndrome. *Ann Surg* 1985; **202**: 425-439 [PMID: 3901940 DOI: 10.1097/00000658-198510000-00004]

16 **Parish JM**, Gracey DR, Southorn PA, Pairolero PA, Wheeler JT. Differential mechanical ventilation in respiratory failure due to severe unilateral lung disease. *Mayo Clin Proc* 1984; **59**: 822-828 [PMID: 6390009 DOI: 10.1016/s0025-6196(12)65616-x]

17 **Stow PJ**, Grant I. Asynchronous independent lung ventilation. Its use in the treatment of acute unilateral

lung disease. *Anaesthesia* 1985; **40**: 163-166 [PMID: 3977033]
18 **Minhas JS**, Halligan K, Dargin JM. Independent lung ventilation in the management of ARDS and bronchopleural fistula. *Heart Lung* 2016; **45**: 258-260 [PMID: 27045902 DOI: 10.1016/j.hrtlng.2016.02.007]
19 **Sarnaik A**. The use of independent lung ventilation for unilateral pulmonary hemorrhage. *Int J Respir Pulm Med* 2015; **2**: 13 [DOI: 10.23937/2378-3516/1410013]
20 **Rico FR**, Cheng JD, Gestring ML, Piotrowski ES. Mechanical ventilation strategies in massive chest trauma. *Crit Care Clin* 2007; **23**: 299-315, xi [PMID: 17368173 DOI: 10.1016/j.ccc.2006.12.007]
21 **Pilcher DV**, Auzinger GM, Mitra B, Tuxen DV, Salamonsen RF, Davies AR, Williams TJ, Snell GI. Predictors of independent lung ventilation: an analysis of 170 single-lung transplantations. *J Thorac Cardiovasc Surg* 2007; **133**: 1071-1077 [PMID: 17382655 DOI: 10.1016/j.jtcvs.2006.10.028]
22 **Ladha K**, Vidal Melo MF, McLean DJ, Wanderer JP, Grabitz SD, Kurth T, Eikermann M. Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. *BMJ* 2015; **351**: h3646 [PMID: 26174419 DOI: 10.1136/bmj.h3646]
23 **Seefelder C**. Use of the 26-French double-lumen tube for lung isolation in children. *J Cardiothorac Vasc Anesth* 2014; **28**: e19-e21 [PMID: 24594109 DOI: 10.1053/j.jvca.2013.11.012]
24 **Inoue S**, Nishimine N, Kitaguchi K, Furuya H, Taniguchi S. Double lumen tube location predicts tube malposition and hypoxaemia during one lung ventilation. *Br J Anaesth* 2004; **92**: 195-201 [PMID: 14722168 DOI: 10.1093/bja/aeh055]
25 **Brodsky JB**, Adkins MO, Gaba DM. Bronchial cuff pressures of double-lumen tubes. *Anesth Analg* 1989; **69**: 608-610 [PMID: 2802196 DOI: 10.1213/00000539-198911000-00010]
26 **Lohser J**, Slinger P. Lung Injury After One-Lung Ventilation: A Review of the Pathophysiologic Mechanisms Affecting the Ventilated and the Collapsed Lung. *Anesth Analg* 2015; **121**: 302-318 [PMID: 26197368 DOI: 10.1213/ANE.0000000000000808]
27 **Amato MB**, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; **372**: 747-755 [PMID: 25693014 DOI: 10.1056/NEJMsa1410639]
28 **Del Sorbo L**, Pisani L, Filippini C, Fanelli V, Fasano L, Terragni P, Dell'Amore A, Urbino R, Mascia L, Evangelista A, Antro C, D'Amato R, Sucre MJ, Simonetti U, Persico P, Nava S, Ranieri VM. Extracorporeal Co2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med* 2015; **43**: 120-127 [PMID: 25230375 DOI: 10.1097/CCM.0000000000000607]
29 **Gattinoni L**, Agostoni A, Pesenti A, Pelizzola A, Rossi GP, Langer M, Vesconi S, Uziel L, Fox U, Longoni F, Kolobow T, Damia G. Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO2. *Lancet* 1980; **2**: 292-294 [PMID: 6105441 DOI: 10.1016/s0140-6736(80)90237-8]
30 **Ng J**, Ferguson ND. High-frequency oscillatory ventilation: still a role? *Curr Opin Crit Care* 2017; **23**: 175-179 [PMID: 28157820 DOI: 10.1097/MCC.0000000000000387]
31 **Cinnella G**, Dambrosio M, Brienza N, Giuliani R, Bruno F, Fiore T, Brienza A. Independent lung ventilation in patients with unilateral pulmonary contusion. Monitoring with compliance and EtCO(2). *Intensive Care Med* 2001; **27**: 1860-1867 [PMID: 11797020 DOI: 10.1007/s00134-001-1149-6]
32 **Anantham D**, Jagadesan R, Tiew PE. Clinical review: Independent lung ventilation in critical care. *Crit Care* 2005; **9**: 594-600 [PMID: 16356244 DOI: 10.1186/cc3827]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2019 September 11; 8(5): 59-86

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Irregular Volume 8 Number 5 September 11, 2019

REVIEW

CASE REPORT

Contents

World Journal of Critical Care Medicine

Volume 8 Number 5 September 11, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*. Huaiwu He, MD, PhD, Associate Professor, Doctor, Deptartment of Critical Care Medicine, Peking Union Medical College Hospital, Beijing 100730, China

AIMS AND SCOPE

World Journal of Critical Care Medicine (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJCCM* covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, *etc*.

We encourage authors to submit their manuscripts to *WJCCM*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Mei-Yi Liu*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
September 11, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Medl 2019 September 11; 8(5): 59-71

DOI: 10.5492/wjccm.v8.i5.59

ISSN 2220-3141 (online)

REVIEW

Diagnosis and treatment of acute pulmonary inflammation in critically ill patients: The role of inflammatory biomarkers

Sarah Chalmers, Ali Khawaja, Patrick M Wieruszewski, Ognjen Gajic, Yewande Odeyemi

ORCID number: Sarah Chalmers (0000-0001-6565-9023); Ali Khawaja (0000-0002-1595-9316); Patrick M Wieruszewski (0000-0002-5871-5186); Ognjen Gajic (0000-0003-4218-0890); Yewande Odeyemi (0000-0002-4446-198X).

Author contributions: Chalmers S, Khawaja A, Wieruszewski PM, Ognjen G, and Odeyemi Y, contributed to writing of the manuscript, provided intellectual contributions

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Manuscript source: Invited manuscript

Received: May 2, 2019
Peer-review started: May 5, 2019
First decision: June 6, 2019
Revised: July 2, 2019
Accepted: August 6, 2019
Article in press: August 7, 2019

Sarah Chalmers, Ali Khawaja, Patrick M Wieruszewski, Ognjen Gajic, Yewande Odeyemi, Multidisciplinary Epidemiology and Translational Research in Intensive Care Group, Mayo Clinic, Rochester, MN 55905, United States

Sarah Chalmers, Ali Khawaja, Ognjen Gajic, Yewande Odeyemi, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Patrick M Wieruszewski, Department of Pharmacy, Mayo Clinic, Rochester, MN 55905, United States

Corresponding author: Sarah Chalmers, MD, Fellow, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States.
chalmers.sarah@mayo.edu
Telephone: +1-507-2663958
Fax: +1-507-2664372

Abstract

Pneumonia and acute respiratory distress syndrome are common and important causes of respiratory failure in the intensive care unit with a significant impact on morbidity, mortality and health care utilization despite early antimicrobial therapy and lung protective mechanical ventilation. Both clinical entities are characterized by acute pulmonary inflammation in response to direct or indirect lung injury. Adjunct anti-inflammatory treatment with corticosteroids is increasingly used, although the evidence for benefit is limited. The treatment decisions are based on radiographic, clinical and physiological variables without regards to inflammatory state. Current evidence suggests a role of biomarkers for the assessment of severity, and distinguishing sub-phenotypes (hyper-inflammatory versus hypo-inflammatory) with important prognostic and therapeutic implications. Although many inflammatory biomarkers have been studied the most common and of interest are C-reactive protein, procalcitonin, and pro-inflammatory cytokines including interleukin 6. While extensively studied as prognostic tools (prognostic enrichment), limited data are available for the role of biomarkers in determining appropriate initiation, timing and dosing of adjunct anti-inflammatory treatment (predictive enrichment)

Key words: Acute pulmonary inflammation; Inflammatory biomarkers; Acute respiratory distress syndrome; Pneumonia; Critical illness; Diagnosis; Treatment

Published online: September 11, 2019

P-Reviewer: Aurilio C, Yeh YC, Inchauspe AA
S-Editor: Dou Y
L-Editor: A
E-Editor: Liu MY

Core tip: Community acquired pneumonia and acute respiratory distress syndrome are common and important causes of respiratory failure in the intensive care unit. Both clinical entities are characterized by acute pulmonary inflammation in response to direct or indirect lung injury and current evidence suggests a role of biomarkers for the assessment of severity, and distinguishing sub-phenotypes (hyper-inflammatory versus hypo-inflammatory) with important prognostic and therapeutic implications.

Citation: Chalmers S, Khawaja A, Wieruszewski PM, Gajic O, Odeyemi Y. Diagnosis and treatment of acute pulmonary inflammation in critically ill patients: The role of inflammatory biomarkers. *World J Crit Care Medl* 2019; 8(5): 59-71
URL: https://www.wjgnet.com/2220-3141/full/v8/i5/59.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i5.59

INTRODUCTION

Inflammation is a natural body response to infectious and non-infectious insults resulting in a complex variety of mechanisms that eventually lead to tissue repair. Inflammatory response in the lungs is most commonly due to infections, and exposure to toxins, allergens and irritants. Normal inflammation is intended to be protective but when excessive and/or prolonged can have deleterious effects associated with worse outcomes[1]. The most common acute pulmonary inflammatory conditions in the intensive care unit (ICU) are pneumonia, community or health care acquired, and acute respiratory distress syndrome (ARDS), a complication of other acute illnesses.

Community acquired pneumonia (CAP) is a leading infectious cause of hospitalizations worldwide accounting for over 1 million inpatient hospitalizations annually in the United States[2,3]. Limited data suggests about 20% of adults hospitalized for pneumonia required an ICU admission which was directly associated with a 50% increase in length of hospital stay[4]. Although less common than pneumonia, ARDS accounts for approximately 10.4% of ICU admissions worldwide with an associated 40% mortality rate depending on severity[5]. It usually occurs as a sequela of other acute illnesses including pneumonia and non-pulmonary sepsis. Other risk factors are aspiration pneumonia, trauma and transfusion of blood products.

Together, both conditions have a significant impact on morbidity and mortality in the ICU with an associated increase in overall health care utilization despite early antimicrobial therapy and lung protective mechanical ventilation[5,6]. Acute and sometimes exaggerated inflammatory response is a common and important feature in both clinical entities with important prognostic implications and reflective of an ineffective regulatory mechanism to limit inflammation-induced damage[7,8]. Adjunct anti-inflammatory treatment (*i.e.*, corticosteroids) is often used, however the treatment decisions are based on severity of illness without regards to inflammatory state.

Several inflammatory biomarkers have been identified and implicated in the pathophysiology of inflammatory response in pneumonia and ARDS. More recently, several studies have assessed the role of biomarkers as key evaluation and management tools specifically aiding diagnoses, assessing severity, prognostication and informing therapeutic strategies.

This review focuses on biomarkers and their potential role in the evaluation and management of acute inflammation in CAP and ARDS in critically ill patients.

PATHOPHYSIOLOGY OF ACUTE PULMONARY INFLAMMATION

Acute pulmonary inflammation involves both the innate and adaptive immune responses. When a pathogen is encountered, the airway epithelium acts as the first line of defense mechanism. It is well equipped to release several enzymes including defensins, mucins and lyzozymes along with reactive oxygen species (ROS), nitric oxide, platelet activating factor and cytokines to attract inflammatory cells. In addition, plasma cells secrete IgA which creates an overlying epithelial protective barrier preventing microbial adherence, and surfactant proteins A and D in the alveoli

sacs stick to surface bacterial molecules to facilitate opsonization[1,9]. If a pathogen is able to overcome the epithelium's defenses, it encounters a group of inflammatory cells particularly macrophages, dendritic cells and lymphocytes, residing in the airways and throughout the lung parenchyma and interstitium. Dendritic cells are antigen presenting cells which not only stimulate the naïve T cell lymphocytes but also potentiate macrophages and assist in phagocytosis. They do so with the help of toll like receptors on their surfaces also referred to as pattern-recognition receptors which identify pathogen associated molecular patterns on pathogens' surfaces[1,10]. Stimulated naïve T cells activate either a T helper 1 (Th 1) and Th2 response which results in both cell-mediated and humoral mediated immune responses against the invading organism. This culminates in further stimulation of macrophages and T lymphocytes resulting in the release of a variety of chemokines and cytokines based on the type of invading pathogen, including interferon gamma, tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-4, IL-5, IL-6, IL-8, IL-9, IL-12 and IL-13. Simultaneously, the lung insult activates the capillary endothelial cells which in addition to contributing towards chemokine release, upregulate the surface adhesion molecules facilitating the attachment and migration of inflammatory cells to the site of insult[1]. In acute inflammation, neutrophils are the primary cells to respond to the cytokine release; IL-8 being the primary neutrophil chemotactic cytokine. Neutrophils kill the phagocytosed pathogens with ROS, antimicrobial proteins and elastase. If the lung insult has been successfully controlled, a rise in anti-inflammatory cytokines particularly IL-10, TGF-β and IL-1Ra is expected. These assist in down regulating the defense system and facilitate apoptosis of the inflammatory cells by macrophages[11]. However, in cases of overwhelming infection, the anti-inflammatory mechanisms are unable to control the underlying inflammation resulting in continuous lung injury.

In early ARDS, increased capillary permeability is the hallmark outcome of the inflammatory process resulting from direct or indirect lung injury with disruption of the capillary-alveolar interface. This leads to leakage of protein-rich fluid from the capillary into the alveoli resulting in diffuse alveolar injury triggering an overwhelming release of pro-inflammatory cytokines mainly TNF, IL-1 and IL-6 and creating an imbalance between pro-inflammatory and anti-inflammatory cytokines. This initiates the inflammation cascade and recruits' neutrophils which again play a crucial role in causing inflammation by releasing ROS and proteases. It has been noted that patients with ARDS, have transcription abnormalities involving NF-kappa B which is required for transcription of genes responsible for pro-inflammatory mediators. Other substances such as endothelin-1, angiotensin-2 and phospholipase A2 have also been found to worsen vascular permeability and underlying inflammation causing increased lung injury[12-15]. A hyper- inflammatory sub phenotype in ARDS has been recently identified and associated with worse outcomes compared to a hypo-inflammatory sub phenotype[8].

DIAGNOSIS, EVALUATION, AND MANAGEMENT OF CAP AND ARDS-EVIDENCE ON INFLAMMATORY BIOMARKERS

Early identification and assessment of severity are essential for institution of timely antibiotic therapy and appropriate supportive care in CAP and ARDS. As current diagnostic, evaluation, and management strategies are based on radiographic, clinical and physiological variables only, the use of biomarkers in these conditions has been proposed and extensively evaluated.

A biomarker is "a defined characteristic that is measureable and an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention"[16]. The quintessential biomarker that can aid early identification, prognostication, as well as guide and monitor response to treatment in critically ill patients with acute pulmonary inflammation has been long sought-after. Several other fields have successfully identified biomarkers with therapeutic implications and improvement in outcomes. The identification of the programed cell death ligand-1 (PD-L1) and its role in several malignancies, led to the development of PD-L1 inhibitors which have revolutionized the treatment of several types of cancer. Asthma is another example of a heterogeneous disease that was revolutionized by the identification of various phenotypes and the associated biomarker(s) leading to treatments such as anti-IL-5 inhibitors. Recent evidence and ongoing efforts suggests a potential for similar success in CAP and ARDS with the recent identification of hyper-inflammatory phenotypes with important prognostic and therapeutic implications[8,17]. The biomarkers that have been most extensively studied in CAP include C-reactive protein (CRP) and procalcitonin (PCT) and in ARDS, cytokines which will henceforth be reviewed.

CRP

CRP was first discovered in 1930. Scientists William S Tillet and Thomas Francis Jr, discovered a novel antigen on the surface of pneumococcal bacteria that was present in the initial stages of infection and resolved as the patient improved[18]. Several years later, it was discovered that this "antigen" was a protein involved in acute systemic inflammation, CRP.

CRP is an acute phase protein predominately synthesized in hepatocytes in response to IL-6. As part of the innate immune response, it binds to microorganisms and stimulates phagocytosis and activation of the classical complement pathway[19]. It is detectable in serum within 6-10 h of inflammation initiation and has a half-life of approximately 25 h accounting for its rapid disappearance as inflammation subsides[20]. It is a non-specific acute phase reactant and has been shown to be elevated in various types of inflammation including infection regardless of pathogen type, malignancy, autoimmune disorders, and systemic inflammatory response syndrome (SIRS) PCT was more recentlyoccurring without active infection[21]. Current literature supports its use in diagnosis of pneumonia, assessment of severity of illness, prognostication, and assessment of clinical stability though the literature can be difficult to interpret due to the heterogeneous populations studied and the wide array of cut off levels suggested[22] (Table 1). Given its non-specific but direct correlation with the innate immune system, its rapid turn-around time, low cost, and wide availability, it could be used as a biomarker to help identify and guide treatment in patients with hyper-inflammatory phenotypes of CAP. Further studies are needed to help define the natural history of CRP in hyper-inflammatory CAP phenotypes.

PCT

PCT was more recently discovered. It is a 116 amino acid peptide precursor to calcitonin and is encoded by the *CALC-1* gene. In non-infectious states, it is produced in the C cells of the thyroid gland. In the presence of infection, and in particular, systemic bacterial infection, *CALC-1* gene expression is induced in non-neuroendocrine cells throughout the body and transcription and translation of PCT occurs. In addition, release of interferon stimulated by viral infection has been shown to down-regulate the production of PCT. It is detec in serum within 4 h of onset of infection and peaks within 12-48 h[23-25].

While it is often used as a marker of systemic bacterial infection, it may not be elevated in isolated infections such as abscesses or empyema. Similar to CRP, it can be elevated in SIRS without infection. Accuracy in patients with renal dysfunction has been brought into questions as levels can be falsely elevated due at least in part to impaired clearance though higher cut off levels have been proposed in this population[26]. Similar to CRP, current literature supports its use in diagnosis, assessment of severity of illness, prognostication, and assessment of clinical stability in patients with CAP. In addition, it has been shown to be effective in identifying bacterial pathogens as the source of infection and in de-escalation of antibiotic therapy[22]. (Table 1)

CRP and PCT in CAP

CRP and PCT have been shown to aid in diagnosis in CAP particularly in comparison to clinical signs and symptoms alone and in patients with co-morbid conditions that contribute to clinical ambiguity, such as chronic obstructive pulmonary disease and acute heart failure.[25,27]. However, time from symptom onset to initial healthcare presentation may impact initial levels of CRP and PCT. A study looked at 541 patients who presented to the emergency department with CAP and were differentiated into early presenters (< 3 d since onset of symptoms) and late presenters (> 3 d). Results showed that CRP and PCT were lower in patients who were early presenters suggesting that time to presentation may affect the interpretation of these biomarkers[28].

Both CRP and PCT have demonstrated moderate positive correlation with severity of disease assessed by CURB-65 with a receiver operating characteristic curves of 0.61 and 0.72 respectively[29].

Evidence of CRP and PCT in prognostication of CAP is variable. One recent cross-sectional study of 93 hospitalized adult patients with CAP showed a statistically significant association with mortality in patients with PCT > 0.5 ng/mL[29]. Another study assessed prognostication ability of PCT alone and in conjunction with CURB-65 compared with CRP and leukocytes , and demonstrated a better prediction of mortality of PCT alone which was increased in combination with CURB-65[30]. Yet another study showed that elevated PCT was able to predict an increase in adverse events but not mortality[30,31]. The correlation of CRP with prognosis in CAP has varied with some studies demonstrating prognostic value of initial CRP while other studies demonstrate the prognostic ability of CRP trend but not initial measurement[32-34]. A

Table 1 Summary of current evidence on biomarkers and their role in the evaluation and management of community acquired pneumonia[22]

Role	Biomarker
Diagnosis	CRP, PCT, Ang 1, Ang 2
Severity of illness	CRP, PCT, Ang 1, Ang 2, Pro-ADM, Pro-ANP, Pro-VNP, SP-D, YKL-40, CCL 18, Endocan, NETs, FGF21,
Clinical instability	CRP, PCT, NETs, FGF21
De-escalation antibiotic	PCT
Prognostication	CRP, PCT, Ang 1, Ang 2, Pro-ADM, Pro-ANP, Pro-VNP, SP-D, YKL-40, CCL 18, NETs, FGF21

CRP: C-reactive protein; PCT: Procalcitonin; Ang 1: Barrier stabilizing angiopoietin 1; Ang 2: Barrier stabilizing angiopoietin 2; pro-ADM: Pro-adrenomedullin; pro-ANP: Pro-atrial natriuretic peptide; pro-VNP: pro-vasopressin; SP-D: Surfactant protein-D; YKL-40: Human cartilage glycoprotein YKL-40; CCL18: Chemokine ligand 18; NET: Neutrophil extracellular trap; FGF21: Fibroblast growth factor 21.

recent prospective observational study evaluated the natural history of CRP in hospitalized patients with CAP, and showed that CRP at day 3 and 5 as opposed to initial CRP measurement, predicted mortality[32]. One study even demonstrated that lack of CRP decline regardless of initial value was predictive of 30-day mortality[35]. A recent study compared independent prognostication for PCT, CRP, and three pneumonia severity scores (Pneumonia Severity Index, CURB-65, IDSA/ATS defined severe CAP) and three mortality prediction tools [Acute Physiology Chronic Health Evaluation II, Sequential Organ Failure Assessment (SOFA), and quick SOFA]. AUC for each clinical prediction tool was similar to PCT and slightly higher than CRP (AUC range of pneumonia severity scores 0.77-0.87; AUC range of mortality scores 0.81-0.85; AUC for PCT 0.83; AUC for CRP 0.77)[36]. With justification from prior studies demonstrating improved predictability with combination clinical predictor tools as well as CRP and/or PCT levels, a study proposed a new clinical decision tool for in hospital mortality in patients with severe CAP that incorporated previous prediction tool elements in conjunction with CRP[37].

In a large multi-center randomized control trial, evaluating steroid treatment in hospitalized patients with severe community-acquired pneumonia (CAP), an inclusion criterion of CRP > 150 mg/L on admission was utilized. The results of this study demonstrate a reduction in treatment failure in the steroid group compared with placebo and indicates that, CRP may be a useful tool to help identify the population that may benefit from adjunctive corticosteroid therapy[17]. In addition, CRP may have the potential to help guide duration of treatment as steroid therapy has been shown to decrease the level of CRP[38]. PCT has been used to guide initiation and duration of antibiotic therapy without worse outcomes but has not been used to guide treatment with corticosteroids or other anti-inflammatory specific treatments[39-41]. Other less studied biomarkers are listed in Table 1.

Cytokines in pneumonia

Elevated pro-inflammatory cytokine (include IL-1, 6, and 8; TNF-alpha; and macrophage inflammatory protin-1beta) levels in CAP are indicative of a hyper-inflammatory phenotype and are associated with increased disease severity, length of ICU and hospital stay, ventilator days, and mortality[7,42,43]. This phenotype may benefit from tailored treatments such as corticosteroids[17]. While cytokine panels may accurately identify the hyper-inflammatory phenotype, these panels are expensive, not universally available, and have a slow turn-around time that limits their ability to help guide potential treatments. Correlation of the natural history of CRP in relation to these cytokine patterns may allow for CRP to be a surrogate of these more expensive and cumbersome diagnostic panels.

Biomarkers in ARDS

Similar to CAP, biomarkers have the potential to aid in diagnosis, risk stratification, prognostication, and treatment response in ARDS. A wide variety of biomarkers have been studied in the ARDS population and many have been found to correlate with worse outcomes[44] (Table 2). A combination of biomarkers that pull from multiple areas described in conjunction with clinical predictors was found to be superior to any single component at mortality prediction[45].

Cytokines in ARDS

Inflammatory cytokines have been extensively studied in ARDS and have proven useful at identifying hyper-inflammatory phenotypes. Utilizing latent class analysis and cytokine panels consisting of protein C, plasminogen activator inhibitor-1 (PAI-1),

Table 2 Biomarkers in acute respiratory distress syndrome[44]

Pathways	Biomarkers	
Epithelial	RAGE	
	SP-D	
	KL-6	
	CC16	
	KGF	
Endothelial	Ang-1/2	
	vWF	
	VEGF	
Inflammatory	Pro-inflammatory	IL-1β
		IL-6
		TNFα
		IL-8
		IL-18
	Anti-Inflammatory	ILRA
		sTNF-RI/II
		IL-10
Coagulation and Fibrinolysis	PAI-1	

RAGE: Receptor for advanced glycation end-product; SP-D: Serum surfactant protein D; KL-6: Kreb von den Lungen-6; CC16: Clara cell secretory protein; KGF: Keratinocyte growth factor; Ang 1/2: Barrier stabilizing angiopoietin 1/2; vWF: Von willebrand factor; VEGF: Vascular endothelial growth factor; IL: Interleukin; sTNF-RI/II: Soluble tissue necrosis factor receptor I/II; PAI-1: Plasminogen activator inhibitor-a.

IL-6 and 8, TNF receptor-I, intercellular adhesion molecule-1 (ICAM-1), surfactant protein D, and von Willebrand factor antigen, Calfee *et al*[8] identified two ARDS phenotypes, a hyper and hypo-inflammatory type. The hyper-inflammatory phenotype was associated with increased inflammatory biomarker levels (IL-6 and 8, TNFr1, PAI-1, and ICAM-1) vasopressor use, prevalence of sepsis, acidosis, and 90-d mortality, and decreased ventilator and organ failure free days. Furthermore, a high PEEP strategy was associated with a significant decrease in mortality in the hyper-inflammatory group suggesting a possible therapeutic implication of distinguishing phenotypes[8]. These two types persisted over time with > 94% of patients remaining within their initial phenotype by hospital day three[46]. A follow up study with 2 distinct cohorts demonstrated increased levels of markers of epithelial cell injury with decreased levels of markers of endothelial injury in direct ARDS (defined as those with pulmonary cause such as pneumonia) compared with indirect ARDS (caused by non-pulmonary etiologies such as sepsis)[47]. To stratify even further, inflammatory biomarkers have been shown to be elevated in mixed ICU patients but not in trauma patients[48-50]. More recently, a study utilizing logistic regression, evaluated 20 biomarkers including those in the inflammatory, coagulation, and endothelial activation categories and again identified a hyper and hypo-inflammatory phenotype with the hyper-inflammatory phenotype demonstrating higher ICU mortality. Furthermore, it was discovered that a mere 4 biomarkers (IL-6, interferon gamma, angiopoetin 1/2 and PAI-1) could be used to identify the hyper-inflammatory phenotype (AUC 0.98)[51].

CRP and PCT in ARDS

The combination of PCT and CRP have been shown to correlate with severity of disease in patients with ARDS however, this is not true for either biomarker independently, and even less so for CRP[52]. However, serial CRP levels have been shown to correlate with treatment response to corticosteroids[53]. In addition, and in agreement with previous studies that found higher levels of inflammatory biomarkers in indirect ARDS, PCT levels are significantly higher in ARDS patients with sepsis making it a useful tool in identification of this population[54].

CURRENT EVIDENCE ON ADJUNCT ANTI-INFLAMMATORY THERAPIES

Early antimicrobial therapy and lung protective ventilation are essential management strategies in pneumonia and ARDS. In addition early neuromuscular blockade has been associated with improved survival and decreased ventilator days in severe ARDS[55]. As antimicrobial therapy alone is insufficient to curb an exaggerated inflammatory response, several studies have evaluated the use of anti-inflammatory agents including corticosteroids in these conditions.

Corticosteroids

Corticosteroids have wide-ranging therapeutic application in the critically ill, particularly as anti-inflammatory agents for a variety of acute illnesses. Corticosteroids bind to glucocorticoid receptors intracellularly prompting genomic signaling with subsequent effects on gene transcription and post-translation[56]. These result in downstream inhibition and blockade of a variety of pro-inflammatory mediators including ILs, TNF nuclear factor-kB, and suppression of inflammatory eicosanoids and cyclooxygenase 2.

Insufficient suppression of nuclear factor-kB and increased levels of pro-inflammatory cytokines are thought to be a major driver of pulmonary inflammation in ARDS[57-59] and severe CAP[60] associated with worse outcomes[61]. Therefore the use of corticosteroids to blunt these effects has been proposed[62,63]. Translational efforts of these hypotheses however have been inconsistent in demonstrating clinical benefit.

CAP

Early studies and subsequent meta-analyses found improvements in mortality, ventilator-free days, time to clinical stabilization, and reduced lengths of stays[64-66]. The recent society of critical care medicine (SCCM)/ European society of intensive care medicine (ESICM) guidelines thus suggest the use of adjunctive corticosteroids in hospitalized patients with CAP[67].

Unfortunately, these studies included heterogeneous populations and more importantly patients with CAP of wide-ranging severities. Nonetheless, there appeared to be early signal that patients with severe CAP may be those who benefit greatest from corticosteroids. A more contemporary meta-analysis of nine randomized controlled trials and six observational studies found no difference in survival, even in patients with severe CAP[68]. Interestingly, progression to ARDS was reduced in corticosteroid recipients. Furthermore, an individual patient data meta-analysis of six studies found corticosteroids reduced time to clinical stabilization and time in the hospital, but had no effects on survival, regardless of severity of the disease[69]. More recently, a meta-analysis of ten studies of severe CAP found corticosteroids were associated with improved in-hospital survival, but no clinical effect or differences in ventilator duration[70].

The ESCAPe trial a multicenter, randomized controlled study in patients with severe CAP requiring ICU admission who met IDSA/ATS guideline criteria (NCT01283009) was recently concluded and results due to be published. Patients were randomized to methylprednisolone 40 mg per day for 7 d followed by 20 mg per d for 7 d followed by 12 mg per day for 6 d followed by 4 mg per day for 6 d or placebo with a primary outcome of 60-d all-cause mortality.

Corticosteroid use in pathogen-specific CAPs has had somewhat more consistent findings. Studies of corticosteroids for CAP from influenza have rather consistently shown delayed viral clearance and increased mortality[71]. While corticosteroids provide considerable mortality benefit in CAP from *Pneumocystis* in HIV-positive individuals[72], their benefit in other immune-suppressed hosts without HIV has not been substantiated[73]. Corticosteroid use in CAP from *Aspergillus* has shown increased mortality amongst hematopoietic cell transplant recipients[74,75], whereas solid organ transplant recipients have reduced mortality[76].

Because of their propensity to induce hyperglycemia, neuropsychiatric effects, immune-suppression and thereby potentially increased infection, suppressed wound healing, sodium retention, among other adverse effects[56], judicious use of corticosteroids in the critically ill - a population already at high risk of poor outcome - is becoming increasingly more important. Use of biomarkers may therefore inform steroid use, dosing and duration in patients with severe CAP and may potentially provide individualized selection of patients most likely to benefit. However, evaluation of contemporary clinical practice reveals corticosteroid use in CAP is not consistent with CRP and PCT concentrations[77], and requires further investigation.

ARDS

A major contributor to the controversy of using corticosteroids for treatment of ARDS is the heterogeneity of studies published, wherein different dosing strategies are used, timing of initiation of steroids varies, outcomes studied are different, and the evolution of identifying and classifying the syndrome overtime. While a meta-

analysis of nine studies found increase ventilator-free days but did not demonstrate survival benefit[78], a subsequent individual patient data analysis and trial level meta-analysis showed prolonged corticosteroids increased both survival and ventilator-free days[79]. More recently, a study of hydrocortisone initiated within 12 hours of severe sepsis-associated ARDS found improved oxygenation but not time to liberation of the ventilator or survival[80].

Timing of corticosteroid initiation may be an important consideration in ARDS. The ARDSNet trial randomized patients with ARDS that was persistent beyond 7 d and found improved oxygenation and ventilator compliance resulting in increased ventilator-free days, but again, no survival benefit[81]. More importantly, when corticosteroids were initiated late after ARDS onset (defined by 14 d), they were associated with increased mortality. Other studies have had similar findings where greater survival and ventilator-free days were observed if corticosteroids were initiated within 72 h[53]. When concomitant pneumonia is present, initiation of corticosteroids within 12 h may result in more beneficial outcomes including reduced need for and duration on the ventilator and reduced hospital mortality[82].

Based on this cumulative evidence, the recent SCCM/ESICM guidelines suggests the use of corticosteroid in patients with early moderate to severe ARDS within 14 d of onset[67].

The DEXA-ARDS trial a multicenter, randomized controlled study in patients with moderate to severe ARDS persistent beyond 24 h was recently concluded and results due to be published[83]. Patients were randomized to dexamethasone 20 mg per day for 5 d followed by 10 mg per day for 5 d or placebo with ventilator-free days as primary outcome.

OTHER ANTI-INFLAMMATORY THERAPIES

Many different pharmacotherapies exerting anti-inflammatory actions have been mechanistically believed to provide benefits for pulmonary inflammation in ARDS and CAP. The majority of these therapies have failed to show clinical benefit, including statins[84], neutrophil elastase inhibitors[85], and ibuprofen[86]. An open-label study of moderate to severe ARDS found improved oxygenation at 48 h and reductions in inflammatory markers with use of inhaled sevoflurane[87].

Anti-platelet agents have been proposed to suppress neutrophil-recruitment induced by platelet activation. Early observational studies found a signal of aspirin use prior to admission to the hospital reduced progression to ARDS[88,89]. In a randomized study, early administration of aspirin to patients at risk of ARDS did not reduce the risk of ARDS[90]. There have been no investigations of aspirin for the treatment of those who have already developed ARDS.

Macrolide antimicrobials have been shown to suppress proinflammatory actions of nuclear factor-kB and inhibition of the nitric oxide pathway-driven inflammatory effects[91]. In an observational ARDS study, LARMA, a subset of patients who received macrolide antimicrobials as part of their clinical management had a signal towards improved long-term mortality[92], though these benefits have not been substantiated in larger, controlled studies.

The PETAL network recently completed a study evaluating the effect of early vitamin D3 administration in patients at high risk of ARDS and is awaiting release of results (NCT03096314). A study evaluating the efficacy, safety, and effects on inflammatory biomarkers of inhaled carbon monoxide in ARDS will be recruiting soon (NCT03799874).

FUTURE DIRECTIONS

In the era of precision medicine, biomarkers have the potential to guide disease specific evaluation and management strategies in critically ill patients with CAP and ARDS with the goal of improvement in outcomes of both conditions and early ARDS prevention. The ideal biomarker should be accurate, reproducible[22], detected early[44], clearly reflect the degree of inflammation, response to treatment[25] and trajectory of illness, and identify patients at risk of worse outcomes[93]. Furthermore, an ideal biomarker in pneumonia and ARDS should be inexpensive, easily available, rapidly analyzable and consistent across all groups of patients for generalizability to be useful in clinical practice.

Pragmatic clinical trials with an adaptive design are needed to further define the roles of inflammatory biomarkers (individually or as a panel) as predictive and/or prognostic enrichment tools as well as therapeutic guides in acute pulmonary

inflammation in critically ill patients.

CONCLUSION

In addition to early antibiotics, safe lung ventilation strategies and neuromuscular blockade, corticosteroids are the only anti-inflammatory medications with potential benefits in these conditions. Inflammatory biomarkers have been used for early diagnosis, assessment of severity, and prognostication in CAP and ARDS. The use of biomarkers for patient selection and for guiding adjunct anti-inflammatory treatment is appealing however, further studies are needed to define their role in clinical practice.

REFERENCES

1 **Moldoveanu B**, Otmishi P, Jani P, Walker J, Sarmiento X, Guardiola J, Saad M, Yu J. Inflammatory mechanisms in the lung. *J Inflamm Res* 2009; **2**: 1-11 [PMID: 22096348 DOI: 10.2147/JIR.S4385]
2 **Ramirez JA**, Wiemken TL, Peyrani P, Arnold FW, Kelley R, Mattingly WA, Nakamatsu R, Pena S, Guinn BE, Furmanek SP, Persaud AK, Raghuram A, Fernandez F, Beavin L, Bosson R, Fernandez-Botran R, Cavallazzi R, Bordon J, Valdivieso C, Schulte J, Carrico RM; University of Louisville Pneumonia Study Group. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. *Clin Infect Dis* 2017; **65**: 1806-1812 [PMID: 29020164 DOI: 10.1093/cid/cix647]
3 **Kochanek KD**, Murphy SL, Xu J, Tejada-Vera B. Deaths: Final Data for 2014. *Natl Vital Stat Rep* 2016; **65**: 1-122 [PMID: 27378572]
4 **Storms AD**, Chen J, Jackson LA, Nordin JD, Naleway AL, Glanz JM, Jacobsen SJ, Weintraub ES, Klein NP, Gargiullo PM, Fry AM. Rates and risk factors associated with hospitalization for pneumonia with ICU admission among adults. *BMC Pulm Med* 2017; **17**: 208 [PMID: 29246210 DOI: 10.1186/s12890-017-0552-x]
5 **Bellani G**, Laffey JG, Pham T, Fan E; LUNG SAFE Investigators and the ESICM Trials Group. The LUNG SAFE study: a presentation of the prevalence of ARDS according to the Berlin Definition! *Crit Care* 2016; **20**: 268 [PMID: 27608629 DOI: 10.1186/s13054-016-1443-x]
6 **Restrepo MI**, Mortensen EM, Velez JA, Frei C, Anzueto A. A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. *Chest* 2008; **133**: 610-617 [PMID: 17989157 DOI: 10.1378/chest.07-1456]
7 **Martínez R**, Menéndez R, Reyes S, Polverino E, Cillóniz C, Martínez A, Esquinas C, Filella X, Ramírez P, Torres A. Factors associated with inflammatory cytokine patterns in community-acquired pneumonia. *Eur Respir J* 2011; **37**: 393-399 [PMID: 20595152 DOI: 10.1183/09031936.00040710]
8 **Calfee CS**, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014; **2**: 611-620 [PMID: 24853585 DOI: 10.1016/S2213-2600(14)70097-9]
9 **Adler KB**, Fischer BM, Wright DT, Cohn LA, Becker S. Interactions between respiratory epithelial cells and cytokines: relationships to lung inflammation. *Ann N Y Acad Sci* 1994; **725**: 128-145 [PMID: 8030984 DOI: 10.1111/j.1749-6632.1994.tb00275.x]
10 **Kaisho T**, Akira S. Toll-like receptor function and signaling. *J Allergy Clin Immunol* 2006; **117**: 979-87; quiz 988 [PMID: 16675322 DOI: 10.1016/j.jaci.2006.02.023]
11 **Toossi Z**, Hirsch CS, Hamilton BD, Knuth CK, Friedlander MA, Rich EA. Decreased production of TGF-beta 1 by human alveolar macrophages compared with blood monocytes. *J Immunol* 1996; **156**: 3461-3468 [PMID: 8617974]
12 **Pierrakos C**, Karanikolas M, Scolletta S, Karamouzos V, Velissaris D. Acute respiratory distress syndrome: pathophysiology and therapeutic options. *J Clin Med Res* 2012; **4**: 7-16 [PMID: 22383921 DOI: 10.4021/jocmr761w]
13 **Windsor AC**, Mullen PG, Fowler AA, Sugerman HJ. Role of the neutrophil in adult respiratory distress syndrome. *Br J Surg* 1993; **80**: 10-17 [PMID: 8428262 DOI: 10.1002/bjs.1800800106]
14 **Gadek JE**, Pacht ER. The interdependence of lung antioxidants and antiprotease defense in ARDS. *Chest* 1996; **110**: 273S-277S [PMID: 8989164 DOI: 10.1378/chest.110.6_Supplement.273S]
15 **Moine P**, McIntyre R, Schwartz MD, Kaneko D, Shenkar R, Le Tulzo Y, Moore EE, Abraham E. NF-kappaB regulatory mechanisms in alveolar macrophages from patients with acute respiratory distress syndrome. *Shock* 2000; **13**: 85-91 [PMID: 10670837 DOI: 10.1097/00024382-200013020-00001]
16 **Amur S**. Biomarker Terminology: Speaking The Same Language [Internet]. 2019. Available from: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/UCM533161.pdf
17 **Torres A**, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, Gabarrús A, Sellarés J, Restrepo MI, Anzueto A, Niederman MS, Agustí C. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015; **313**: 677-686 [PMID: 25688779 DOI: 10.1001/jama.2015.88]
18 **Tillett WS**, Francis T. SEROLOGICAL REACTIONS IN PNEUMONIA WITH A NON-PROTEIN SOMATIC FRACTION OF PNEUMOCOCCUS. *J Exp Med* 1930; **52**: 561-571 [PMID: 19869788 DOI: 10.1084/jem.52.4.561]
19 **Male D**, Brostoff J, Roth D. Chapter 6: Mechanisms of Innate Injury. In: Immunology. 8th ed. Elsevier 2013;
20 **Chernecky CC**, Berger BJ. Laboratory Tests and Diagnostic Procedures. In: Laboratory tests and diagnostic procedures. 6th ed. St. Louis, MO: Elsevier Saunders; 2013;
21 **Ballou SP**, Kushner I. C-reactive protein and the acute phase response. *Adv Intern Med* 1992; **37**: 313-336 [PMID: 1558000]
22 **Sibila O**, Restrepo MI. Biomarkers in community-acquired pneumonia: still searching for the one. *Eur*

Respir J 2019; 53 [PMID: 30819808 DOI: 10.1183/13993003.02469-2018]
23 **Jin M**, Khan AI. Procalcitonin: Uses in the Clinical Laboratory for the Diagnosis of Sepsis. *Lab Med* 2010; **41**: 173-177 [DOI: 10.1309/LMQ2GRR4QLFKHCH9]
24 **Gilbert DN**. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. *J Clin Microbiol* 2010; **48**: 2325-2329 [PMID: 20421436 DOI: 10.1128/JCM.00655-10]
25 **Shaddock EJ**. How and when to use common biomarkers in community-acquired pneumonia. *Pneumonia (Nathan)* 2016; **8**: 17 [PMID: 28702296 DOI: 10.1186/s41479-016-0017-7]
26 **Amour J**, Birenbaum A, Langeron O, Le Manach Y, Bertrand M, Coriat P, Riou B, Bernard M, Hausfater P. Influence of renal dysfunction on the accuracy of procalcitonin for the diagnosis of postoperative infection after vascular surgery. *Crit Care Med* 2008; **36**: 1147-1154 [PMID: 18379240 DOI: 10.1097/CCM.0b013e3181692966]
27 **Müller B**, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, Nusbaumer C, Tamm M, Christ-Crain M. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infect Dis* 2007; **7**: 10 [PMID: 17335562 DOI: 10.1186/1471-2334-7-10]
28 **Méndez R**, Menéndez R, Cillóniz C, Amara-Elori I, Amaro R, González P, Posadas T, Gimeno A, España PP, Almirall J, Torres A. Initial Inflammatory Profile in Community-acquired Pneumonia Depends on Time since Onset of Symptoms. *Am J Respir Crit Care Med* 2018; **198**: 370-378 [PMID: 29509439 DOI: 10.1164/rccm.201709-1908OC]
29 **Keramat F**, Ghasemi Basir HR, Abdoli E, Shafiei Aghdam A, Poorolajal J. Association of serum procalcitonin and C-reactive protein levels with CURB-65 criteria among patients with community-acquired pneumonia. *Int J Gen Med* 2018; **11**: 217-223 [PMID: 29942144 DOI: 10.2147/IJGM.S165190]
30 **Krüger S**, Ewig S, Marre R, Papassotiriou J, Richter K, von Baum H, Suttorp N, Welte T; CAPNETZ Study Group. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J* 2008; **31**: 349-355 [PMID: 17959641 DOI: 10.1183/09031936.00054507]
31 **Schuetz P**, Suter-Widmer I, Chaudri A, Christ-Crain M, Zimmerli W, Mueller B; Procalcitonin-Guided Antibiotic Therapy and Hospitalisation in Patients with Lower Respiratory Tract Infections (ProHOSP) Study Group. Prognostic value of procalcitonin in community-acquired pneumonia. *Eur Respir J* 2011; **37**: 384-392 [PMID: 20595156 DOI: 10.1183/09031936.00035610]
32 **Guo S**, Mao X, Liang M. The moderate predictive value of serial serum CRP and PCT levels for the prognosis of hospitalized community-acquired pneumonia. *Respir Res* 2018; **19**: 193 [PMID: 30285748 DOI: 10.1186/s12931-018-0877-x]
33 **Ito A**, Ishida T, Tachibana H, Ito Y, Takaiwa T. Serial procalcitonin levels for predicting prognosis in community-acquired pneumonia. *Respirology* 2016; **21**: 1459-1464 [PMID: 27398948 DOI: 10.1111/resp.12846]
34 **Farah R**, Khamisy-Farah R, Makhoul N. Consecutive Measures of CRP Correlate with Length of Hospital Stay in Patients with Community-Acquired Pneumonia. *Isr Med Assoc J* 2018; **20**: 345-348 [PMID: 29911753]
35 **Andersen SB**, Baunbæk Egelund G, Jensen AV, Petersen PT, Rohde G, Ravn P. Failure of CRP decline within three days of hospitalization is associated with poor prognosis of Community-acquired Pneumonia. *Infect Dis (Lond)* 2017; **49**: 251-260 [PMID: 27887037 DOI: 10.1080/23744235.2016.1253860]
36 **Kim MW**, Lim JY, Oh SH. Mortality prediction using serum biomarkers and various clinical risk scales in community-acquired pneumonia. *Scand J Clin Lab Invest* 2017; **77**: 486-492 [PMID: 28678546 DOI: 10.1080/00365513.2017.1344298]
37 **Wang X**, Jiao J, Wei R, Feng Y, Ma X, Li Y, Du Y. A new method to predict hospital mortality in severe community acquired pneumonia. *Eur J Intern Med* 2017; **40**: 56-63 [PMID: 28320569 DOI: 10.1016/j.ejim.2017.02.013]
38 **Fernández-Serrano S**, Dorca J, Garcia-Vidal C, Fernández-Sabé N, Carratalà J, Fernández-Agüera A, Corominas M, Padrones S, Gudiol F, Manresa F. Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. *Crit Care* 2011; **15**: R96 [PMID: 21406101 DOI: 10.1186/cc10103]
39 **Christ-Crain M**, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Müller B. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; **363**: 600-607 [PMID: 14987884 DOI: 10.1016/S0140-6736(04)15591-8]
40 **Christ-Crain M**, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Müller B. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006; **174**: 84-93 [PMID: 16603606 DOI: 10.1164/rccm.200512-1922OC]
41 **Schuetz P**, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, Neidert S, Fricker T, Blum C, Schild U, Regez K, Schoenenberger R, Henzen C, Bregenzer T, Hoess C, Krause M, Bucher HC, Zimmerli W, Mueller B; ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009; **302**: 1059-1066 [PMID: 19738090 DOI: 10.1001/jama.2009.1297]
42 **Fernández-Serrano S**, Dorca J, Coromines M, Carratalà J, Gudiol F, Manresa F. Molecular inflammatory responses measured in blood of patients with severe community-acquired pneumonia. *Clin Diagn Lab Immunol* 2003; **10**: 813-820 [PMID: 12965910 DOI: 10.1128/CDLI.10.5.813-820.2003]
43 **Ramírez P**, Ferrer M, Martí V, Reyes S, Martínez R, Menéndez R, Ewig S, Torres A. Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia. *Crit Care Med* 2011; **39**: 2211-2217 [PMID: 21705887 DOI: 10.1097/CCM.0b013e3182257445]
44 **Spadaro S**, Park M, Turrini C, Tunstall T, Thwaites R, Mauri T, Ragazzi R, Ruggeri P, Hansel TT, Caramori G, Volta CA. Biomarkers for Acute Respiratory Distress syndrome and prospects for personalised medicine. *J Inflamm (Lond)* 2019; **16**: 1 [PMID: 30675131 DOI: 10.1186/s12950-018-0202-y]
45 **Ware LB**, Koyama T, Billheimer DD, Wu W, Bernard GR, Thompson BT, Brower RG, Standiford TJ, Martin TR, Matthay MA; NHLBI ARDS Clinical Trials Network. Prognostic and pathogenetic value of combining clinical and biochemical indices in patients with acute lung injury. *Chest* 2010; **137**: 288-296 [PMID: 19858233 DOI: 10.1378/chest.09-1484]
46 **Delucchi K**, Famous KR, Ware LB, Parsons PE, Thompson BT, Calfee CS; ARDS Network. Stability of ARDS subphenotypes over time in two randomised controlled trials. *Thorax* 2018; **73**: 439-445 [PMID: 29477989 DOI: 10.1136/thoraxjnl-2017-211090]

47 **Calfee CS**, Janz DR, Bernard GR, May AK, Kangelaris KN, Matthay MA, Ware LB. Distinct molecular phenotypes of direct vs indirect ARDS in single-center and multicenter studies. *Chest* 2015; **147**: 1539-1548 [PMID: 26033126 DOI: 10.1378/chest.14-2454]

48 **Meade P**, Shoemaker WC, Donnelly TJ, Abraham E, Jagels MA, Cryer HG, Hugli TE, Bishop MH, Wo CC. Temporal patterns of hemodynamics, oxygen transport, cytokine activity, and complement activity in the development of adult respiratory distress syndrome after severe injury. *J Trauma* 1994; **36**: 651-657 [PMID: 8189465 DOI: 10.1097/00005373-199405000-00009]

49 **Cepkova M**, Brady S, Sapru A, Matthay MA, Church G. Biological markers of lung injury before and after the institution of positive pressure ventilation in patients with acute lung injury. *Crit Care* 2006; **10**: R126 [PMID: 16956410 DOI: 10.1186/cc5037]

50 **Nakamura T**, Sato E, Fujiwara N, Kawagoe Y, Maeda S, Yamagishi S. Increased levels of soluble receptor for advanced glycation end products (sRAGE) and high mobility group box 1 (HMGB1) are associated with death in patients with acute respiratory distress syndrome. *Clin Biochem* 2011; **44**: 601-604 [PMID: 21211520 DOI: 10.1016/j.clinbiochem.2010.12.014]

51 **Bos LD**, Schouten LR, van Vught LA, Wiewel MA, Ong DSY, Cremer O, Artigas A, Martin-Loeches I, Hoogendijk AJ, van der Poll T, Horn J, Juffermans N, Calfee CS, Schultz MJ; MARS consortium. Identification and validation of distinct biological phenotypes in patients with acute respiratory distress syndrome by cluster analysis. *Thorax* 2017; **72**: 876-883 [PMID: 28450529 DOI: 10.1136/thoraxjnl-2016-209719]

52 **Yu Z**, Ji M, Hu X, Yan J, Jin Z. [Value of procalcitonin on predicting the severity and prognosis in patients with early ARDS: a prospective observation study]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2017; **29**: 34-38 [PMID: 28459401 DOI: 10.3760/cma.j.issn.2095-4352.2017.01.008]

53 **Meduri GU**, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, Gibson M, Umberger R. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest* 2007; **131**: 954-963 [PMID: 17426195 DOI: 10.1378/chest.06-2100]

54 **Brunkhorst FM**, Eberhard OK, Brunkhorst R. Discrimination of infectious and noninfectious causes of early acute respiratory distress syndrome by procalcitonin. *Crit Care Med* 1999; **27**: 2172-2176 [PMID: 10548201 DOI: 10.1097/00003246-199910000-00016]

55 **Papazian L**, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; **363**: 1107-1116 [PMID: 20843245 DOI: 10.1056/NEJMoa1005372]

56 **Rhen T**, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med* 2005; **353**: 1711-1723 [PMID: 16236742 DOI: 10.1056/NEJMra050541]

57 **Franchimont D**, Kino T, Galon J, Meduri GU, Chrousos G. Glucocorticoids and inflammation revisited: the state of the art. NIH clinical staff conference. *Neuroimmunomodulation* 2002; **10**: 247-260 [PMID: 12759562 DOI: 10.1159/000069969]

58 **Meduri GU**, Annane D, Chrousos GP, Marik PE, Sinclair SE. Activation and regulation of systemic inflammation in ARDS: rationale for prolonged glucocorticoid therapy. *Chest* 2009; **136**: 1631-1643 [PMID: 19801579 DOI: 10.1378/chest.08-2408]

59 **Thompson BT**, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med* 2017; **377**: 562-572 [PMID: 28792873 DOI: 10.1056/NEJMra1608077]

60 **Puren AJ**, Feldman C, Savage N, Becker PJ, Smith C. Patterns of cytokine expression in community-acquired pneumonia. *Chest* 1995; **107**: 1342-1349 [PMID: 7750329 DOI: 10.1378/chest.107.5.1342]

61 **Meduri GU**, Headley S, Kohler G, Stentz F, Tolley E, Umberger R, Leeper K. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. *Chest* 1995; **107**: 1062-1073 [PMID: 7705118 DOI: 10.1378/chest.107.4.1062]

62 **Meduri GU**, Marik PE, Chrousos GP, Pastores SM, Arlt W, Beishuizen A, Bokhari F, Zaloga G, Annane D. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. *Intensive Care Med* 2008; **34**: 61-69 [PMID: 18000649 DOI: 10.1007/s00134-007-0933-3]

63 **Confalonieri M**, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della Porta R, Giorgio C, Blasi F, Umberger R, Meduri GU. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005; **171**: 242-248 [PMID: 15557131 DOI: 10.1164/rccm.200406-808OC]

64 **Siemieniuk RA**, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, Alexander PE, Fei Y, Vandvik PO, Loeb M, Guyatt GH. Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. *Ann Intern Med* 2015; **163**: 519-528 [PMID: 26258555 DOI: 10.7326/M15-0715]

65 **Horita N**, Otsuka T, Haranaga S, Namkoong H, Miki M, Miyashita N, Higa F, Takahashi H, Yoshida M, Kohno S, Kaneko T. Adjunctive Systemic Corticosteroids for Hospitalized Community-Acquired Pneumonia: Systematic Review and Meta-Analysis 2015 Update. *Sci Rep* 2015; **5**: 14061 [PMID: 26374694 DOI: 10.1038/srep14061]

66 **Marti C**, Grosgurin O, Harbarth S, Combescure C, Abbas M, Rutschmann O, Perrier A, Garin N. Adjunctive Corticotherapy for Community Acquired Pneumonia: A Systematic Review and Meta-Analysis. *PLoS One* 2015; **10**: e0144032 [PMID: 26641253 DOI: 10.1371/journal.pone.0144032]

67 **Pastores SM**, Annane D, Rochwerg B, Corticosteroid Guideline Task Force of SCCM and ESICM. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2018; **46**: 146-148 [PMID: 29095205 DOI: 10.1097/CCM.0000000000002840]

68 **Wan YD**, Sun TW, Liu ZQ, Zhang SG, Wang LX, Kan QC. Efficacy and Safety of Corticosteroids for Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis. *Chest* 2016; **149**: 209-219 [PMID: 26501852 DOI: 10.1378/chest.15-1733]

69 **Briel M**, Spoorenberg SMC, Snijders D, Torres A, Fernandez-Serrano S, Meduri GU, Gabarrús A, Blum CA, Confalonieri M, Kasenda B, Siemieniuk RAC, Boersma W, Bos WJW, Christ-Crain M; Ovidius Study Group; Capisce Study Group; STEP Study Group. Corticosteroids in Patients Hospitalized With Community-Acquired Pneumonia: Systematic Review and Individual Patient Data Metaanalysis. *Clin Infect Dis* 2018; **66**: 346-354 [PMID: 29020323 DOI: 10.1093/cid/cix801]

70 **Wu WF**, Fang Q, He GJ. Efficacy of corticosteroid treatment for severe community-acquired pneumonia: A meta-analysis. *Am J Emerg Med* 2018; **36**: 179-184 [PMID: 28756034 DOI:

10.1016/j.ajem.2017.07.050]
71 **Wieruszewski PM**, Linn DD. Contemporary management of severe influenza disease in the intensive care unit. *J Crit Care* 2018; **48**: 48-55 [PMID: 30172033 DOI: 10.1016/j.jcrc.2018.08.015]
72 **National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia**. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med* 1990; **323**: 1500-1504 [PMID: 2136587 DOI: 10.1056/NEJM199011223232131]
73 **Wieruszewski PM**, Barreto JN, Frazee E, Daniels CE, Tosh PK, Dierkhising RA, Mara KC, Limper AH. Early Corticosteroids for Pneumocystis Pneumonia in Adults Without HIV Are Not Associated With Better Outcome. *Chest* 2018; **154**: 636-644 [PMID: 29705221 DOI: 10.1016/j.chest.2018.04.026]
74 **Nivoix Y**, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Amé S, Fohrer C, Lioure B, Bilger K, Lutun P, Marcellin L, Launoy A, Freys G, Bergerat JP, Herbrecht R. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis* 2008; **47**: 1176-1184 [PMID: 18808352 DOI: 10.1086/592255]
75 **Upton A**, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. *Clin Infect Dis* 2007; **44**: 531-540 [PMID: 17243056 DOI: 10.1086/510592]
76 **Baddley JW**, Andes DR, Marr KA, Kontoyiannis DP, Alexander BD, Kauffman CA, Oster RA, Anaissie EJ, Walsh TJ, Schuster MG, Wingard JR, Patterson TF, Ito JI, Williams OD, Chiller T, Pappas PG. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clin Infect Dis* 2010; **50**: 1559-1567 [PMID: 20450350 DOI: 10.1086/652768]
77 **Odeyemi Y**, Herasevich S, Schwegman A, Barreto E, Gajic O, Yadav H. Biomarker concordant steroid use in critically ill patients with pneumonia. *Crit Care Med* 2019; **47**: 521 [DOI: 10.1097/01.ccm.0000551834.00753.8a]
78 **Peter JV**, John P, Graham PL, Moran JL, George IA, Bersten A. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ* 2008; **336**: 1006-1009 [PMID: 18434379 DOI: 10.1136/bmj.39537.939039.BE]
79 **Meduri GU**, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med* 2016; **42**: 829-840 [PMID: 26508525 DOI: 10.1007/s00134-015-4095-4]
80 **Tongyoo S**, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, Meduri GU. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care* 2016; **20**: 329 [PMID: 27741949 DOI: 10.1186/s13054-016-1511-2]
81 **Steinberg KP**, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; **354**: 1671-1684 [PMID: 16625008 DOI: 10.1056/NEJMoa051693]
82 **Herasevich S**, Odeyemi Y, Wieruszewski P, Gajic O, Yadav H. Timeliness of corticosteroid use in ICU patients with pneumonia and ARDS. *Crit Care Med* 2019; **47**: 557 [DOI: 10.1097/01.ccm.0000551906.96335.48]
83 **Villar J**, Belda J, Añón JM, Blanco J, Pérez-Méndez L, Ferrando C, Martínez D, Soler JA, Ambrós A, Muñoz T, Rivas R, Corpas R, Díaz-Dominguez FJ, Soro M, García-Bello MA, Fernández RL, Kacmarek RM; DEXA-ARDS Network. Evaluating the efficacy of dexamethasone in the treatment of patients with persistent acute respiratory distress syndrome: study protocol for a randomized controlled trial. *Trials* 2016; **17**: 342 [PMID: 27449641 DOI: 10.1186/s13063-016-1456-4]
84 **National Heart, Lung, and Blood Institute ARDS Clinical Trials Network**. Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, Brower RG, Shanholtz C, Rock P, Douglas IS, deBoisblanc BP, Hough CL, Hite RD, Thompson BT. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014; **370**: 2191-2200 [PMID: 24835849 DOI: 10.1056/NEJMoa1401520]
85 **Iwata K**, Doi A, Ohji G, Oka H, Oba Y, Takimoto K, Igarashi W, Gremillion DH, Shimada T. Effect of neutrophil elastase inhibitor (sivelestat sodium) in the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): a systematic review and meta-analysis. *Intern Med* 2010; **49**: 2423-2432 [PMID: 21088343 DOI: 10.2169/internalmedicine.49.4010]
86 **Bernard GR**, Wheeler AP, Russell JA, Schein R, Summer WR, Steinberg KP, Fulkerson WJ, Wright PE, Christman BW, Dupont WD, Higgins SB, Swindell BB. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997; **336**: 912-918 [PMID: 9070471 DOI: 10.1056/NEJM199703273361303]
87 **Jabaudon M**, Boucher P, Imhoff E, Chabanne R, Faure JS, Roszyk L, Thibault S, Blondonnet R, Clairefond G, Guérin R, Perbet S, Cayot S, Godet T, Pereira B, Sapin V, Bazin JE, Futier E, Constantin JM. Sevoflurane for Sedation in Acute Respiratory Distress Syndrome. A Randomized Controlled Pilot Study. *Am J Respir Crit Care Med* 2017; **195**: 792-800 [PMID: 27611637 DOI: 10.1164/rccm.201604-0686OC]
88 **Chen W**, Janz DR, Bastarache JA, May AK, O'Neal HR, Bernard GR, Ware LB. Prehospital aspirin use is associated with reduced risk of acute respiratory distress syndrome in critically ill patients: a propensity-adjusted analysis. *Crit Care Med* 2015; **43**: 801-807 [PMID: 25559436 DOI: 10.1097/CCM.0000000000000789]
89 **Erlich JM**, Talmor DS, Cartin-Ceba R, Gajic O, Kor DJ. Prehospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: a population-based cohort study. *Chest* 2011; **139**: 289-295 [PMID: 20688925 DOI: 10.1378/chest.10-0891]
90 **Kor DJ**, Carter RE, Park PK, Festic E, Banner-Goodspeed VM, Hinds R, Talmor D, Gajic O, Ware LB, Gong MN; US Critical Illness and Injury Trials Group: Lung Injury Prevention with Aspirin Study Group (USCIITG: LIPS-A). Effect of Aspirin on Development of ARDS in At-Risk Patients Presenting to the Emergency Department: The LIPS-A Randomized Clinical Trial. *JAMA* 2016; **315**: 2406-2414 [PMID: 27179988 DOI: 10.1001/jama.2016.6330]
91 **Emmet O'Brien M**, Restrepo MI, Martin-Loeches I. Update on the combination effect of macrolide antibiotics in community-acquired pneumonia. *Respir Investig* 2015; **53**: 201-209 [PMID: 26344609 DOI: 10.1016/j.resinv.2015.05.003]
92 **Walkey AJ**, Wiener RS. Macrolide antibiotics and survival in patients with acute lung injury. *Chest* 2012;

141: 1153-1159 [PMID: 22116799 DOI: 10.1378/chest.11-1908]
93 **Krüger S**, Welte T. Biomarkers in community-acquired pneumonia. *Expert Rev Respir Med* 2012; **6**: 203-214 [PMID: 22455492 DOI: 10.1586/ers.12.6]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Medl 2019 September 11; 8(5): 72-81

DOI: 10.5492/wjccm.v8.i5.72

ISSN 2220-3141 (online)

CASE REPORT

Tuberculosis septic shock, an elusive pathophysiology and hurdles in management: A case report and review of literature

Rashmi Mishra, Harish K Patel, Rakesh Singasani, Trupti Vakde

ORCID number: Rashmi Mishra (0000-0001-6747-6490); Harish Patel (0000-0003-3638-9495); Rakesh Singasani (0000-0001-5094-7663); Trupti Vakde (0000-0002-5154-3051).

Author contributions: All authors have reviewed the literature and contributed to manuscript drafting; Vakde T, Mishra R and Patel HK were responsible for the revision of the manuscript for important intellectual content; All authors issued final approval for the version to be submitted.

Informed consent statement: All patients have deceased, as per the recommendation of the editorial office, the initial consent for the treatment and hospitalization have been uploaded.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2013), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Rashmi Mishra, Pulmonary and Critical Care, Penn Highlands Healthcare, Dubois, PA 15801, United States

Harish K Patel, Division of Gastroenterology, Department of Medicine, Bronx Care Health system, Bronx, NY 10457, United States

Rakesh Singasani, Department of Medicine, SBH Health System, Bronx, NY 10457, United States

Trupti Vakde, Division of Pulmonary and Critical Care, Department of Medicine, Bronx Care Health System, Bronx, NY 10457, United States

Corresponding author: Trupti Vakde, MD, Attending Doctor, Attending Physician, Division of Pulmonary and Critical Care, Department of Medicine, Bronx Care Health System, 1650 Grand concourse, Bronx, NY 10457, United States. tvakde@bronxcare.org
Telephone: +1-718-9601234
Fax: +1-917-7780876

Abstract

BACKGROUND

Tuberculosis (TB) is a rare etiology of the septic shock. Timely administration of the anti-microbial agents has shown mortality benefit. Prompt diagnosis and a high index of suspicion are crucial to the management. We present three cases of TBSS with poor outcome in the majority despite timely and susceptible antibiotic administration.

CASE SUMMARY

Sixty-seven-year-old woman with latent TB presented with fever, cough, and shortness of breath. She was promptly diagnosed with active TB and started on the appropriate anti-microbial regimen; she had a worsening clinical course with septic shock and multi-organ failure after initiation of antibiotics. Thirty-three-year-old man immunocompromised with acquired immune deficiency syndrome presented with fever, anorexia and weight loss. He had no respiratory symptoms, and first chest X-ray was normal. He had enlarged liver, spleen and lymph nodes suspicious for lymphoma. Despite broad-spectrum antibiotics, he succumbed to refractory septic shock and multi-organ failure. It was shortly before his death that anti-TB antimicrobials were initiated based on pathology reports of bone marrow and lymph node biopsies. Forty-nine-year-old woman with asthma and latent TB admitted with cough and shortness of breath. Although Initial sputum analysis was negative, a subsequent broncho-alveolar lavage turned out to be

Manuscript source: Unsolicited manuscript

Received: April 6, 2019
Peer-review started: April 8, 2019
First decision: August 2, 2019
Revised: August 13, 2019
Accepted: August 21, 2019
Article in press: August 21, 2019
Published online: September 11, 2019

P-Reviewer: Mousa HAL
S-Editor: Yan JP
L-Editor: A
E-Editor: Liu MY

positive for acid fast bacilli followed by initiation of susceptible ant-TB regimen. She had a downward spiral clinical course with shock, multi-organ failure and finally death.

CONCLUSION
Worse outcome despite timely initiation of appropriate antibiotics raises suspicion of TB immune reconstitution as a possible pathogenesis for TB septic shock.

Key words: Tuberculosis septic shock; Tuberculosis and immune reconstitution; Tuberculosis in intensive care unit; Case fatality for tuberculosis septic shock; Case report

Core tip: Tuberculosis septic shock is a rare entity. We present three cases of tuberculosis septic shock with varied clinical manifestations. Mycobacterium tuberculosis culture or nucleic acid amplification testing confirmed diagnosis of tuberculosis. All of our presented cases had poor outcome despite timely administration of appropriate anti-tuberculosis regimen. There was clinical and radiological deterioration after administration of anti-microbial agents. This deteriorating clinical course raises a concern for immune reconstitution as possible pathogenesis for tuberculosis septic shock.

Citation: Mishra R, Patel HK, Singasani R, Vakde T. Tuberculosis septic shock, an elusive pathophysiology and hurdles in management: A case report and review of literature. *World J Crit Care Med* 2019; 8(5): 72-81
URL: https://www.wjgnet.com/2220-3141/full/v8/i5/72.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i5.72

INTRODUCTION

Sepsis is a significant burden on healthcare across the globe[1]. In United States, there are 970000 cases of sepsis annually[2]. In United States overall sepsis, related mortality is 12.5%. The severity of sepsis affects outcomes, with 35% mortality in septic shock[2]. Prompt diagnosis and early treatment is key to management. Any delay in antibiotics administration is associated with the worsening of sepsis severity[3].

Martin *et al*[4] analyzed 2.6 million sepsis cases from the premier database in United States, for six years. Fifteen percent of patients did not manifest sepsis at the time of hospitalization. The mortality outcomes were worst in this group of patients. The group of patients with sepsis at presentation have lower mortality. This improved outcome may be attributed to the timely diagnosis and prompt antibiotics administration.

Empiric antibiotic administration within one hour of presentation has been proven to lower sepsis-related mortality[5]. Broad spectrum anti-microbial agents are selected based on the most common gram positive and gram negative bacterial infection[6]. Respiratory tract infection is the most common etiology for sepsis and septic shock[7]. Tuberculosis (TB) is an uncommon but well-recognized etiology of sepsis and is seldom discussed in the western population.

Mycobacterium tuberculosis is an acid-fast bacteria with a predominant pulmonary presentation[8], though not a frequent cause of pneumonia in the western population. Only twenty percent of the cases have a sole extra-pulmonary manifestation[8]. The incidence of TB septic shock (TBSS) though not reported, is sporadic. The Center for Disease Control and Prevention have reported a declining incidence in the diagnosis of TB[9]. The rarity of TBSS makes this case series novel. We describe three cases of TBSS that presented in our institution. Despite the diagnosis of sepsis at presentation, case fatality rate is very high, as opposed to the general expectation in sepsis epidemiology[2]. Each case is unique with its presentation, and this case series provides an excellent opportunity to analyze the demographic features, clinical characteristics, radiologic and laboratory findings as well as the pitfalls in the management of patients with TBSS.

CASE PRESENTATION

Case 1

Chief complaint: A 67-year-old female presented to the emergency department with progressively worsening shortness of breath and fever.

History of present illness: The patient complained of twenty pounds' weight loss over three months. She had shortness of breath, fever and productive cough for a duration of four weeks.

History of past illness: She had medical conditions of hypertension, chronic obstructive pulmonary disease, gastroesophageal reflux disease, gout and a 40-pack year history of smoking. She lived at home and had a history of exposure to TB when she was 9 years old as well as a known positive tuberculin skin test. She had never traveled outside the country.

Physical examination: Her vital signs were significant for low-grade fever of 37.9 °C, heart rate of 110 beats per minute, blood pressure of 165/100 mm of Hg and oxygen saturation of 96% on room air. She had bilateral rales on lung auscultation and rest of the physical exam was unremarkable

Laboratory examinations: Blood analysis was significant for hyponatremia (sodium 118 mEq/L) and anemia (Hemoglobin 7.3g/dL).

Imaging examinations: Chest X-ray and computed tomography (CT) scan on admission showed bilateral patchy infiltrates predominantly in the upper lobes (Figure 1A and B).

Treatment: Ceftriaxone and azithromycin were initiated for community-acquired pneumonia (CAP), and she was admitted to intensive care unit (ICU) for sepsis and hyponatremia. She was also placed in respiratory isolation due to high suspicion for TB. On day 2 of admission, sputum acid fast bacilli (AFB) stain was reported positive, and the patient was started on isoniazid, rifampin, ethambutol, and pyrazinamide (RIPE) for *Mycobacterium tuberculosis*. Human immunodeficiency virus (HIV) test was negative. *Mycobacterium tuberculosis* was confirmed by polymerase chain reaction (PCR) before the final culture report. Subsequently, she became progressively more hypoxic and hypotensive requiring mechanical ventilation and vasopressor support. Chest X-ray after intubation showed worsening of bilateral lung infiltrates (Figure 1C). She developed multi-organ failure secondary to shock including hepatic and renal dysfunction requiring hemodialysis. Patient was also initiated on high dose steroids, and antibiotic coverage was broadened with no significant improvement in hemodynamic status.

Final diagnosis: Septic shock due to *Mycobacterium tuberculosis*.

Outcome and follow up: Due to poor prognosis and no improvement in the patient's condition, the family wished for transfer to hospice care and patient died on day 22 of hospitalization. Final culture and susceptibility reports confirmed sensitivity to RIPE.

Case 2

Chief complaints: A 33-year-old man was called to come to the emergency department for abnormal laboratory results.

History of present illness: In the emergency department he reported subjective fever, poor appetite and weight loss for one month. He also reported diarrhea for past few days but no abdominal pain, nausea, vomiting, cough or shortness of breath.

History of past illness: Patient had known history of HIV/acquired immune deficiency syndrome (AIDS) not adherent to antiretroviral medications with very high viral load and CD4 count of less than 20, past intravenous drug use and active tobacco dependence. He had history of anemia and deep vein thrombosis and was living in a nursing home for few months prior to presentation. He was born in Puerto Rico and came to the Unites States a year ago.

Physical examination upon admission: His vital signs were significant for hypotension with blood pressure of 91/60 mmHg, tachycardia with heart rate of 130 beats per minute and fever with temperature of 39.4 °C. On physical examination he was lethargic and confused. Hypotension initially improved with intravenous fluids

Laboratory examinations: Initial laboratory data was significant for leukocytosis of 31151/μL and hyponatremia (sodium 121 mEq/L).

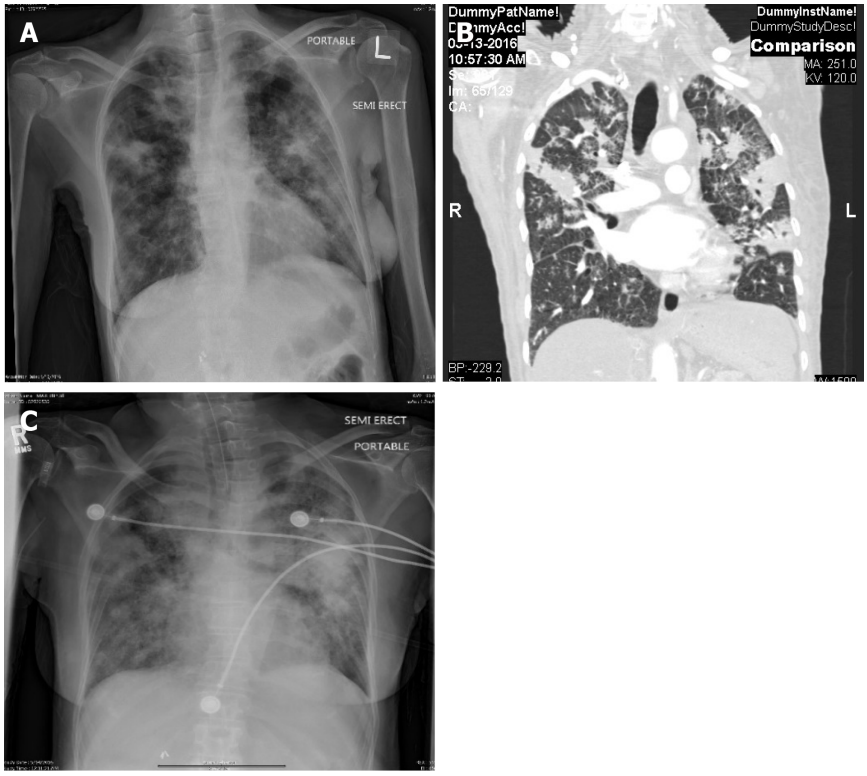


Figure 1 Chest X-ray and computed tomography (case 1). A: Chest X-ray demonstrating the bilateral patchy infiltrates at the time of admission; B: Computed tomography scans of chest with coronal section demonstrating bilateral patchy infiltrates at the time of admission; C: X-ray chest demonstrating worsening of the bilateral infiltrates after intubation and initiation of anti tuberculosis medications.

Imaging examinations: Chest X-ray on admission showed no infiltrates (Figure 2A). Ultrasound of abdomen was significant for hepatosplenomegaly, ascites and enlarged peri-pancreatic lymph nodes

Treatment: Patient was admitted to the critical care unit with a presumptive diagnosis of sepsis and initiated on the broad spectrum antibiotics (vancomycin and piperacillin-tazobactam). He was started on metronidazole for suspected *Clostridium difficile* colitis. Subsequently he developed acute hypoxic respiratory failure and septic shock requiring intubation and vasopressor support. Chest X-ray after intubation showed new bilateral infiltrates (Figure 2B). Blood cultures were negative. He underwent lumbar puncture which showed an opening pressure of 35 cm of H_2O, red blood cell (RBC) of 1825 cells/dL, white blood cell count of 1 cell/dL, glucose of 65 mg/dL and protein 36 mg/dL. In view of significant RBC count in cerebrospinal fluid (CSF) and high opening pressure, he was also initiated on acyclovir as empiric treatment for herpes simplex encephalitis. Broncho alveolar lavage (BAL) was negative for bacterial, viral, fungal and *Pneumocystis jirovecii* cultures. Initial smears for AFB were negative. The CSF bacterial cultures and herpes simplex virus PCR were negative. He was initiated on antiretroviral therapy on day 8 of hospitalization after preliminary cultures were negative. In view of persistent fever spikes and lymphadenopathy, hematology consultation was obtained and patient underwent bone marrow biopsy, and right axillary lymph node biopsy. Caspofungin was added to his antibiotic regimen for refractory septic shock and persistent fever. Bone marrow biopsy was positive for acid fast organisms. Pathology of right axillary lymph node biopsy reported as necrotizing granulomas with mycobacteria. An empiric treatment for *Mycobacterium tuberculosis* and mycobacterium avium complex with Isoniazide, Ethambutol, Rifabutin, pyrazinamide and clarithromycin was initiated awaiting final confirmation

Final diagnosis: Septic shock due to *Mycobacterium tuberculosis*.

Outcome and follow up: Patient died secondary to worsening shock and multi organ failure after 22 d of admission. Sputum, BAL and peritoneal fluid cultures were reported positive for *Mycobacterium tuberculosis* complex post mortem and susceptibility reports confirmed no resistance.

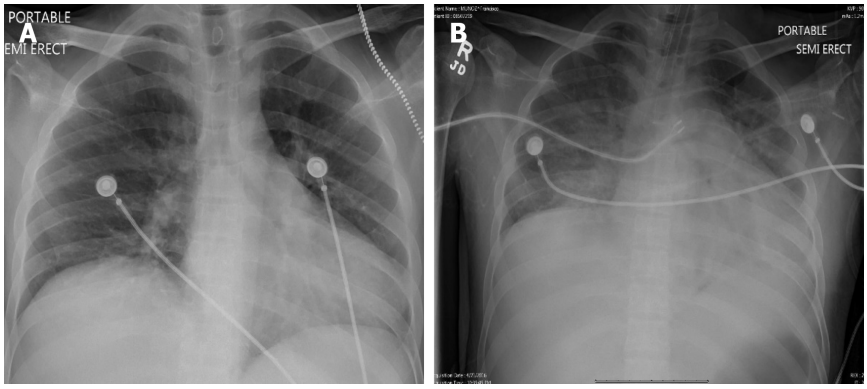


Figure 2 X-ray chest (case 2). A: X-ray chest with no infiltrates at the time of admission; B: X-ray chest with new infiltrates and hypoxia requiring intubation and mechanical ventilation.

Case 3

Chief complaints: A 49-year-old woman presented to the hospital with productive cough for three to four weeks.

History of present illness: Patient presented with worsening cough, shortness of breath and wheezing. She denied fever, chills, weight loss, recent travel or sick contacts.

History of past illness: Her medical conditions included hypertension, latent TB (treated for 6 mo in 2007 as per patient), Asthma and smoking.

Physical examination upon admission: Vital signs were significant for mild tachycardia with heart rate of 114 beats per minute. She was afebrile with normal blood pressure and oxygen saturation of 98% on room air. There was bilateral wheezing on auscultation and rest of the examination was unremarkable.

Laboratory examinations: Initial blood analysis revealed leukocytosis with white blood cell count of 11300 cells/μL. Her electrolytes and liver function tests were normal except a high alkaline phosphatase level of 111 unit/dL.

Imaging examinations: Chest X-ray on admission showed a stable left upper lobe thick walled cavity and new left lower lobe infiltrates in comparison to the chest X-ray done few weeks ago (Figure 3A). CT of the chest was done which revealed additional left lung thick walled cavities and multiple nodules on both sides (Figure 3B).

Treatment: Given the high suspicion for TB she was placed on respiratory isolation, and started on broad spectrum antibiotics with intravenous piperacillin-tazobactam and vancomycin. Three sputum samples were initially negative for AFB. Differential diagnoses included pulmonary TB, atypical mycobacteria and fungal infections. She underwent bronchoscopy, BAL and trans bronchial biopsy. The BAL stains were positive for AFB and mycobacterium TB was identified with DNA probe and subsequent cultures. Cultures from BAL also grew pseudomonas aeruginosa in low colony counts of 1000-9000 CFU/mL. Pseudomonas was pan sensitive. Antibiotics were titrated, with initiation of RIPE and discontinuation of vancomycin.

Final diagnosis: Septic shock due to *Mycobacterium tuberculosis*.

Outcome and follow up: On day 6 of admission, her respiratory status declined to require intubation for hypoxic respiratory failure and transfer to ICU. She developed worsening bilateral infiltrates (Figure 3C), hyponatremia (sodium 125 mEq/L) and septic shock. She remained in shock and died on day 12 of hospitalization.

DISCUSSION

There is ample literature to support the case fatality of TBSS[10]. It is evident that prompt identification and early antibiotic administration improves mortality. The mortality risk factors of TB patient who are critically ill have been identified[11]. However, given the scantiness of TBSS, no standard protocol is constructed to improve the outcomes of this rare entity. We reviewed our cases and analyzed them to determine the hurdles in the management of TBSS. To better understand the

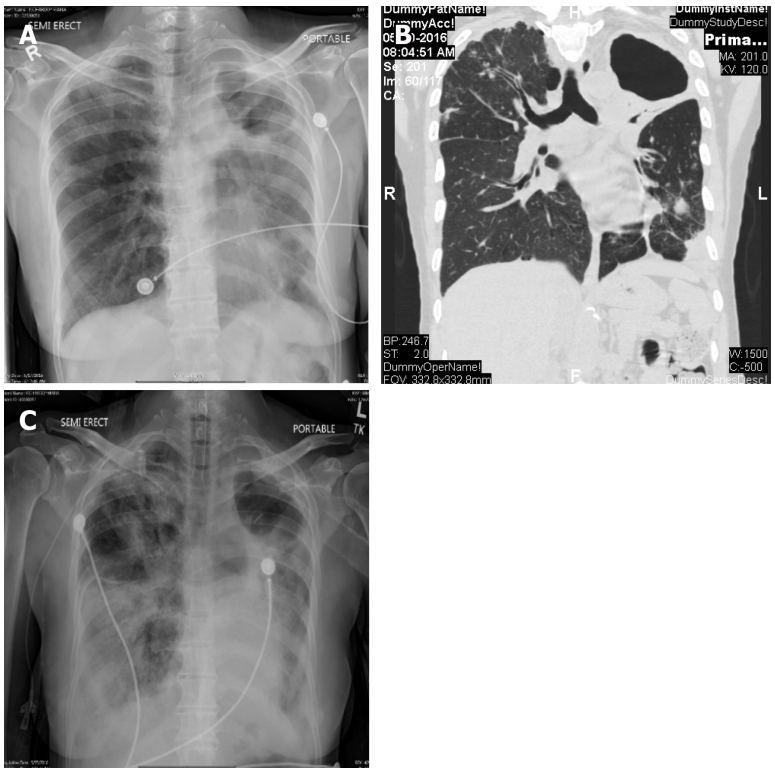


Figure 3 X-ray chest and computerized axial tomography (case 3). A: X-ray chest revealing the left upper lobe cavity and left lower lobe infiltrates at time of admission; B: Computerized axial tomography scan of the chest at time of admission revealing left lung thick walled cavities and multiple nodules on both side; C: X-ray chest revealing worsening of the bilateral infiltrate after intubation and of the anti-tuberculosis medications.

management of TBSS we divided it into several categories. This includes understanding pathophysiology of TBSS, high risk clinical features, modalities for prompt diagnosis and utility of empiric TB treatment based on clinical suspicion.

TBSS is extremely rare. Kethireddy *et al*[10], in a limited institutional review across the globe, could identify TBSS as etiology of septic shock in 1% of the cases in a pool of 5419 patients. A Majority of them were identified outside the United States. The incidence in United States was almost undetectable. Given the clinical rarity of TB in a low prevalence area[10] the suspicion for diagnosis is low. Hence areas of high prevalence of TB should be identified. California leads the TB incidence rate in United States, followed by Texas, New York, and Florida[12]. Over a one-year duration in New York, there was a 10% increase in the number of TB cases from 2016 to 2017[13]. Each institution should identify their level of risk for TB based on the geography and the time trends in the incidence of TB.

Clinical features such as fever of prolonged duration, typical chest radiograph findings, latent TB as diagnosed by a positive skin tuberculin test[14] are highly suspicious for active TB infection. Akin to these clinical parameters a predictive model has been proposed for the diagnosis of TB in hospitalized patients[15]. Hence, the amalgam of high geographic prevalence along with time trends and symptomatic suspicion for active TB should be used towards the clinical acumen for early identification of high-risk cases.

An efficient testing protocol should be promptly paired with high clinical suspicion for TB to arrive at a definitive diagnosis. Pulmonary manifestations are the most common presentations. Typical chest radiologic findings have a major role in high clinical suspicion. However, it lacks specificity[16]. Chest X-ray and clinical features can be miss-interpreted as CAP[17]. Patients are frequently managed with the CAP targeted anti-microbial agents prior to diagnosis of TB[18]. Sputum microscopy with acid-fast staining, the initial step in diagnosis, is prompt and simple though at the expense of reliability due to low sensitivity[19]. The determination of pulmonary TB, as per WHO recommendation, requires demonstration of bacteria in the sputum[20]. A sputum culture is reliable, preferred and gold standard for diagnosis of pulmonary TB. However, cultures come with the expense of time and take two to six weeks for them to be reported[19]. The nucleic acid amplification testing (NAAT) in sputum is a perfect blend of swiftness and reliability[21] to derive a microbiological conclusion and to initiate the TB anti-microbial agents. The sensitivities differ in the sputum positive

and negative TB patient[21]. There is an increase in the utilization of the NAAT over time[22]. There is no consensus on performing NAA for all hospitalized patients with suspected active TB. Centers for Disease Control recommends sputum NAAT on at least one sputum specimen in a patient with clinical signs suggestive of TB if the intended test changes the management by establishing the diagnosis[23,24].

The clinical manifestations of TB for patients with HIV induced immunosuppression are unalike to immunocompetent host. HIV infected individuals are more likely to have extra-pulmonary TB as compared to HIV negative individuals[25]. Those with lower CD4 count are more likely to have extra-pulmonary TB[26]. A wide array of the differentials for the systemic illness in patients with advanced AIDS, as in our scenario, makes the diagnosis of the disseminated TB challenging. HIV infected individuals with TB can have atypical chest radiological findings[27], with a small proportion of them with normal chest radiographs[24]. These adversities of atypical manifestations in conjunction with uncharacteristic radiological findings in patients with HIV hinders the early administration of anti-TB medication and hence can have worse outcomes in TBSS.

The culture of empiric treatment of TB differs across the globe. We assume that the incidence and prevalence of the disease guides the trend. The term "empiric" depicts two fundamental concepts. First is the presumptive treatment for a suspicious disease while awaiting the diagnosis. Second is the presumptive regimen while expecting the culture and sensitivity. Both parameters will affect the outcomes in sepsis. Molecular drug-resistance tests is prompt in detecting the drug resistance to isoniazid and rifampicin[28] and can be used to titrate the anti-TB medication. However, given our limited experience and the rare entity of TBSS, it is difficult to opine on routine use of molecular drug-resistance tests for the management of TBSS. We performed a standard drug susceptibility testing in the management of our patients, and no drug resistance was identified.

Time is of the essence in the management of sepsis. The timing of the antibiotics is categorized as: (1) The timing from emergency room triage; and (2) Timing from the onset of sepsis or septic shock[29]. We carefully dissected Kethireddy *et al*[10]'s findings to review the "timing" of antibiotics administration and outcome of TBSS. The administration of the anti-tuberculous medications within 24 h of septic shock had improved mortality outcomes. In our cases, we used our clinical acumen to arrive at a prompt diagnosis of TB with appropriate susceptibility testing and timely administration of anti-TB medications. Despite optimal management, the outcomes were worst. These paradoxical findings ignited our curiosity to dig deeper into the pathogenesis of TBSS.

The systemic inflammatory response syndrome (SIRS) is defined by the host immune response in the form of four variables: Heart rate, respiratory rate, temperature and leukocytosis[30]. Given the variable immune response, there were some shortcomings to this definition of sepsis[31]. The inflammatory response can be severe enough to cause the circulatory and metabolic abnormality identified as a septic shock[32]. A prompt antibiotic administration targeting the inciting etiology of SIRS should lead to the prevention of septic shock. However, in our cases, we observed a paradoxical clinical worsening after administration of TB anti-microbial agents which may be explained by post-antibiotic immune reconstitution inflammatory syndrome (IRIS).

In our immunocompetent patients, the clinical course worsened after the initiation of anti-TB medications. In Kethireddy *et al*[10]'s cases and other series[33] of critically ill TB patients, we were unable to retrieve any similar observations of exacerbation of TB induced sepsis after antibiotics administration. In HIV coinfection the entity of IRIS is well recognized[34]. However, a paradoxical worsening during the anti-TB therapy may be linked to TB IRIS in the HIV negative population[35]. In HIV uninfected TB IRIS has an extra-pulmonary presentation and a chronic course[36]. The pathogenesis of TB IRIS in the non-HIV has been proposed[37] but is not widely implemented in clinical practice. TB bacillary load has been identified as one of the risk factors for TB IRIS[38]. Prednisone has been utilized for the prevention of IRIS[39]. However, there is no clear consensus on steroid use in HIV negative patients, but can be considered[37]. A careful review of the clinical course in a few case reports and series depicts a similar clinical course[40-42]. Hence, one should evaluate the possibility of IRIS in clinical scenarios of TBSS after TB antimicrobial administration.

Hyponatremia is another striking feature in our patients. Hyponatremia is prevalent in patients with pulmonary TB and severity correlates with extensive pulmonary parenchymal involvement and sputum positivity[43]. This correlation depicts the possibility of a high TB bacterial load in patients with hyponatremia. The pathogenies of hyponatremia, though poorly understood, has been linked to inappropriate secretion of the antidiuretic hormone[44]. Hyponatremia, though not statistically significant, has been related to high mortality rates in a patient with

pulmonary TB[45]. But the rapid demise of the immunocompetent patients after TB antimicrobial administration begs to ask the question if there is any correlation of hyponatremia to high TB bacterial load and IRIS. To our knowledge, there is no study protocol exploring this specific rationale. Given the scarcity of data, we do want to conclude on this fact of hyponatremia and TB IRIS as an "observation" rather than "strong association".

The pathogenesis and clinical course of TB differ in immunocompromised patients with frequent atypical presentation and extrapulmonary dissemination[46]. TB may lead to worsening of HIV viremia and acceleration of immunosuppression[47], hence increasing HIV related mortality[48]. In our patient with HIV co-infection, the onset of the septic shock was before the TB diagnosis and medication administration. Clinical findings were suggestive of the disseminated TB. The patient was on intravenous steroids prior to the anti-TB microbial administration. This reveals different pathophysiology then our immunocompetent hosts. The immune dysregulation is more likely from the bacterial infection rather than immune-reconstruction. However, advanced HIV could have contributed to the mortality despite anti-TB microbial administration.

CONCLUSION

TBSS is well recognized and widely reported though at risk of delayed diagnosis because of rare incidence in the United States. Antibiotics administration within 24 hours of the septic shock has been shown to improve mortality outcome in TBSS. High degree of suspicion and sputum NAA can be utilized towards rapid diagnosis and prompt administration of susceptible antibiotics. The pathogenesis of TBSS does differ in immunocompromised patients as opposed to immunocompetent. The paradoxical clinical worsening of patients with TB after susceptible antibiotics administration leading to TBSS does arise the possibility of TB IRIS. Our series though limited to 'observational remark' for TB IRIS as pathogenesis in an immunocompetent host does appeal a need for the future registry to evaluate this phenomenon.

REFERENCES

1 **Rudd KE**, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, Angus DC, West TE. The global burden of sepsis: Barriers and potential solutions. *Crit Care* 2018; **22**: 232 [PMID: 30243300 DOI: 10.1186/s13054-018-2157-z]

2 **Paoli CJ**, Reynolds MA, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. *Crit Care Med* 2018; **46**: 1889-1897 [PMID: 30048332 DOI: 10.1097/CCM.0000000000003342]

3 **Whiles BB**, Deis AS, Simpson SQ. Increased Time to Initial Antimicrobial Administration Is Associated With Progression to Septic Shock in Severe Sepsis Patients. *Crit Care Med* 2017; **45**: 623-629 [PMID: 28169944 DOI: 10.1097/CCM.0000000000002262]

4 **Martin GS**, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; **348**: 1546-1554 [PMID: 12700374 DOI: 10.1056/NEJMoa022139]

5 **Ferrer R**, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: Results from a guideline-based performance improvement program. *Crit Care Med* 2014; **42**: 1749-1755 [PMID: 24717459 DOI: 10.1097/CCM.0000000000000330]

6 **Buckman SA**, Turnbull IR, Mazuski JE. Empiric Antibiotics for Sepsis. *Surg Infect (Larchmt)* 2018; **19**: 147-154 [PMID: 29341844 DOI: 10.1089/sur.2017.282]

7 **Mayr FB**, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence* 2014; **5**: 4-11 [PMID: 24335434 DOI: 10.4161/viru.27372]

8 **Heemskerk D**, Caws M, Marais B, Farrar J. Tuberculosis in Adults and Children 2015 [PMID: 26937536 DOI: 10.1007/978-3-319-19132-4]

9 **Sosa LE**, Njie GJ, Lobato MN, Morris SB, Buchta W, Casey ML, Goswami ND, Gruden M, Hurst BJ, Khan AR, Kuhar DT, Lewinsohn DM, Mathew TA, Mazurek GH, Reves R, Paulos L, Thanassi W, Will L, Belknap R. Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019. *MMWR Morb Mortal Wkly Rep* 2019; **68**: 439-443 [DOI: 10.1111/ajt.15512]

10 **Kethireddy S**, Light RB, Mirzanejad Y, Maki D, Arabi Y, Lapinsky S, Simon D, Kumar A, Parrillo JE, Kumar A; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Group. Mycobacterium tuberculosis septic shock. *Chest* 2013; **144**: 474-482 [PMID: 23429859 DOI: 10.1378/chest.12-1286]

11 **Silva DR**, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PT. Mortality among patients with tuberculosis requiring intensive care: A retrospective cohort study. *BMC Infect Dis* 2010; **10**: 54 [PMID: 20205952 DOI: 10.1186/1471-2334-10-54]

12 **Talwar A**, Tsang CA, Price SF, Pratt RH, Walker WL, Schmit KM, Langer AJ. Tuberculosis—United States, 2018. *MMWR Morb Mortal Wkly Rep* 2019; **68**: 257-262 [DOI: 10.15585/mmwr.mm6811a2]

13 **New York city bureau of tuberculosis control**. Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/tb/tb2017.pdf

14 **Frigati L**, Maskew M, Workman L, Munro J, Andronikou S, Nicol MP, Zar HJ. Clinical Predictors of Culture-confirmed Pulmonary Tuberculosis in Children in a High Tuberculosis and HIV Prevalence Area.

Pediatr Infect Dis J 2015; **34**: e206-e210 [PMID: 26376315 DOI: 10.1097/INF.0000000000000792]
15 **Wisnivesky JP**, Kaplan J, Henschke C, McGinn TG, Crystal RG. Evaluation of clinical parameters to predict Mycobacterium tuberculosis in inpatients. *Arch Intern Med* 2000; **160**: 2471-2476 [PMID: 10979058 DOI: 10.1001/archinte.160.16.2471]
16 **Kumar N**, Bhargava SK, Agrawal CS, George K, Karki P, Baral D. Chest radiographs and their reliability in the diagnosis of tuberculosis. *JNMA J Nepal Med Assoc* 2005; **44**: 138-142 [PMID: 16751817]
17 **Woodring JH**, Vandiviere HM, Fried AM, Dillon ML, Williams TD, Melvin IG. Update: The radiographic features of pulmonary tuberculosis. *AJR Am J Roentgenol* 1986; **146**: 497-506 [PMID: 3484866 DOI: 10.2214/ajr.146.3.497]
18 **Wang M**, Fitzgerald JM, Richardson K, Marra CA, Cook VJ, Hajek J, Elwood RK, Bowie WR, Marra F. Is the delay in diagnosis of pulmonary tuberculosis related to exposure to fluoroquinolones or any antibiotic? *Int J Tuberc Lung Dis* 2011; **15**: 1062-1068 [PMID: 21740669 DOI: 10.5588/ijtld.10.0734]
19 **WHO**. World Health Organization. Early detection of tuberculosis: An overview of approaches, guidelines and tools. Geneva: World Health Organization 2011;
20 **WHO**. World Health Organization. Definitions and reporting framework for tuberculosis: 2013 revision (updated December 2014). Geneva: World Health Organization, 2013.
21 **Greco S**, Girardi E, Navarra A, Saltini C. Current evidence on diagnostic accuracy of commercially based nucleic acid amplification tests for the diagnosis of pulmonary tuberculosis. *Thorax* 2006; **61**: 783-790 [PMID: 16738037 DOI: 10.1136/thx.2005.054908]
22 **Tyrrell F**, Stafford C, Yakrus M, Youngblood M, Hill A, Johnston S. Trends in Testing for Mycobacterium tuberculosis Complex From US Public Health Laboratories, 2009-2013. *Public Health Rep* 2017; **132**: 56-64 [PMID: 28005481 DOI: 10.1177/0033354916679989]
23 **Centers for Disease Control and Prevention**. Available from: https://www.cdc.gov/tb/publications/guidelines/amplification_tests/reccomendations.htm
24 **Ryu YJ**. Diagnosis of pulmonary tuberculosis: Recent advances and diagnostic algorithms. *Tuberc Respir Dis (Seoul)* 2015; **78**: 64-71 [PMID: 25861338 DOI: 10.4046/trd.2015.78.2.64]
25 **Chaisson RE**, Schecter GF, Theuer CP, Rutherford GW, Echenberg DF, Hopewell PC. Tuberculosis in patients with the acquired immunodeficiency syndrome. Clinical features, response to therapy, and survival. *Am Rev Respir Dis* 1987; **136**: 570-574 [PMID: 3631730 DOI: 10.1164/ajrccm/136.3.570]
26 **Jones BE**, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis* 1993; **148**: 1292-1297 [PMID: 7902049 DOI: 10.1164/ajrccm/148.5.1292]
27 **Geng E**, Kreiswirth B, Burzynski J, Schluger NW. Clinical and radiographic correlates of primary and reactivation tuberculosis: A molecular epidemiology study. *JAMA* 2005; **293**: 2740-2745 [PMID: 15941803 DOI: 10.1001/jama.293.22.2740]
28 **Chavalertsakul K**, Boonsarngsuk V, Saengsri S, Santanirand P. TB-PCR and drug resistance pattern in BALF in smear-negative active pulmonary TB. *Int J Tuberc Lung Dis* 2017; **21**: 1294-1299 [PMID: 28992819 DOI: 10.5588/ijtld.17.0326]
29 **Sterling SA**, Miller WR, Pryor J, Puskarich MA, Jones AE. The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Med* 2015; **43**: 1907-1915 [PMID: 26121073 DOI: 10.1097/CCM.0000000000001142]
30 **Marik PE**, Taeb AM. SIRS, qSOFA and new sepsis definition. *J Thorac Dis* 2017; **9**: 943-945 [PMID: 28523143 DOI: 10.21037/jtd.2017.03.125]
31 **Vincent JL**, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: Time for change. *Lancet* 2013; **381**: 774-775 [PMID: 23472921 DOI: 10.1016/S0140-6736(12)61815-7]
32 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]
33 **Duro RP**, Figueiredo Dias P, Ferreira AA, Xerinda SM, Lima Alves C, Sarmento AC, Dos Santos LC. Severe Tuberculosis Requiring Intensive Care: A Descriptive Analysis. *Crit Care Res Pract* 2017; **2017**: 9535463 [PMID: 28250986 DOI: 10.1155/2017/9535463]
34 **Meintjes G**, Lawn SD, Scano F, Maartens G, French MA, Worodria W, Elliott JH, Murdoch D, Wilkinson RJ, Seyler C, John L, van der Loeff MS, Reiss P, Lynen L, Janoff EN, Gilks C, Colebunders R, International Network for the Study of HIV-associated IRIS. Tuberculosis-associated immune reconstitution inflammatory syndrome: Case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008; **8**: 516-523 [PMID: 18652998 DOI: 10.1016/S1473-3099(08)70184-1]
35 **Cheng VC**, Ho PL, Lee RA, Chan KS, Chan KK, Woo PC, Lau SK, Yuen KY. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2002; **21**: 803-809 [PMID: 12461590 DOI: 10.1007/s10096-002-0821-2]
36 **Lanzafame M**, Vento S. Tuberculosis-immune reconstitution inflammatory syndrome. *J Clin Tuberc Other Mycobact Dis* 2016; **3**: 6-9 [DOI: 10.1016/j.jctube.2016.03.002]
37 **Sun HY**, Singh N. Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. *Curr Opin Infect Dis* 2009; **22**: 394-402 [PMID: 19483618 DOI: 10.1097/QCO.0b013e32832d7aff]
38 **Cheng SL**, Wang HC, Yang PC. Paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2007; **11**: 1290-1295 [PMID: 18034948 DOI: 10.1080/01902140701756778]
39 **Meintjes G**, Stek C, Blumenthal L, Thienemann F, Schutz C, Buyze J, Ravinetto R, van Loen H, Nair A, Jackson A, Colebunders R, Maartens G, Wilkinson RJ, Lynen L; PredART Trial Team. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. *N Engl J Med* 2018; **379**: 1915-1925 [PMID: 30428290 DOI: 10.1056/NEJMoa1800762]
40 **Bridges DA**, Bedimo RG. Severe tuberculosis sepsis in an immunocompetent patient. *Am J Med* 2006; **119**: e11-e14 [PMID: 16490454 DOI: 10.1016/j.amjmed.2005.08.033]
41 **Nidadavolu VG**, Shah M, Kuriti M. Tuberculosis Presenting As "SEPSIS"! -An Interesting Presentation Of Miliary Tuberculosis. *ATS J* 2013; A3213-A3213
42 **Michel P**, Barbier C, Loubière Y, Hayon JH, Ricôme JL. Three cases of septic shock due to tuberculosis without HIV pathology. *Intensive Care Med* 2002; **28**: 1827-1828 [PMID: 12447531 DOI: 10.1007/s00134-002-1526-9]
43 **Bokam BR**, Badikillaya VU. Prevalence of hyponatremia in pulmonary tuberculosis–A pilot study from a

tertiary care center in south India. *Int J Med Sci Public Health* 2017; **6**: 75-79 [DOI: 10.5455/ijmsph.2017.20062016560]

44 **Lee P**, Ho KK. Hyponatremia in pulmonary TB: Evidence of ectopic antidiuretic hormone production. *Chest* 2010; **137**: 207-208 [PMID: 20051406 DOI: 10.1378/chest.09-0405]

45 **Vargasa T**, Morales-Garza LA, Maya R, Llamas-Lopez A. Available from: https://idsa.confex.com/idsa/2018/webprogram/Paper72122.html

46 **Aaron L**, Saadoun D, Calatroni I, Launay O, Mémain N, Vincent V, Marchal G, Dupont B, Bouchaud O, Valeyre D, Lortholary O. Tuberculosis in HIV-infected patients: A comprehensive review. *Clin Microbiol Infect* 2004; **10**: 388-398 [PMID: 15113314 DOI: 10.1111/j.1469-0691.2004.00758.x]

47 **Garrait V**, Cadranel J, Esvant H, Herry I, Morinet P, Mayaud C, Israël-Biet D. Tuberculosis generates a microenvironment enhancing the productive infection of local lymphocytes by HIV. *J Immunol* 1997; **159**: 2824-2830 [PMID: 9300705]

48 **Whalen C**, Horsburgh CR, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med* 1995; **151**: 129-135 [PMID: 7812542 DOI: 10.1164/ajrccm.151.1.7812542]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Medl 2019 September 11; 8(5): 82-86

DOI: 10.5492/wjccm.v8.i5.82

ISSN 2220-3141 (online)

CASE REPORT

Successfully non-surgical management of flail chest as first manifestation of multiple myeloma: A case report

Rosana Muñoz-Bermúdez, Eugenia Abella, Flavio Zuccarino, Joan Ramon Masclans, Juan Nolla-Salas

ORCID number: Rosana Muñoz-Bermúdez (0000-0002-9210-3976); Eugenia Abella (0000-0001-9605-8458); Flavio Zuccarino (0000-0002-3446-3770); Joan Ramon Masclans (0000-0002-0809-6823); Juan Nolla-Salas (0000-0002-7780-9743).

Author contributions: Muñoz-Bermúdez R and Nolla-Salas J were the patient's doctors at critical care unit and wrote the paper; Abella E was the patient's hematologist, and contributed to manuscript drafting; Muñoz-Bermúdez R, Nolla-Salas J, and Abella E reviewed literature; Zuccarino F, radiologist, described the TC scan images and contributed to manuscript drafting; Nolla-Salas J and Masclans JR were responsible for the revision of the manuscript for important intellectual content.

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist, and the manuscript was prepared and revised according to the CARE Checklist (2016).

Rosana Muñoz-Bermúdez, Joan Ramon Masclans, Juan Nolla-Salas, Department of Critical Care, Hospital del Mar, Barcelona 08003, Spain

Eugenia Abella, Department of Hematology, Hospital del Mar, Barcelona 08003, Spain

Flavio Zuccarino, Department of Radiology, Hospital del Mar, Barcelona 08003, Spain

Corresponding author: Rosana Muñoz-Bermúdez, MD, Staff Physician, Critical Care, Hospital del Mar, Passeig Marítim 25-29, Barcelona 08003, Spain.
rmunozbermudez@parcdesalutmar.cat
Telephone: +34-93-2483000

Abstract

BACKGROUND

Multiple myeloma is a malignant neoplasm of the bone marrow characterized by neoplastic proliferation of monoclonal plasma cells with a high relationship with destructive bone disease. We present a case of a patient diagnosed with multiple myeloma and sternal fracture in association with multiple bilateral rib fractures and thoracic kyphosis, who developed a severe acute respiratory failure, thus complicating the initial presentation of multiple myeloma. We discuss the therapeutic implications of this uncommon presentation.

CASE SUMMARY

A 56-year-old man presented to Hematological Department after he had been experiencing worsening back pain over the last five months, with easy fatigability and progressive weight loss. He had no history of previous trauma. The chemical blood tests were compatible with a diagnosis of multiple myeloma. A radiographic bone survey of all major bones revealed, in addition to multiple bilateral rib fractures, a sternal fracture and compression fracture at T9, T10, T11 and L1 vertebrae. Subcutaneous fat biopsy was positive for amyloid. We started treatment with bortezomib and dexamethasone. After 24 h of treatment, he presented dyspnea secondary to flail chest. He required urgent intubation and ventilatory support being transferred to intensive care unit for further management. The patient remained connected to mechanical ventilation (positive pressure) as treatment which stabilized the thorax. A second cycle of bortezomib plus dexamethasone was started and analgesia was optimized. The condition of the patient improved, as evidenced by callus formation on successive computed tomography scans. The patient was taken off the ventilator one month later, and he was extubated successfully, being able to breathe unaided without paradoxical

Manuscript source: Unsolicited manuscript

Received: March 12, 2019
Peer-review started: March 15, 2019
First decision: June 7, 2019
Revised: July 23, 2019
Accepted: August 15, 2019
Article in press: August 16, 2019
Published online: September 11, 2019

P-Reviewer: Cascella M, Lin JA
S-Editor: Yan JP
L-Editor: A
E-Editor: Liu MY

motion.

CONCLUSION
This case highlights the importance of combination between bortezomib and dexamethasone to induce remission of multiple myeloma and the initiation of positive airway pressure with mechanical ventilation to stabilize chest wall to solve the respiratory failure. This combined approach allowed to obtain a quick and complete resolution of the clinical situation.

Key words: Multiple myeloma; Flail chest; Bortezomib; Mechanical ventilation; Case report

Core tip: This case report describes an adult patient with acute respiratory failure, secondary to flail chest because of a multiple myeloma. It shows how positive pressure in airway, in conjunction with an early treatment with bortezomib and dexamethasone, may lead to a successful outcome for such patients with an otherwise poor prognosis.

Citation: Muñoz-Bermúdez R, Abella E, Zuccarino F, Masclans JR, Nolla-Salas J. Successfully non-surgical management of flail chest as first manifestation of multiple myeloma: A case report. *World J Crit Care Medl* 2019; 8(5): 82-86
URL: https://www.wjgnet.com/2220-3141/full/v8/i5/82.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i5.82

INTRODUCTION

Multiple myeloma is a malignant neoplasm of the bone marrow characterized by neoplastic proliferation of monoclonal plasma cells[1]. Approximately 70%-80% of patients with multiple myeloma eventually develop destructive bone disease[2]. Most of the lesions are localized in the spine, pelvis or proximal extremities, according to the regions of hematological active bone marrow[1,3].

CASE PRESENTATION

Chief complaints

We present a case of multiple bilateral rib fractures in association with sternal fracture and thoracic kyphosis who developed a severe acute respiratory insufficiency complicating the initial presentation of multiple myeloma.

History of present illness

A 56-year-old man presented to Hematological Department after he had been experiencing worsening back pain over the last five months, with easy fatigability, and progressive weight loss. He had no history of previous trauma.

History of past illness

Hypertension and mellitus diabetes, both under pharmacological treatment.

Physical examination

At intake, his blood pressure was 130/70 mmHg; pulse rate 70 beats/min; respiratory rate 14/min and body temperature 35.7 °C.

Laboratory examinations

Blood chemical test results were as follows: creatinine 4.22 mg/dL; glomerular filtration rate 15 mL/min; calcium 15.9 mg/dL and hemoglobin 6.7 g/dL. Serum β2-microglulin level was elevated at 9.42 mg/L and serum albumin level was 2.7 g/dL. The diagnosis of Kappa -light chain Bence-Jones multiple myeloma was established on the basis of a bone marrow infiltration by 66% atypical plasmatic cells and a monoclonal component kappa in serum (86 mg/dL) and in urine with a proteinuria of 2.9 g/24 h. Urine was positive for Bence-Jones proteins

Imaging examinations

A radiographic bone survey of all major bones revealed, in addition to multiple bilateral rib fractures (4th to 11th), the presence of a sternal fracture and compression fracture at T9, T10, T11 and L1 vertebrae. The thoracic computed tomography (CT) scan confirmed a depressed pathological fracture of the sternum (Figure 1A).

Further diagnostic work-up

With the results of the different tests, the patient was diagnosed with multiple myeloma. It was staged as Durie-Salmon stage IIIB and International Staging System IIIB. Subcutaneous fat biopsy was positive for amyloid.

FINAL DIAGNOSIS

The final diagnosis of the presented case was spontaneous sternal fracture secondary to multiple myeloma, with flail chest and acute respiratory failure as the main consequence.

TREATMENT

On the third day bortezomib was initiated at dose of 1.3 mg/m^2 and dexamethasone at dose of 40 mg/24 h by intravenous route as remission induction. After 24 h of treatment, the patient suddenly presented dyspnea secondary to flail chest resulting from multiple bilateral rib and sternum fractures (Figure 1B). Oxygen saturation by pulse oximetry was 86% (FiO_2 0.21). He required urgent intubation and ventilatory support being transferred to intensive care unit (ICU) for further management. At the ICU, paradoxical inward movements of the rib cage were evident bilaterally on inspiration. The patient remained connected to mechanical ventilation as treatment which stabilized the thorax on pressure control ventilation of 15 cm H_2O and positive end expiratory pressure of 7 cm H_2O. The arterial pH was 7.4, PaO_2 80 mmHg and $PaCO_2$ 43 mmHg, breathing 28% oxygen. The patient, at ICU admission, was febrile (axillary temperature, 38 °C), with white blood cells, 19000/μL. Chest radiography revealed an infiltrate in the right lower lung. Methicillin-sensitive *Staphylococcus aureus* was identified from tracheobronchial aspirates and the patient was treated with cloxacillin at dose of 2 g/6 h by i.v. route, resulting in the eradication of the infection after 14 d of treatment. The patient received selective digestive decontamination during ICU-stay. Attempts to wean the patient caused the return of paradoxical movements and respiratory failure. A second cycle of bortezomib plus dexamethasone was started and analgesia was optimized. Surgical stabilization with an external fixator was considered by Thoracic Surgery team but the idea was finally dropped.

OUTCOME AND FOLLOW-UP

The condition of the patient improved, as evidenced by callus formation on successive CT scans (Figure 1C and D), improvement in his respiratory status and a marked decrease in urine kappa light chain levels to less than half the original value (0.55 g/24 h). The patient was taken off the ventilator one month later, and was extubated successfully, being able to breathe unaided without paradoxical motion. On breathing room air, arterial blood gas analysis revealed: pH, 7.49, PaO_2, 70 mmHg and $PaCO_2$, 40 mmHg. He was discharged from ICU and from the hospital 5 and 9 wk after his hospitalization, respectively. The patient received further treatment with 4 cycles of bortezomib with a good response. An allogenic transplantation was planned five months after, but patient refused the therapy and subsequently was re-treated with 2 cycles of bortezomib at low doses. One year after his hospital admission the patient is being followed up at the Department of Hemato-Oncology without further dyspnea.

DISCUSSION

Spontaneous flail chest is rare in multiple myeloma[4-7]. The main interest of this case resides in restoring chest stabilization with the use of continuous positive pressure ventilation during a short period of time, without need to perform surgery and tracheostomy, while providing definitive chemotherapy. This objective was achieved

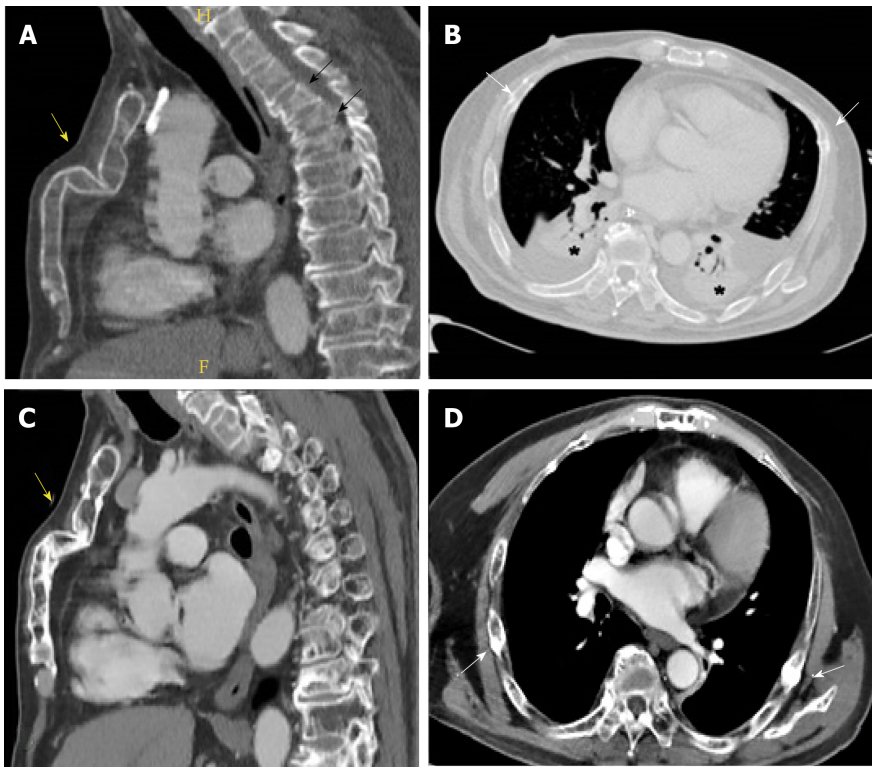


Figure 1 Sagittal computed tomography image. A: A depressed pathological fracture of the sternum (yellow arrow) resulting in an evident deformity of the anterior chest wall. Multiple spontaneous compression fractures of the thoracic spine can also be observed (black arrows); B: Axial computed tomography (CT) image demonstrates multiple rib fractures (white arrows) associated to bilateral lung consolidations (asterisks) and pleural effusion; C and D: Control CT scan, realized months later, shows important improvement of both sternal (C, yellow arrow) and rib fractures (D, white arrows), with the appearance of fracture calluses. Complete resolution of lung consolidations and pleural effusion (D).

as determinated by the relationship between the substantially decreased urine kappa light chain level, the tolerance to the weaning of the ventilator and the signs of partial bone healing in the control by CT. It is well known that bortezomib has significant activity in patients with relapsed/refractory multiple myeloma and its efficacy and safety in renal failure has been observed in phase II studies[8] and more recently the Phase III HOVON-65/GMMG-HD4 trial[9] describes the potential benefit of bortezomib in patients with organ failure. The role of surgery for pathological sternal fractures is not well defined and to date there is no standard treatment method for his clinical condition[10]. Recently, Lee *et al*[6] described a case of multiple myeloma, who presented flail chest and severe respiratory failure following blunt trauma successfully treated by the Nuss operation. On the other hand, Abisheganaden *et al*[4] described the use of continuous positive airway pressure ventilation through a tracheostomy for pathological flail chest in multiple myeloma but after a long period of ICU stay (> 3 mo). Surgery was not required in this case.

CONCLUSION

Despite its alarming presentation, the association of multiple myeloma and flail chest does not necessarily predict a poor prognosis. Starting positive airway pressure to stabilize the chest wall, as well as the association of bortezomib and dexamethasone to induce a remission, may solve the respiratory insufficiency, in a short period of time, without requiring surgical fixation.

REFERENCES

1 **Angtuaco EJ**, Fassas AB, Walker R, Sethi R, Barlogie B. Multiple myeloma: Clinical review and diagnostic imaging. *Radiology* 2004; **231**: 11-23 [PMID: 14990813 DOI: 10.1148/radiol.2311020452]
2 **Terpos E**, Dimopoulos MA. Myeloma bone disease: Pathophysiology and management. *Ann Oncol* 2005; **16**: 1223-1231 [PMID: 15928069 DOI: 10.1093/annonc/mdi235]

3 **Kyle RA**, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003; **78**: 21-33 [PMID: 12528874 DOI: 10.4065/78.1.21]

4 **Abisheganaden J**, Chee CB, Wang YT. Use of bilevel positive airway pressure ventilatory support for pathological flail chest complicating multiple myeloma. *Eur Respir J* 1998; **12**: 238-239 [PMID: 9701444 DOI: 10.1183/09031936.98.12010238]

5 **Muldoon K**, Chu P, Pathria M, Resnick D. Association of posterior rib fractures with exaggerated kyphosis and sternal collapse. *Clin Imaging* 1999; **23**: 311-313 [PMID: 10665349 DOI: 10.1016/S0899-7071(99)00153-9]

6 **Lee SA**, Hwang JJ, Chee HK, Kim YH, Lee WS. Flail chest stabilization with Nuss operation in presence of multiple myeloma. *J Thorac Dis* 2014; **6**: E43-E47 [PMID: 24822124 DOI: 10.3978/j.issn.2072-1439.2014.02.10]

7 **Pickard L**, Whittaker C, Jayakar V. Spontaneous sternal collapse in multiple myeloma. *Br J Haematol* 2015; **168**: 316 [PMID: 25377148 DOI: 10.1111/bjh.13204]

8 **Chanan-Khan AA**, Kaufman JL, Mehta J, Richardson PG, Miller KC, Lonial S, Munshi NC, Schlossman R, Tariman J, Singhal S. Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: A multicenter retrospective study. *Blood* 2007; **109**: 2604-2606 [PMID: 17138816 DOI: 10.1182/blood-2006-09-046409]

9 **Sonneveld P**, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, Zweegman S, Vellenga E, Broyl A, Blau IW, Weisel KC, Wittebol S, Bos GM, Stevens-Kroef M, Scheid C, Pfreundschuh M, Hose D, Jauch A, van der Velde H, Raymakers R, Schaafsma MR, Kersten MJ, van Marwijk-Kooy M, Duehrsen U, Lindemann W, Wijermans PW, Lokhorst HM, Goldschmidt HM. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol* 2012; **30**: 2946-2955 [PMID: 22802322 DOI: 10.1200/JCO.2011.39.6820]

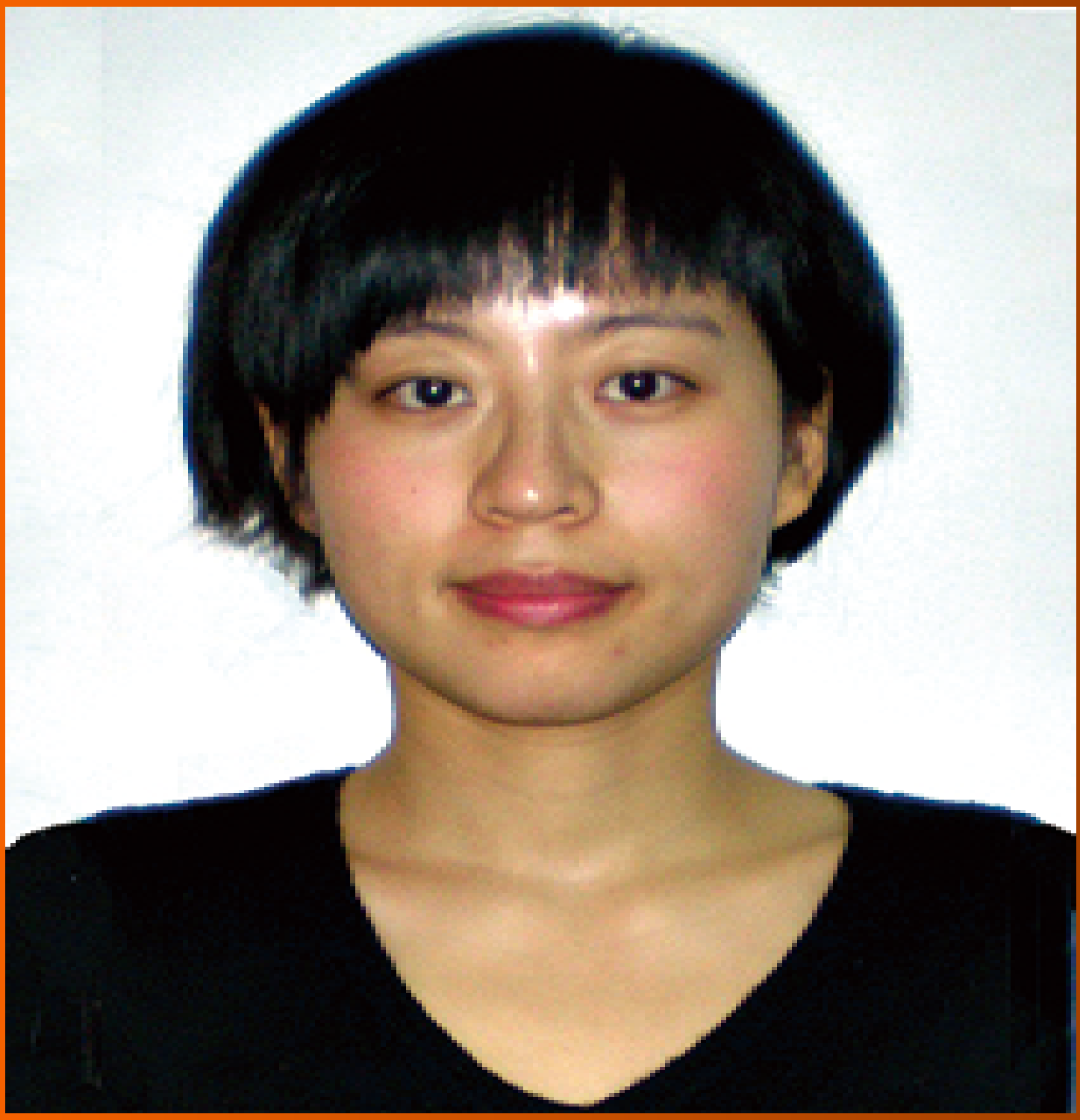
10 **Slobogean GP**, MacPherson CA, Sun T, Pelletier ME, Hameed SM. Surgical fixation vs nonoperative management of flail chest: A meta-analysis. *J Am Coll Surg* 2013; **216**: 302-311.e1 [PMID: 23219148 DOI: 10.1016/j.jamcollsurg.2012.10.010]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2019 October 16; 8(6): 87-105



Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Irregular Volume 8 Number 6 October 16, 2019

REVIEW

CASE REPORT

Contents

World Journal of Critical Care Medicine

Volume 8 Number 6 October 16, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*. Hai-Yan Liu, MD, PhD, Assistant Professor, Chief Doctor, Doctor, Lecturer, Department of Critical Care Medicine, The First Affiliated Hospital of Anhui medical University, Hefei 230022, Anhui Province, China

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, infection and anti-infection treatment, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, severe infection, and shock and multiple organ dysfunction syndrome.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Mei-Yi Liu*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

EDITORIAL OFFICE
Jia-Ping Yan, Director

PUBLICATION DATE
October 16, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 October 16; 8(6): 87-98

DOI: 10.5492/wjccm.v8.i6.87

ISSN 2220-3141 (online)

REVIEW

Anticoagulation with direct thrombin inhibitors during extracorporeal membrane oxygenation

Barry Burstein, Patrick M Wieruszewski, Yan-Jun Zhao, Nathan Smischney

ORCID number: Barry Burstein (0000-0003-0203-9294); Patrick M Wieruszewski (0000-0002-5871-5186); Yan-Jun Zhao (0000-0003-1938-9848); Nathan Smischney (0000-0003-1051-098X).

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest to declare.

Manuscript source: Invited manuscript

Received: April 28, 2019
Peer-review started: May 9, 2019
First decision: August 2, 2019
Revised: August 13, 2019
Accepted: September 5, 2019
Article in press: September 5, 2019

Barry Burstein, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Patrick M Wieruszewski, Yan-Jun Zhao, Department of Pharmacy, Mayo Clinic, Rochester, MN 55905, United States

Nathan Smischney, Department of Anesthesia, Mayo Clinic, Rochester, MN 55905, United States

Corresponding author: Nathan Smischney, MD, MSc, Assistant Professor, Department of Anesthesia, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. smischney.nathan@mayo.edu
Telephone: +1-507-2554305
Fax: +1-507-2554267

Abstract

Use of extracorporeal membrane oxygenation to support patients with critical cardiorespiratory illness is increasing. Systemic anticoagulation is an essential element in the care of extracorporeal membrane oxygenation patients. While unfractionated heparin is the most commonly used agent, unfractionated heparin is associated with several unique complications that can be catastrophic in critically ill patients, including heparin-induced thrombocytopenia and acquired antithrombin deficiency. These complications can result in thrombotic events and subtherapeutic anticoagulation. Direct thrombin inhibitors (DTIs) are emerging as alternative anticoagulants in patients supported by extracorporeal membrane oxygenation. Increasing evidence supports DTIs use as safe and effective in extracorporeal membrane oxygenation patients with and without heparin-induced thrombocytopenia. This review outlines the pharmacology, dosing strategies and available protocols, monitoring parameters, and special use considerations for all available DTIs in extracorporeal membrane oxygenation patients. The advantages and disadvantages of DTIs in extracorporeal membrane oxygenation relative to unfractionated heparin will be described.

Key words: Extracorporeal membrane oxygenation; Anticoagulants; Antithrombins; Bivalirudin; Argatroban; Heparin

Core tip: In contrast to unfractionated heparin, direct thrombin inhibitors are not

Published online: October 16, 2019

P-Reviewer: Drabek T, Qi XS, Willms DC
S-Editor: Yan JP
L-Editor: A
E-Editor: Liu MY

associated with heparin-induced thrombocytopenia or acquired antithrombin deficiency. Direct thrombin inhibitors, specifically bivalirudin and argatroban, are equally safe and possibly more efficacious than unfractionated heparin. Dosage and monitoring parameters are easily manageable and more predictable than unfractionated heparin. As extracorporeal membrane oxygenation increases in use, direct thrombin inhibitors may potentially be considered as a primary anticoagulant in patients with or without complications of unfractionated heparin.

Citation: Burstein B, Wieruszewski PM, Zhao YJ, Smischney N. Anticoagulation with direct thrombin inhibitors during extracorporeal membrane oxygenation. *World J Crit Care Med* 2019; 8(6): 87-98
URL: https://www.wjgnet.com/2220-3141/full/v8/i6/87.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i6.87

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is increasingly used in patients with refractory respiratory or cardiogenic shock[1]. Patients can be supported in either a veno-venous (VV) or veno-arterial (VA) configuration. Systemic anticoagulation is necessary and crucial due to continuous contact between the patient's blood and the foreign surfaces of all components of the ECMO circuit. This interaction triggers the coagulation cascade and can lead to pump or oxygenator thrombi, or fibrin stranding within the inflow cannula resulting in potentially devastating thromboembolic events[2]. The ideal anticoagulant has rapid onset and offset, is easily titratable based on available monitoring parameters, is reversible, and is not affected by organ dysfunction commonly seen in ECMO patients[3]. Intravenous unfractionated heparin (UFH) is the standard anticoagulant in most centers due to its availability, rapid onset of action, reversibility, cost profile, and familiarity among practitioners[4].

Complications related to UFH are common: bleeding, non-immune and immune heparin-induced thrombocytopenia (HIT), and heparin-resistance have all been described[5,6]. HIT is of particular concern, with mortality as high as 20%-30%[7]. The incidence of HIT in patients treated with UFH is approximately 2.6%, although this does not reflect the incidence in ECMO patients[8]. HIT is often suspected in ECMO patients; however available data are inconsistent, suggesting that the incidence ranges from less than 0.36% to 17%[9-12]. HIT reverses the anticoagulant effect of heparin and leads to massive platelet activation and thrombosis, which can be catastrophic[13]. All forms of heparin must be immediately discontinued once the diagnosis of HIT is suspected. In ECMO patients, the heparin-coated elements of the circuit must also be exchanged. UFH can also lead to acquired antithrombin deficiency which may result in heparin resistance and suboptimal anticoagulation[2]. This is of particular concern in patients receiving ECMO secondary to the inability to liberate from cardiopulmonary bypass due to high intraoperative heparin loads. Alternative anticoagulation strategies have been proposed. In non-ECMO patients with suspected or confirmed HIT, direct thrombin inhibitors (DTIs) are the primary alternative[13]. This article will review DTI anticoagulation strategies in adult ECMO patients, as well as available safety and outcome data. Heparin alternatives in pediatric ECMO patients have previously been reviewed[14].

PHARMACOLOGY OF DIRECT THROMBIN INHIBITORS

Thrombin is a serine protease that plays a crucial role in the coagulation cascade and the generation and stabilization of clot. Upon activation, thrombin facilitates the formation of insoluble fibrin from soluble fibrinogen[15,16]. Thrombin contains three binding sites that are essential to its coagulant-and thereby anticoagulant-effects, including the catalytic site, exosite-1, and exosite-2.

The DTIs obtain their name from their direct binding to thrombin to exert anticoagulant effects. This is in contrast to UFH and low molecular weight heparins, which are indirect thrombin inhibitors. These indirect inhibitors bind to antithrombin, a hepatically-synthesized glycoprotein, forming a heparin-antithrombin complex which subsequently binds to exosite-2 on thrombin and blocks the catalytic site[16,17]. Because of this binding, indirect thrombin inhibitors only exert effects on circulating

thrombin, as the catalytic site of fibrin-bound thrombin is occupied in preformed clot[17]. DTIs, on the other hand, bind directly to either the catalytic site or both the catalytic site and exosite-1 on thrombin, depending on the valency of the agent, in the absence of antithrombin[15,17]. Because of this, a major pharmacologic advantage over indirect thrombin inhibitors is the ability of DTIs to bind both circulating and fibrin-bound thrombin. DTIs for clinical use vary based on their valency, modality of binding (reversible *vs*. irreversible), and pharmacokinetic profile (Table 1).

ADVANTAGES OF DIRECT THROMBIN INHIBITORS

Anticoagulation is an essential element of ECMO support. While UFH remains the standard at most ECMO centers, DTIs are emerging as a reasonable and safe alternative due to several advantages when compared to UFH. The advantages of DTIs over UFH are: (1) Direct binding of both circulating and clot-bound thrombin, which results in increased efficacy relative to UFH[17]; (2) Anticoagulant effect that is independent of antithrombin, allowing for more consistent and predictable effect without concern for antithrombin depletion[15,17]; (3) Avoidance of HIT, as thrombocytopenia is common among ECMO patients and the diagnosis of HIT in this setting is challenged by the multitude of factors that can precipitate a drop in platelet count. Healthcare teams must maintain a low threshold of concern when HIT is suspected. DTIs appear to be at least as safe as UFH with no evidence of increased bleeding or thrombosis, and evidence suggests that patients who receive DTIs are more often in therapeutic targeted range of anticoagulation. While DTIs are an appropriate choice in the setting of suspected or confirmed HIT, they may be a reasonable option as first-line anticoagulation for better efficacy in maintaining ECMO circuit patency and to avoid concerns for HIT altogether. Although DTIs do not have target-specific antidote, their half-life is very short and the anticoagulant effect tapers off rapidly despite the widely prevalent end organ dysfunction in ECMO patients. ECMO patients rarely require complete reversal of anticoagulation given the high risk of thrombosis.

AVAILABLE AGENTS

Bivalirudin

Bivalirudin is a synthetic, bivalent DTI, which binds directly to both the catalytic site and exosite-1 on thrombin in a reversible fashion[16] (Table 1). Bivalirudin dissociates from the catalytic site following proteolytic cleavage, reconstituting thrombin's ability to facilitate fibrin formation[18]. This may be problematic during states of blood stasis as will be discussed. It is administered by intravenous infusion, has an onset of action within minutes, and has a half-life of 25 min in patients with normal renal function[18]. Bivalirudin has a low volume of distribution and is therefore widely distributed in plasma and has negligible protein binding.

Bivalirudin is available as an adjunct to anticoagulation therapy during percutaneous coronary interventions, as well as the primary anticoagulant during coronary artery bypass grafting in patients with HIT[19]. Use in ECMO, with or without HIT, is off-label. The available literature for use in adults supported by ECMO is derived from retrospective studies, a single case control trial, and multiple case reports[20-26] (Table 2). Two studies compared bivalirudin to a matched control group who received UFH[20,25]. Four studies described patients with suspected or confirmed HIT due to previous UFH use[21,23,24,26]; the remaining studies used bivalirudin as the initial anticoagulation strategy[20,22,24,25]. Both VV and VA configurations are described. There is one published protocol describing initial bivalirudin dosing and subsequent dose adjustments[22].

In most reported studies of bivalirudin, initial bolus doses were administered followed by a weight-based infusion. The described dosing is heterogeneous; bolus dosing ranges from 0.04 mg/kg to 2.5 mg/kg. In reports without bolus dosing there was no sign of increased thromboembolic risk during the time until therapeutic anticoagulation was achieved[21,24-26]. The maintenance infusion was adjusted based on monitoring parameters, and doses ranged from 0.025 mg/kg/h to 2.5 mg/kg/h. In studies where average infusion rate is described, the dose ranges from 0.05 mg/kg/h to 0.26 mg/kg/h to maintain therapeutic targets[21,23,26]. When compared to patients receiving UFH infusions, patients treated with bivalirudin are more often in therapeutic range[20,24].

Renal dysfunction: Bivalirudin is metabolized in the plasma by proteolytic cleavage

Table 1 Pharmacology of direct thrombin inhibitors

	Valence	Thrombin binding	Onset of action	Half-life	Protein binding	Metabolism	Special considerations
Bivalirudin	Bivalent	Reversible	2-4 min	25 min	None	Serum proteases	Avoid during low-flow states Removed by non-diffusive dialysis modalities Dose reductions necessary in renal dysfunction
Argatroban	Univalent	Reversible	30 min	45 min	20% albumin 34% alpha-acid glycoprotein	Hepatic (hydroxylation, aromatization)	Dose reductions necessary in hepatic dysfunction

and has a prolonged half-life in the setting of renal dysfunction[27]. Renal dysfunction is therefore an important consideration when initiating and adjusting bivalirudin infusions. Initial dosing, as well as adjustments in the maintenance infusion rate, may vary, and over-anticoagulation is an important concern in these patients. Limited studies with established protocols describe lower initial bolus doses in patients with renal dysfunction[25], while others use the same bolus dose as patients without renal dysfunction while adjusting subsequent maintenance infusion rates[22]. Ranucci *et al*[25] administered half-dose initially in patients with renal dysfunction, followed by the regular dose adjustment protocol. The protocol by Netley *et al*[22] stratified patients based on creatinine clearance above 30 mL/min, between 10-29 mL/min, and less than 10 mL/min or requiring intermittent hemodialysis. The initial bolus dose was standardized for all patients regardless of creatinine clearance, and subsequent dose adjustments were limited as the severity of renal dysfunction progressed.

Continuous renal replacement therapy (CRRT) utilizing convective (hemofiltration) or combination convective/diffusive (hemodiafiltration) modes has been found to modestly remove bivalirudin, but purely diffusive modalities are not expected to be major determinants of clearance due to bivalirudin's larger molecular size (1980 Da)[28]. There are multiple reports of successful anticoagulation with bivalirudin while supporting patients with CRRT[20,22,24]. Walker *et al*[26] described moderately reduced dose requirements in patients on CRRT, although the doses were higher than those with renal dysfunction who were not receiving CRRT. While it would be expected that patients with renal dysfunction require less bivalirudin to maintain a similar anticoagulation profile, retrospective data suggest that these patients may require higher doses[24]. The reasons for this finding are unclear. Given the tendency to reduce initial and/or maintenance bivalirudin doses in patients with renal dysfunction, careful attention should be paid to avoid under-anticoagulation which may result in thrombotic events. The currently available reports do not signal an increased risk of thrombosis in patients with renal dysfunction, although the number of studied patients is limited.

Hepatic dysfunction: There is no bivalirudin dose adjustment necessary in patients with hepatic dysfunction, although there are no specific reports of outcomes in patients with hepatic disease.

Monitoring: Bivalirudin prolongs the activated clotting time (ACT), activated partial thromboplastic time (aPTT), thrombin time, prothrombin time, and international normalized ratio[19]. Ecarin clotting time and chromogenic anti-factor IIa assay are the most reliable methods for DTI monitoring; however, they are not readily available in clinical laboratories. The aPTT testing is the most commonly used and well validated assay to monitor DTIs. The manufacturer recommends monitoring with ACT in certain conditions, namely HIT, with an ACT target greater than 225 s. No specific recommendation from the manufacturer is available in ECMO patients as this is an off-label indication. Most reviewed studies, including available protocols, used aPTT as a monitoring parameter. Netley *et al*[22] used aPTT alone with adjustable target based on physician preference; 40-60 s, 50-70 s, or 60-80 s were all described, with adjustments in bivalirudin doses based on the difference between the measured aPTT and the target aPTT. The aPTT was measured 2 h after the initial dose and then every 4 h afterwards. Ranucci *et al*[25] adjusted bivalirudin dosing based on ACT primarily (target 160-180 s), followed by aPTT (target 50-80 s) and then kaolin-activated thromboelastography (TEG, TEG 5000; Haemonetics Corp, Braintree, MA, United

Table 2 Summary of studies reporting on argatroban in adult patients supported with extracorporeal membrane oxygenation

First author, Year	Study type	Population	Circuit (VA/VV)	CRRT	Bolus dose (mg/kg)	Initial infusion (mg/kg/min)	Monitoring	Duration	Major bleeding	Thrombosis	Other adverse events	Outcome
Jyoti *et al*[21], 2013	Case report	54M ARDS, HIT	VV	No	NA	0.6	ACT 200-220 s aPTT 60-80 s	552 h (23 d)	NA	NA	NA	
Pappalardo *et al*[23], 2009	Case report	71F post-cardiotomy, HIT	VA	No	0.5	0.5	ACT 180-220 s	6 d	NA	Ventricular fibrillation due to LA thrombus, suspected to be due to heparin in tubing with residual HIT. BIV dosing increased	NA	Decannulated and discharged in stable condition
Pieri *et al*[24], 2013	Case control	*n* = 10 (4 HIT)	VV (*n* = 5) VA (*n* = 5)	*n* = 7 (70%)	N/A	0.025	aPTT 45-60 s	8 d (range 6-23)	*n* = 3 (30%)	*n* = 1 (10%)	No difference in bleeding or thrombosis compared to UFH patients Less dose corrections than UFH Less supra-therapeutic aPTTs than UFH	*n* = 4 (40%) died
Berei *et al*[20], 2018	Retrospective	*n* = 44 CS (*n* = 37) Sepsis (*n* = 11) Respiratory (*n* = 3) Mixed (*n* = 4)	VA (*n* = 26) VV (*n* = 2)	*n* = 17 (39%)	UFH 80 units/kg at cannulation No BIV bolus	0.04	aPTT 45-65 s (low intensity) or 60-80 s (high intensity)	156.9 h (mean)	*n* = 20 (45.5%)	*n* = 10 (22.7%)	Increased flow rates during first 96 h High intensity BIV had more TTR with no difference in outcomes	No difference in death at 30 d between BIV and UFH (36% *vs* 32%)
Netley *et al*[22], 2017	Retrospective	*n* = 11 ARDS (*n* = 8) ECLS (*n* = 3)	VA (*n* = 4) VV (*n* = 7)	*n* = 4 (36%)	NA	2.5	aPTT 40-60 s, 50-70 s, or 60-80 s	Mean 9.9 d (range 4-22)	*n* = 8 (72.7%)	*n* = 2 (18.2%), both after hospital discharge	NA	*n* = 5 (45%) died after withdrawal of care *n* = 6 (55%) discharged from hospital
Ranucci *et al*[25], 2011	Retrospective	*n* = 8, post-cardiotomy	VA	NA	NA	0.03-0.05 ½ dose if reduced CrCl	ACT 160-180 s or aPTT 50-80 s or TEG *r* 12-30 min	39-262 h	NA	None	Bleeding not reported, but less average blood loss (mL/kg/d) in BIV patients	*n* = 2 (25%) survived *n* = 2 (25%) dead on ECMO *n* = 4 (50%) weaned but died

Walker *et al*[26], 2019	Retrospective	*n* = 14 ARDS (*n* = 12) Post-cardiotomy (*n* =2) HIT (*n* = 11/13)	VV (*n* = 11) VA (*n* = 3)	*n* = 6 (43%)	0.2 (*n* = 1, others NA)	0.04-0.26	aPTT 1.5-2.5 × baseline	Median 5.2 d (range 0.9-28.4 d)	*n* = 4 (29%)	Circuit clotting (*n* = 5, 36%)	Infusion held during major bleeding episodes with no need for correction Higher infusion rates noted with CRRT	*n* = 9 (64%) decannulated *n* = 7 (50%) survived to discharge

ACT: Activated clotting time; aPTT: Activated partial thromboplastin time; ARDS: Acute respiratory distress syndrome; BIV: Bivalirudin; CRRT: Continuous renal replacement therapy; CS: Cardiogenic shock; ECLS: Extra-corporeal life support; HIT: Heparin-induced thrombocytopenia; NA: Not available; TEG: Thromboeslastography; UFH: Unfractionated heparin; VA: Veno-arterial; VV: Veno-venous.

States) *r* time (target 12-30 min). Parameters were checked every 4, 12, and 8 h, respectively. In the retrospective study by Berei *et al*[20], aPTT targets between 45-65 s (low intensity) and 60-80 s (high intensity) were chosen based on physician preference. Given the wide variability of monitoring modalities used and goal ranges reported in the literature, and the possibility of DTI resistance and unreliable aPTT monitoring at very high DTI doses, it is of utmost importance to use clinical indicators including ECMO circuit patency and potential thrombotic and bleeding complications as ultimate guidance for anticoagulation titration rather than solely relying on numbers of certain lab values.

Safety and outcomes: Bivalirudin appears to be a safe anticoagulation strategy for patients supported by ECMO, with no overall evidence of increased bleeding or thrombotic complications relative to UFH[20,24,25]. One study demonstrated an increased incidence of bleeding events in patients treated with bivalirudin compared to those receiving UFH, without meeting statistical significance[20]. Walker *et al*[26] described 4 of 14 patients who required reduction in aPTT targets or complete suspension of bivalirudin due to bleeding, although this rate is similar to reported bleeding rates in UFH patients. Some reports suggest a lower risk of thrombosis and vascular complications, as well as decreased transfusion requirements relative to UFH[20,25], although cases requiring circuit exchange due to thrombosis have been reported[26]. Reports of patients who required ECMO support up to 23 d suggest that outcomes with prolonged bivalirudin use are similar to UFH[21,24].

Argatroban

Argatroban is a synthetic, univalent DTI, and thereby binds directly to the catalytic site on thrombin in a reversible fashion[16]. Compared to the other DTIs, it has a relatively small molecular size (527 Da). It is administered by intravenous infusion, has an onset of action within 30 minutes, and has a half-life of 45 min in patients with normal hepatic function (Table 1). Of the DTIs, argatroban has the greatest serum protein binding, with 20% to albumin and 34% to alpha$_1$-acid glycoprotein. Lidocaine-an antiarrhythmic used on occasion in cardiothoracic surgical patients-may decrease argatroban concentrations up to 20% due to its high affinity for alpha$_1$-acid glycoprotein[29].

Argatroban is available as therapeutic anticoagulation for confirmed or suspected HIT in patients who develop thrombocytopenia while on ECMO support. There are limited data available regarding argatroban use in ECMO; most are case reports and case series (Table 3)[30-37]. There is one retrospective study of 39 adult patients treated with argatroban, which also included a small proportion of patients supported with pumpless extracorporeal lung assist[38]. Patients supported with both VV and VA systems are described, and all are limited to patient population with suspected or confirmed HIT. There are no reported cases with argatroban as a first-line anticoagulant in ECMO patients.

Dosing: Only one patient in the reviewed literature received the manufacturer-recommended initial dose of 2 μg/kg/min. The patient subsequently suffered major bleeding complications and required a rapid dose reduction[30]. In all other reported cases, patients subsequently received doses at a rate approximately 10% the manufacturer recommended dose, with most initial doses ranging from 0.1-0.3 μg/kg/min. This is consistent with literature from other critically ill populations

Table 3 Summary of studies reporting on argatroban in adult patients supported with extracorporeal membrane oxygenation

First author, Year	Study type	Population	Circuit (VA/VV)	CRRT	Bolus dose	Initial infusion	Monitoring	Duration	Majorbleeding	Thrombosis	Other adverse events	Outcome
Sin *et al*[37], 2017	Case report	27M ARDS, HIT	VV	Yes	NA	0.2 μg/kg/min	aPTT 50-60 s	60 d	Hemothorax developed while on heparin, resolved on ARGA day 27	None	Transient elevations in liver enzymes, no clinical consequence	Patient transferred for lung transplantation
Ratzlaff *et al*[35], 2016	Case report	58M ARDS, HIT	VV	No	NA	0.1-0.3 μg/kg/min	aPTT 60-90 s	11 d	None	None	NA	Withdrawal of care after 28 d of ECMO support
Johnston *et al*[34], 2002	Case report	32M CS, HIT	VA	No	10 mg	2 μg/kg/h	ACT 200-400 s aPTT 80-90 s	7 d	None	NA	NA	Decannulated on ECMO day 10
Dolch *et al*[32], 2010	Case report	40M ARDS, HIT	VV	No	NA	0.35 μg/kg/min	aPTT 45-60 s	108 d	Major bleeding after lung transplant (ECMO day 114) – ARGA held	NA	Hepatic failure post-transplant Infusion reduced to 0.02 μg/kg/min	Patient underwent lung transplant on ECMO day 114, complicated by graft failure Died on post-operative day 17 (multi-organ failure)
Fernandes *et al*[33], 2019	Case report	44M CS, HIT	VA	Yes	NA	1.5 mg/h	aPTT 60-70 s	20 d	Mediastinal bleeding due to pulmonary edema Massive intraoperative hemorrhage during LVAD insertion, DIC	LV and RV thrombus during intraoperative DIC	NA	Survived to discharge
Cornell *et al*[31], 2007	Case series	*n* = 4 with HIT ARDS (*n* = 3) CS (*n* = 1)	VA (*n* = 2) VV (*n* = 2)	No	NA	0.2-2.0 μg/kg/min	ACT 210-230 s	88-184 h	Major bleeding (*n* = 2)	NA	NA	Survival to discharge (*n* = 2, 50%) Death (*n* = 2, 50%)
Beiderlinden *et al*[30], 2007	Case series	*n* = 9 with ARDS, HIT	VV	*n* = 8	NA	2.0 μg/kg/min (*n* = 1) 0.2 μg/kg/min (*n* = 8)	aPTT 50-60 s	4 ± 1 d (mean)	Major bleeding (*n* = 1) in patient who received higher initial infusion dose	None	NA	Survived (*n* = 6) Died (*n* = 3)

Rougé *et al*[36], 2017	Case series	49M CS, HIT 69M ARDS, HIT	VA	*n* = 1	NA	0.2 μg/kg/min 1 μg/kg/min	aPTT 1.5-3.0 × baseline	10 d 8 d	NA	Circuit clotting (*n* = 1)	ALF requiring dose reduction	Survived (*n* = 1) Decannulated, but died prior to discharge (*n* = 1)
Menk *et al*[38], 2017	Retrospective	*n* = 34 ARDS, HIT or heparin resistance	VV (*n* = 24) pECLA (*n* = 9)	NA	NA	0.3 μg/kg/min	aPTT 50-75 s	265 h (131-460)	*n* = 11—no differences compared to matched UFH cohort	*n* = 6—no differences compared to matched UFH cohort	NA	*n* = 21 (54%) died

ACT: Activated clotting time; aPTT: Activated partial thromboplastin time; ARDS: Acute respiratory distress syndrome; ARGA: Argatroban; CRRT: Continuous renal replacement therapy; CS: Cardiogenic shock; DIC: Disseminated intravascular coagulation; ECLS: Extra-corporeal life support; HIT: Heparin-induced thrombocytopenia; LVAD: Left ventricular assist device; NA: Not available; TEG: Thromboeslastography; UFH: Unfractionated heparin; VA: Veno-arterial; VV: Veno-venous.

which suggests that an initial dose of 0.2 μg/kg/min results in adequate dosing based on aPTT measurement, without excessive bleeding or thrombosis[39].

Renal dysfunction: No dose adjustment is required for patients with renal dysfunction, with or without renal replacement therapy, which is a major advantage relative to other agents. There are several reports of successful clinical outcomes with argatroban in patients who require CRRT while supported by ECMO[30,33,37].

Hepatic dysfunction: Argatroban is metabolized hepatically by hydroxylation and aromatization, and therefore has a prolonged half-life of up to four times normal in the setting of liver dysfunction[40]. While CYP3A4 and CYP3A5 provide a minor metabolic pathway, co-administration of inhibitors or inducers of these enzymes do not result in significant changes in argatroban concentrations[41].

Argatroban is not contraindicated in patients with hepatic dysfunction; however significant dose reductions may be required. There are few described cases of argatroban use in patients with liver dysfunction. One reported case of a patient with acute respiratory distress syndrome who underwent lung transplantation complicated by postoperative hepatic dysfunction describes a maintenance dose of 0.02 μg/kg/min in order to achieve the target aPTT[32]. The patient did not suffer from any adverse bleeding or thrombotic events related to the relatively low dose requirement.

Monitoring: The majority of reported cases and the single retrospective study used aPTT as the target for dose adjustment[30,32,33,35,37,38]. Some cases reported use of ACT, either alone or in conjunction with aPTT, as the therapeutic monitoring parameter[31,34]. In cases where aPTT was used, there was no standardized target; most reported a goal of 50-70 s. Of note, Menk *et al*[38] found that bleeding events occurred when the maximum aPTT was above 50-60 s, and two thirds of bleeding events occurred when the maximum aPTT was above 75 s. Conversely, transient aPTT values below 50 s did not signal an increase in thromboembolic events. The authors of that study therefore recommended strict aPTT monitoring with a target of approximately 50 s. This is consistent with published guidelines which suggest an aPTT goal range of 1.5-2.5 times baseline[38]. ACT monitoring, although less frequently used, varies substantially with reported targets between 200 and 400 s. As discussed previously, clinical end points remain the ultimate guidance for adequacy of anticoagulation in these critically ill and complex ECMO patient populations.

Safety and outcomes: There are many reported cases of successful clinical outcomes using argatroban in ECMO patients with suspected or confirmed HIT. In cases in which patients did not survive, none were reported to be directly associated with argatroban use. The reported duration of support is as long as 95 d. The rate of bleeding or thrombosis is low. In the retrospective study of 39 ECMO patients treated with argatroban, the rate of major bleeding or thrombosis was comparable to patients who received heparin[2,38]. There are few reported major bleeding events with argatroban, many of which were related to surgical interventions. Bleeding at cannulation sites is reported, and blood transfusions were frequent, however the reported rate is similar to that seen with heparin[38].

Other agents

Desirudin and lepirudin are recombinant-DNA forms of the naturally occurring peptide, hirudin, present in the salivary glands of leeches. These recombinant hirudins are bivalent DTIs and thereby bind directly to both the catalytic and exosite-1 of thrombin in an irreversible fashion[42]. Because they are composed of non-human proteins, anti-hirudin antibodies may be formed leading to potential immunologic reactions including anaphylaxis[42]. The clinical use of recombinant hirudins during ECMO is limited by these factors and the more favorable pharmacokinetic profiles of the newer synthetic DTIs. Only lepirudin has been reported in adult patients requiring ECMO support. The single case report noted a successful outcome[43]. Lepirudin was withdrawn from market in 2012 and is no longer in production.

Dabigatran etexilate is an oral, synthetic, peptide-like DTI[44]. The onset of action is approximately 1 h and the half-life is 12 to 17 h. Renal excretion is the primary determinant of dabigatran removal, with up to 80% in the urine, and therefore the half-life is prolonged in the setting of renal dysfunction. Dabigatran is a substrate of p-glycoprotein and is therefore prone to a large number of clinically relevant drug interactions with p-glycoprotein inhibitors or inducers. Because of all of these reasons, there is no role for dabigatran in anticoagulation during ECMO.

LIMITATIONS AND SPECIAL USE CONSIDERATIONS

Bleeding

Bleeding is a common cause of morbidity and mortality among ECMO patients, regardless of anticoagulation strategy[2]. There are no formal recommendations for anticoagulation management when bleeding is encountered while on ECMO. For patients receiving DTI therapy, holding DTIs temporarily or short term can be considered. As previously mentioned, there is no specific antidote for DTIs; however, the short half-life of available agents results in rapid offset of anticoagulant effect when the infusion is held or decreased. Once surgical bleeding has been excluded, treating teams can consider performing TEG to further assess the cause of bleeding and transfuse blood products as needed. In patients with hyperfibrinolysis, successful TEG-guided use of tranexamic acid has been described in patients on ECMO and DTIs[45]. Once hemostasis has been achieved, DTI infusions can be restarted at a lower infusion rate, targeting a lower anticoagulation goal based on aPTT or ACT. In the protocol published by Netley *et al*[22], significant bleeding triggered the reduction of the bivalirudin infusion rate, targeting the lower limit of the therapeutic range (*i.e.*, aPTT 40 s). Prothrombin complex concentrates may be used in life-threatening situations[2]. As a general rule, ECMO flow should be increased whenever anticoagulation is reduced or suspended in order to minimize the risk of thrombus formation.

Prothrombin time interference

DTIs commonly prolong the prothrombin time and international normalized ratio in a dose-dependent manner, which may confound monitoring of warfarin in clinical practice. The derangement in these values may depend on the specific assay used[46]. However, it typically does not interfere with ECMO anticoagulation as we primarily use aPTT/ACT. Factor Xa testing may be considered during DTI transitions to warfarin.

Low circuit flow states

While argatroban undergoes mostly hepatic metabolism, bivalirudin is primary metabolized by proteolytic enzymes which rapidly cleave the molecule. This results in the short half-life that has been described. However, instances where blood is stagnant may induce thrombosis due to rapid local cleavage of bivalirudin[47]. Although ECMO is a continuous circuit without any "low-flow" chambers, in cases of cardiac dysfunction the cardiac chambers may act as a source of stagnation. This may particularly be realized in patients who are undergoing active ECMO "wean" trials where circuit flows are down-titrated to assess ability to decannulate. In addition, any setting wherein the native myocardium experiences low pulsatility and allows blood to pool in the ventricles is of very high concern. This may result in localized thrombosis despite adequate bivalirudin dosing. This can be particularly problematic in post-cardiotomy ECMO patients with prosthetic heart valves as valve thrombosis may lead to significant morbidity and mortality. It has been suggested that these circumstances may be avoided by minimizing intracardiac blood flow in cases of cardiogenic shock or avoid low-pulsatility states, and by using UFH as alternative anticoagulation in cases where intracardiac spontaneous echo contrast, or "smoke

effect," is noted, or low-flow states are suspected[47]. During EMCO weaning and trial-off period, especially in setting of VA ECMO wean and if the duration of the trial-off is prolonged, preemptive heparin administration is essential to minimize thrombus formation.

Direct thrombin inhibitor resistance and high-dose response

Resistance to UFH has been reported both in ECMO and non-ECMO cases, with multiple potential explanations[48,49]. Less is known regarding DTI resistance, although cases have been reported using both bivalirudin and argatroban[50-53]. Very few described cases included patients requiring extracorporeal support. In cases of DTI resistance, increasing doses are required to achieve the target aPTT. This has been reported with initial dosing of DTI, although there are also delayed presentations with therapeutic levels initially followed by progressive unexplained dose increases to maintain therapeutic aPTT levels[26,50,53]. The mechanism of DTI resistance is unclear but may be associated with elevated factor VIII and fibrinogen, which has been reported in some cases[52,53]. Notably, these patients ultimately require very high doses of DTI to achieve aPTT targets, often well above the maximum recommended dose. It has been suggested that increases in DTI dosage may result in less aPTT prolongation at high doses than at low doses, which may explain why patients on high doses of DTI require greater than expected dose increases[51]. Conversely, the increase in the international normalized ratio may be more pronounced at high DTI doses[51,53]. Early recognition and rapid titration are essential, as there are multiple reports of clinical thrombosis due to subtherapeutic anticoagulation during delayed titration to target aPTT levels[53]. This point highlights the importance of applying clinical end points (circuit patency, bleeding vs. thrombosis) as ultimate guidance for ECMO anticoagulation management. In cases of DTI resistance, alternative monitoring parameters have been proposed as aPTT may be unreliable. These include ACT, thrombin time, or direct drug level measurement[53,54]. The therapeutic targets for these parameters, however, are variably defined.

CONCLUSION

Systemic anticoagulation with DTIs in ECMO patients is a feasible and safe alternative, with several advantages over UFH. The primary indication for DTIs is in cases of suspected or confirmed HIT, however reports suggest that DTIs may be effective as an initial anticoagulation strategy for all ECMO patients. Multiple dosing and monitoring protocols have been proposed for both bivalirudin and argatroban, and further prospective trials should determine the optimal pathway to safe, effective anticoagulation in this critically ill population.

REFERENCES

1 **Bartlett RH**, Gattinoni L. Current status of extracorporeal life support (ECMO) for cardiopulmonary failure. *Minerva Anestesiol* 2010; **76**: 534-540 [PMID: 20613694]
2 The Extracorporeal Life Support Organization (ELSO). ELSO Anticoagulation Guideline 2014 [cited April 11, 2019]. Available from: https://www.elso.org/Portals/0/Files/elsoanticoagulationguideline8-2014-table-contents.pdf
3 **Askenazi DJ**, Selewski DT, Paden ML, Cooper DS, Bridges BC, Zappitelli M, Fleming GM. Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation. *Clin J Am Soc Nephrol* 2012; **7**: 1328-1336 [PMID: 22498496 DOI: 10.2215/CJN.12731211]
4 **Bembea MM**, Annich G, Rycus P, Oldenburg G, Berkowitz I, Pronovost P. Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: An international survey. *Pediatr Crit Care Med* 2013; **14**: e77-e84 [PMID: 23287906 DOI: 10.1097/PCC.0b013e31827127e4]
5 **Rastan AJ**, Dege A, Mohr M, Doll N, Falk V, Walther T, Mohr FW. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. *J Thorac Cardiovasc Surg* 2010; **139**: 302-311, 311.e1 [PMID: 20106393 DOI: 10.1016/j.jtcvs.2009.10.043]
6 **Rastan AJ**, Lachmann N, Walther T, Doll N, Gradistanac T, Gommert JF, Lehmann S, Wittekind C, Mohr FW. Autopsy findings in patients on postcardiotomy extracorporeal membrane oxygenation (ECMO). *Int J Artif Organs* 2006; **29**: 1121-1131 [PMID: 17219352 DOI: 10.1177/039139880602901205]
7 **Salter BS**, Weiner MM, Trinh MA, Heller J, Evans AS, Adams DH, Fischer GW. Heparin-Induced Thrombocytopenia: A Comprehensive Clinical Review. *J Am Coll Cardiol* 2016; **67**: 2519-2532 [PMID: 27230048 DOI: 10.1016/j.jacc.2016.02.073]
8 **Martel N**, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: A meta-analysis. *Blood* 2005; **106**: 2710-2715 [PMID: 15985543 DOI: 10.1182/blood-2005-04-1546]
9 **Kimmoun A**, Oulehri W, Sonneville R, Grisot PH, Zogheib E, Amour J, Aissaoui N, Megarbane B, Mongardon N, Renou A, Schmidt M, Besnier E, Delmas C, Dessertaine G, Guidon C, Nesseler N, Labro G, Rozec B, Pierrot M, Helms J, Bougon D, Chardonnal L, Medard A, Ouattara A, Girerd N, Lamiral Z, Borie M, Ajzenberg N, Levy B. Prevalence and outcome of heparin-induced thrombocytopenia diagnosed

under veno-arterial extracorporeal membrane oxygenation: A retrospective nationwide study. *Intensive Care Med* 2018; **44**: 1460-1469 [PMID: 30136139 DOI: 10.1007/s00134-018-5346-y]
10 **Choi JH**, Luc JGY, Weber MP, Reddy HG, Maynes EJ, Deb AK, Samuels LE, Morris RJ, Massey HT, Loforte A, Tchantchaleishvili V. Heparin-induced thrombocytopenia during extracorporeal life support: Incidence, management and outcomes. *Ann Cardiothorac Surg* 2019; **8**: 19-31 [PMID: 30854309 DOI: 10.21037/acs.2018.12.02]
11 **Glick D**, Dzierba AL, Abrams D, Muir J, Eisenberger A, Diuguid D, Abel E, Agerstrand C, Bacchetta M, Brodie D. Clinically suspected heparin-induced thrombocytopenia during extracorporeal membrane oxygenation. *J Crit Care* 2015; **30**: 1190-1194 [PMID: 26363901 DOI: 10.1016/j.jcrc.2015.07.030]
12 **Warkentin TE**, Greinacher A, Koster A. Heparin-induced thrombocytopenia in patients with ventricular assist devices: Are new prevention strategies required? *Ann Thorac Surg* 2009; **87**: 1633-1640 [PMID: 19379937 DOI: 10.1016/j.athoracsur.2008.10.060]
13 **Arepally GM**. Heparin-induced thrombocytopenia. *Blood* 2017; **129**: 2864-2872 [PMID: 28416511 DOI: 10.1182/blood-2016-11-709873]
14 **Pollak U**. Heparin-induced thrombocytopenia complicating extracorporeal membrane oxygenation support in pediatric patients: Review of the literature and alternative anticoagulants. *Perfusion* 2018; **33**: 7-17 [PMID: 29788841 DOI: 10.1177/0267659118766723]
15 **Gurm HS**, Bhatt DL. Thrombin, an ideal target for pharmacological inhibition: A review of direct thrombin inhibitors. *Am Heart J* 2005; **149**: S43-S53 [PMID: 15644793 DOI: 10.1016/j.ahj.2004.10.022]
16 **White CM**. Thrombin-directed inhibitors: Pharmacology and clinical use. *Am Heart J* 2005; **149**: S54-S60 [PMID: 15644794 DOI: 10.1016/j.ahj.2004.10.023]
17 **Di Nisio M**, Middeldorp S, Büller HR. Direct thrombin inhibitors. *N Engl J Med* 2005; **353**: 1028-1040 [PMID: 16148288 DOI: 10.1056/NEJMra044440]
18 **Weitz JI**, Bates ER. Direct thrombin inhibitors in cardiac disease. *Cardiovasc Toxicol* 2003; **3**: 13-25 [PMID: 12668887 DOI: 10.1385/CT:3:1:13]
19 **Hospira Inc**. Product Information: Bivalirudin intravenous injection solution, bivalirudin intravenous injection solution. Lake Forest, IL, United Sates, 2015.
20 **Berei TJ**, Lillyblad MP, Wilson KJ, Garberich RF, Hryniewicz KM. Evaluation of Systemic Heparin Versus Bivalirudin in Adult Patients Supported by Extracorporeal Membrane Oxygenation. *ASAIO J* 2018; **64**: 623-629 [PMID: 29076942 DOI: 10.1097/MAT.0000000000000691]
21 **Jyoti A**, Maheshwari A, Daniel E, Motihar A, Bhathiwal RS, Sharma D. Bivalirudin in venovenous extracorporeal membrane oxygenation. *J Extra Corpor Technol* 2014; **46**: 94-97 [PMID: 24779126]
22 **Netley J**, Roy J, Greenlee J, Hart S, Todt M, Statz B. Bivalirudin Anticoagulation Dosing Protocol for Extracorporeal Membrane Oxygenation: A Retrospective Review. *J Extra Corpor Technol* 2018; **50**: 161-166 [PMID: 30250342]
23 **Pappalardo F**, Maj G, Scandroglio A, Sampietro F, Zangrillo A, Koster A. Bioline heparin-coated ECMO with bivalirudin anticoagulation in a patient with acute heparin-induced thrombocytopenia: The immune reaction appeared to continue unabated. *Perfusion* 2009; **24**: 135-137 [PMID: 19654158 DOI: 10.1177/0267659109106773]
24 **Pieri M**, Agracheva N, Bonaveglio E, Greco T, De Bonis M, Covello RD, Zangrillo A, Pappalardo F. Bivalirudin versus heparin as an anticoagulant during extracorporeal membrane oxygenation: A case-control study. *J Cardiothorac Vasc Anesth* 2013; **27**: 30-34 [PMID: 23036625 DOI: 10.1053/j.jvca.2012.07.019]
25 **Ranucci M**, Ballotta A, Kandil H, Isgrò G, Carlucci C, Baryshnikova E, Pistuddi V; Surgical and Clinical Outcome Research Group. Bivalirudin-based versus conventional heparin anticoagulation for postcardiotomy extracorporeal membrane oxygenation. *Crit Care* 2011; **15**: R275 [PMID: 22099212 DOI: 10.1186/cc10556]
26 **Walker EA**, Roberts AJ, Louie EL, Dager WE. Bivalirudin Dosing Requirements in Adult Patients on Extracorporeal Life Support With or Without Continuous Renal Replacement Therapy. *ASAIO J* 2019; **65**: 134-138 [PMID: 29538017 DOI: 10.1097/MAT.0000000000000780]
27 **Robson R**, White H, Aylward P, Frampton C. Bivalirudin pharmacokinetics and pharmacodynamics: Effect of renal function, dose, and gender. *Clin Pharmacol Ther* 2002; **71**: 433-439 [PMID: 12087346 DOI: 10.1067/mcp.2002.124522]
28 **Tsu LV**, Dager WE. Bivalirudin dosing adjustments for reduced renal function with or without hemodialysis in the management of heparin-induced thrombocytopenia. *Ann Pharmacother* 2011; **45**: 1185-1192 [PMID: 21881032 DOI: 10.1345/aph.1Q177]
29 **Kondo LM**, Wittkowsky AK, Wiggins BS. Argatroban for prevention and treatment of thromboembolism in heparin-induced thrombocytopenia. *Ann Pharmacother* 2001; **35**: 440-451 [PMID: 11302409 DOI: 10.1345/aph.10301]
30 **Beiderlinden M**, Treschan T, Görlinger K, Peters J. Argatroban in extracorporeal membrane oxygenation. *Artif Organs* 2007; **31**: 461-465 [PMID: 17537058 DOI: 10.1111/j.1525-1594.2007.00388.x]
31 **Cornell T**, Wyrick P, Fleming G, Pasko D, Han Y, Custer J, Haft J, Annich G. A case series describing the use of argatroban in patients on extracorporeal circulation. *ASAIO J* 2007; **53**: 460-463 [PMID: 17667231 DOI: 10.1097/MAT.0b013e31805c0d6c]
32 **Dolch ME**, Frey L, Hatz R, Uberfuhr PA, Beiras-Fernandez A, Behr J, Irlbeck M, Lung Transplant Group TM. Extracorporeal membrane oxygenation bridging to lung transplant complicated by heparin-induced thrombocytopenia. *Exp Clin Transplant* 2010; **8**: 329-332 [PMID: 21143102 DOI: 10.1002/dat.20521]
33 **Fernandes P**, O'Neil M, Del Valle S, Cave A, Nagpal D. A 24-hour perioperative case study on argatroban use for left ventricle assist device insertion during cardiopulmonary bypass and veno-arterial extracorporeal membrane oxygenation. *Perfusion* 2019; **34**: 337-344 [PMID: 30583712]
34 **Johnston N**, Wait M, Huber L. Argatroban in adult extracorporeal membrane oxygenation. *J Extra Corpor Technol* 2002; **34**: 281-284 [PMID: 12533066]
35 **Ratzlaff RA**, Ripoll JG, Kassab LL, Diaz-Gomez JL. Acute oxygenator failure: A new presentation of heparin-induced thrombocytopenia in a patient undergoing venovenous extracorporeal membrane oxygenation support. *BMJ Case Rep* 2016; **2016**: pii: bcr2016218179 [PMID: 27986695 DOI: 10.1136/bcr-2016-218179]
36 **Rougé A**, Pelen F, Durand M, Schwebel C. Argatroban for an alternative anticoagulant in HIT during ECMO. *J Intensive Care* 2017; **5**: 39 [PMID: 28680640 DOI: 10.1186/s40560-017-0235-y]
37 **Sin JH**, Lopez ND. Argatroban for Heparin-Induced Thrombocytopenia during Venovenous Extracorporeal Membrane Oxygenation with Continuous Venovenous Hemofiltration. *J Extra Corpor Technol* 2017; **49**: 115-120 [PMID: 28638161]

38 **Menk M**, Briem P, Weiss B, Gassner M, Schwaiberger D, Goldmann A, Pille C, Weber-Carstens S. Efficacy and safety of argatroban in patients with acute respiratory distress syndrome and extracorporeal lung support. *Ann Intensive Care* 2017; **7**: 82 [PMID: 28776204 DOI: 10.1186/s13613-017-0302-5]

39 **Beiderlinden M**, Treschan TA, Görlinger K, Peters J. Argatroban anticoagulation in critically ill patients. *Ann Pharmacother* 2007; **41**: 749-754 [PMID: 17440009 DOI: 10.1345/aph.1H569]

40 **Swan SK**, Hursting MJ. The pharmacokinetics and pharmacodynamics of argatroban: Effects of age, gender, and hepatic or renal dysfunction. *Pharmacotherapy* 2000; **20**: 318-329 [PMID: 10730687 DOI: 10.1592/phco.20.4.318.34881]

41 **Tran JQ**, Di Cicco RA, Sheth SB, Tucci M, Peng L, Jorkasky DK, Hursting MJ, Benincosa LJ. Assessment of the potential pharmacokinetic and pharmacodynamic interactions between erythromycin and argatroban. *J Clin Pharmacol* 1999; **39**: 513-519 [PMID: 10234600]

42 **Schaden E**, Kozek-Langenecker SA. Direct thrombin inhibitors: Pharmacology and application in intensive care medicine. *Intensive Care Med* 2010; **36**: 1127-1137 [PMID: 20425104 DOI: 10.1007/s00134-010-1888-3]

43 **Balasubramanian SK**, Tiruvoipati R, Chatterjee S, Sosnowski A, Firmin RK. Extracorporeal membrane oxygenation with lepirudin anticoagulation for Wegener's granulomatosis with heparin-induced thrombocytopenia. *ASAIO J* 2005; **51**: 477-479 [PMID: 16156317 DOI: 10.1097/01.mat.0000169123.21946.31]

44 **Lee CJ**, Ansell JE. Direct thrombin inhibitors. *Br J Clin Pharmacol* 2011; **72**: 581-592 [PMID: 21241354 DOI: 10.1111/j.1365-2125.2011.03916.x]

45 **Seelhammer TG**, Mangla J, Demirci O. The Use of Thromboelastography to Titrate Tranexamic Acid Therapy for Abatement of Lysis-Induced Hemorrhagic Complications During Venoarterial Extracorporeal Membrane Oxygenation. *J Cardiothorac Vasc Anesth* 2019; **33**: 1059-1062 [PMID: 30765211 DOI: 10.1053/j.jvca.2018.07.024]

46 **Gosselin RC**, Dager WE, King JH, Janatpour K, Mahackian K, Larkin EC, Owings JT. Effect of direct thrombin inhibitors, bivalirudin, lepirudin, and argatroban, on prothrombin time and INR values. *Am J Clin Pathol* 2004; **121**: 593-599 [PMID: 15080313 DOI: 10.1309/D79K-4YG7-8NTN-YY38]

47 **Ranucci M**. Bivalirudin and post-cardiotomy ECMO: A word of caution. *Crit Care* 2012; **16**: 427 [PMID: 22574927 DOI: 10.1186/cc11314]

48 **Hage A**, Louzada M, Kiaii B. Sepsis-induced heparin resistance during extracorporeal membrane oxygenation. *CMAJ* 2019; **191**: E283-E285 [PMID: 30858184 DOI: 10.1503/cmaj.181061]

49 **Finley A**, Greenberg C. Review article: Heparin sensitivity and resistance: Management during cardiopulmonary bypass. *Anesth Analg* 2013; **116**: 1210-1222 [PMID: 23408671 DOI: 10.1213/ANE.0b013e31827e4e62]

50 **Bostwick A**. Direct Thrombin Inhibitor Resistance. Abstract published at Hospital Medicine; 2015 Mar 29-Apr 1, National Harbor, USA.. *J Hosp Med* 2015; **10**: Suppl 2: Abstract 461

51 **Hellwig TR**, Peitz GJ, Gulseth MP. High-dose argatroban for treatment of heparin-induced thrombocytopenia with thrombosis: A case report and review of laboratory considerations. *Am J Health Syst Pharm* 2012; **69**: 490-495 [PMID: 22382479 DOI: 10.2146/ajhp110147]

52 **Kennedy DM**, Alaniz C. Apparent argatroban resistance in a patient with elevated factor VIII levels. *Ann Pharmacother* 2013; **47**: e29 [PMID: 23737512 DOI: 10.1345/aph.1R745]

53 **Cardinale M**, Ha M, Liu MH, Reardon DP. Direct Thrombin Inhibitor Resistance and Possible Mechanisms. *Hosp Pharm* 2016; **51**: 922-927 [PMID: 28057952 DOI: 10.1310/hpj5111-922]

54 **Seelhammer TG**, Bohman JK, Aganga DO, Maltais S, Zhao Y. Bivalirudin and ECLS: Commentary and Considerations. *ASAIO J* 2019; **65**: e52-e53 [PMID: 30299300]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 October 16; 8(6): 99-105

DOI: 10.5492/wjccm.v8.i6.99

ISSN 2220-3141 (online)

CASE REPORT

Fatal *Legionella pneumophila* serogroup 1 pleural empyema: A case report

François Maillet, Nicolas Bonnet, Typhaine Billard-Pomares, Fatma El Alaoui Magdoud, Yacine Tandjaoui-Lambiotte

ORCID number: François Maillet (0000-0002-1773-4735); Nicolas Bonnet (0000-0003-0598-1242); Typhaine Billard-Pomares (0000-0002-2227-8383); Fatma El Alaoui Magdoud (0000-0002-3360-8165); Yacine Tandjaoui-Lambiotte (0000-0003-1123-4788).

Author contributions: Maillet F drafted the manuscript and reviewed the literature. Bonnet N contributed to the manuscript drafting. Billard-Pomares T and El Alaoui Magdoud F performed microbiological analyses and interpretation and contributed to the manuscript drafting. Tandjaoui-Lambiotte Y contributed to the manuscript drafting, reviewed and analyzed the literature and was responsible of the manuscript's revision. All authors issued final approval for the version to be submitted

Informed consent statement: Informed consent was not available due to the death of the patient. No family was available.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The manuscript was prepared and revised according to the CARE Checklist (2016).

François Maillet, Nicolas Bonnet, Yacine Tandjaoui-Lambiotte, Intensive Care Unit, Avicenne Hospital, Assistance Publique – Hôpitaux de Paris, Bobigny 93000, France

Nicolas Bonnet, Paris XIII University, Bobigny 93000, France

Typhaine Billard-Pomares, Microbiology Department, Avicenne Hospital, Assistance Publique – Hôpitaux de Paris, Bobigny 93000, France

Fatma El Alaoui Magdoud, Microbiology Department, Jean Verdier Hospital, Assistance Publique–Hôpitaux de Paris, Bondy 93140, France

Corresponding author: Yacine Tandjaoui-Lambiotte, MD, Doctor, Intensive Care Unit, Avicenne Hospital, APHP, 125 rue de Stalingrad, Bobigny 93000, France.
yacine.tandjaoui-lambiotte@aphp.fr
Telephone: +33-1-48955241
Fax: +33-1-48955090

Abstract

BACKGROUND

Legionella pneumophila (*L. pneumophila*) is a gram-negative intracellular bacillus composed of sixteen different serogroups. It is mostly known to cause pneumonia in individuals with known risk factors as immunocompromised status, tobacco use, chronic organ failure or age older than 50 years. Although parapneumonic pleural effusion is frequent in legionellosis, pleural empyema is very uncommon. In this study, we report a case of fatal pleural empyema caused by *L. pneumophila* serogroup 1 in an 81-year-old man with multiple risk factors.

CASE SUMMARY

An 81-year-old man presented to the emergency with a 3 wk dyspnea, fever and left chest pain. His previous medical conditions were chronic lymphocytic leukemia, diabetes mellitus, chronic kidney failure, hypertension and hyperlipidemia, without tobacco use. Chest X-ray and comouted tomography-scan confirmed a large left pleural effusion, which puncture showed a citrine exudate with negative standard bacterial cultures. Despite intravenous cefotaxime antibiotherapy, patient's worsening condition after 10 d led to thoracocentesis and evacuation of 2 liters of pus. The patient progressively developed severe hypoxemia and multiorgan failure occurred. The patient was treated by antibiotherapy with cefepime and amikacin and with adequate symptomatic shock treatment, but died of uncontrolled sepsis. The next day,

Manuscript source: Unsolicited manuscript

Received: April 22, 2019
Peer-review started: April 23, 2019
First decision: August 1, 2019
Revised: August 29, 2019
Accepted: September 9, 2019
Article in press: September 9, 2019
Published online: October 16, 2019

P-Reviewer: Mehdi I, Zhang ZH
S-Editor: Zhang L
L-Editor: A
E-Editor: Liu MY

cultures of the surgical pleural liquid samples yielded *L. pneumophila* serogroup 1, consistent with the diagnosis of pleural legionellosis.

CONCLUSION
L. pneumophila should be considered in patients with multiple risk factors and undiagnosed pleural empyema unresponsive to conventional antibiotherapy.

Key words: Legionella pneumophila serogroup 1; Legionellosis; Legionnaire's disease; Pleural empyema; Case report

Core tip: *Legionella pneumophila* (*L. pneumophila*) is a gram-negative bacillus known as a common cause of pneumonia, with frequent parapneumonic pleural effusion. In contrast, pleural empyema seems very uncommon. We report here the case of an 81-year-old man with multiple comorbidities who presented with a large left pleural effusion. Despite wide antibiotic courses against extracellular bacteria associated to surgical thoracentesis, patient died of uncontrolled septic shock. *L. pneumophila* serogroup 1 was isolated from the surgical pleural liquid sample, consistent with a pleural localization of Legionnaire's disease. We therefore would emphasize that *L. pneumophila* is an exceptional cause of pleural empyema in patients with multiple risk factors.

Citation: Maillet F, Bonnet N, Billard-Pomares T, El Alaoui Magdoud F, Tandjaoui-Lambiotte Y. Fatal *Legionella pneumophila* serogroup 1 pleural empyema: A case report. *World J Crit Care Med* 2019; 8(6): 99-105
URL: https://www.wjgnet.com/2220-3141/full/v8/i6/99.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i6.99

INTRODUCTION

Legionella pneumophila (*L. pneumophila*) is a Gram-negative, slow-growing intracellular bacillus, originally discovered in 1976 in Philadelphia among the delegates of the American Legion conference[1]. Since then, sixteen different serogroups have been described, with a large predominance of serogroup 1, responsible for approximatively 85% of the cases[2]. Risk factors for infection include male sex, aged more than 50 years, current or historical smoking, alcohol abuse, diabetes, cancer, chronic kidney failure, iron overload and immunocompromising diseases or treatments[3]. Although it is mostly known to cause acute severe pneumonia, with frequent parapneumonic pleural effusion, *L. pneumophila* infection may rarely cause pleural empyema.

We report here a case of pleural empyema caused by *L. pneumophila* serogroup 1 in an immunocompromised patient, followed by a review of the literature.

CASE PRESENTATION

Chief complaints

In august 2018, an 81-year-old caucasian man presented to the emergency department with fever, progressive dyspnea, dry cough and left pleuritic chest pain.

History of present illness

Patients symptoms started 3 wk ago and worsened progressively.

History of past illness

His medical history was consistent with chronic lymphocytic leukemia, initially treated in 2007 with Fludarabine, Cyclophosphamide and Rituximab therapy with chronic lymphocytosis, type 2 diabetes mellitus, hypertension, hyperlipidemia and chronic kidney failure with an eGFR of 28 mL/min/1.73 m^2. He reported no smoking or alcohol abuse and used to work as an upholsterer.

Personal and family history

None.

Physical examination upon admission

Physical examination revealed fever (38.1°C), tachycardia (105 bpm), peripheral percutaneous oxygen saturation was 100% with 2 liters of oxygen with tachypnea, normal blood pressure and almost abolished left vesicular murmur. Adenopathy, hepatomegaly or splenomegaly were not observed. Cardiovascular and neurologic examination were normal.

Laboratory examination

Biology tests revealed neutrophilia (18.7 g/L) and elevated CRP (297 mg/L) consistent with inflammatory response, along with stable lymphocytosis (242 g/L) and anemia (7.8 g/L).

Imaging examination

Chest X-ray at admission (Figure 1) showed a large left pleural effusion with contralateral tracheal deviation. Complementary computed tomography (Figure 2) confirmed a walled-off, loculated left pleural effusion, with right lung parenchyma considered normal.

Further diagnostic work-up

First bedside pleural puncture showed a citrine exudate (pleural protein 37 g/L, pleural fluid protein to serum ratio 0.61), unfortunately cytological examination was not performed.

Despite intravenous treatment with cefotaxime, the patient condition worsened with persistence of fever, neutrophilia, and severe hypoxemia appeared. Bacteriological standard culture of the pleural liquid sample was negative, as well as repeated blood cultures. In order to look for a tuberculosis etiology, auramine stained sputum smears and cultures were performed but remained negative. Spot-test for tuberculosis was not performed. Ten days after his admission, because of the uncontrolled large pleural effusion with acute hypoxemic respiratory failure, the patient underwent surgical thoracentesis with evacuation of 2 liters of purulent liquid. We chose surgery instead of repeated pleural drawings, because local sepsis was not controlled nor bacteriologically documented. Pleura was thick and nodular, with white pseudo-membranes. Treatment with metronidazole was added to cefotaxime after the surgery in order to cover anaerobic bacteria. Cytobacteriological examination and cultures of the liquid were negative. Lymphocyte phenotyping ruled out B-cell lymphoma as a complication of his chronic lymphocytic leukemia. Three days after, the patient progressively developed multiple organ failure requiring intensive care unit admission. As no massive transfusion was initiated during surgery and shock was the main matter, fluid overload could not explain the evolution in multiple organ failure. After a slow unfavorable evolution during the ten first days of hospitalization, the patient's condition worse brutaly three days after surgical thoracocentesis leading to septic shock complicated of multiple organ failure. Despite antibiotherapy with cefepime and amikacin, invasive mechanical ventilation, vasopressor infusion and renal replacement therapy, the patient died of uncontrolled septic shock few hours after ICU admission.

The day after, mycobacterial culture of surgical pleural samples yielded Gram-negative bacilli (Figure 3). Rapid identification using matrix-assisted desorption ionization–time of flight mass spectrometry (MALDI-TOF MS; Microflex LT; Bruker Daltonics, Leipzig, Germany) was performed and *L. pneumophila* was identified. The bacteria were addressed to the National Reference Center of Legionella and molecular typing analysis by sequence-based typing was performed and showed that the strain of *L. pneumophila* serogroup 1 belonged to Sequence Type 1. Urinary antigen research retrospectively performed on a urine sample of the patient confirmed the presence of *L. pneumophila* serogroup 1.

We believe that chances of super infection or co-infection with another bacterium are scarce. Patient indeed received broad spectrum antibiotics directed against common bacteria causing pleural empyema (including anaerobic bacteria, gram-negative bacillus, streptococci and staphylococci), and repeated standard bacteriological cultures remained negative.

Retrospectively, our patient presented the following risk factors: Male sex, aged more than 50 years, chronic lymphocytic leukemia with history of immunocompromising treatments, chronic kidney failure, diabetes mellitus and weaned smoking.

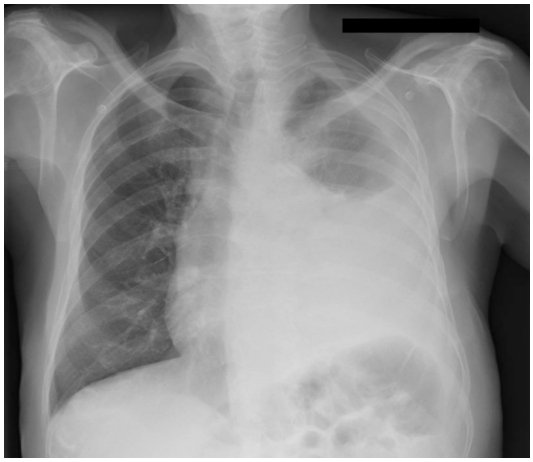


Figure 1 Chest X-ray at admission: Large left pleural effusion with contralateral deviation of the mediastinum.

FINAL DIAGNOSIS

Fatal pleural empyema caused by *L.pneumophila* serogroup 1.

TREATMENT

No specific treatment could have been introduced because of post-mortem diagnosis. Unfortunately, the *L. pneumophila* stain identified in our patient was naturally resistant to all the antibiotics received.

OUTCOME AND FOLLOW-UP

Patient died of uncontrolled sepsis caused by *L. pneumophila* serogroup 1 pleural empyema.

DISCUSSION

Pleural effusion is a common manifestation of Legionnaire's disease. In a case series of 36 microbiologically proven legionellosis, Sakai *et al*[4] reported in 2007 unilateral or bilateral scannographic pleural effusion in 60% of pneumonia caused by *L. pneumophila*, considered as a parapneumonic aseptic transudate. Similarly, Poirier *et al*[5] reported in 2017, in a 33 individuals canadian cohort, a scannographic frequency of 66% (22/33). In contrast, pleural empyema, defined as a septic exudate with presence of *L. pneumophila*, seems exceptional.

Prevalence of pleural empyema in legionellosis is largely unknown. Since 1979, only 11 cases have been reported. These cases involved mostly men with an age ranging between 36 and 83[6-12]. *L. pneumophila* serogroup 1 seems to be involved in most cases, but one serogroup 5 nosocomial *L. pneumophila* has been described in a patient following esophageal perforation after esophageal dilatation for carcinoma[6-8]. All infected patients with detailed history presented classic risk factors: Tobacco use, relative immunosuppression caused by advanced age, high-dose steroids as a treatment for systemic lupus erythematosus[9], immunosuppressive drugs in a kidney transplant recipient[10]. In 1981, Winn and Myerowitz reported two necropsias of fatal legionellosis with unilateral empyema with presence of *L. pneumophila* in pleural fluid[11]. Characteristics of pleural liquid, available for six cases, seem to be those of a classic empyema : Macroscopically purulent or serofibrinous, elevated LDH (5 out of 5, 1 non tested, range 342-2371 UI/L) and proteins (6 out of 6, range 31-57 g/L), with a predominance of neutrophils (6 out of 6) , with hypoglycopleuria and acid pH.

L. pneumophila infection is associated with a poor outcome: In a retrospective study of 136 consecutive cases of communautary *L. pneumophila* infection in Spain between 2001 and 2015, 85% of patients were hospitalized, including 11.7% in intensive care unit, and the mortality rate was 4.4%[13]. Of the 11 patients described, 2 died with unrecorded treatment, 7 patients survived with adequate antibiotic course, and the

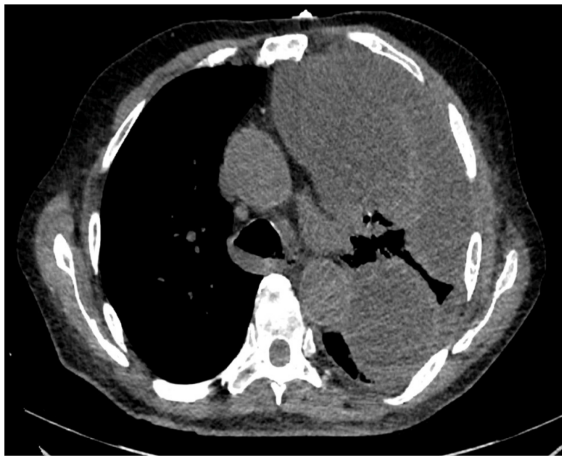


Figure 2 Computed tomography of the chest at admission: Multiloculated left pleural effusion

outcome of the 2 last was unknown. Choice of antibiotic stewardship and duration of antibiotic course for pleural legionellosis is widely empirical: 4 patients received a 4 wk course of IV erythromycin, 2 received a combination of erythromycin and rifampicin during 8 wk, and the last one was treated with levofloxacin for an undetermined duration of time.

Early identification of sepsis and early administration of adapted antibiotherapy is now recommended by international clinical practice guidelines[14]. In our case report, identification of sepsis and its pleural origin was easy. Unfortunately, empirical antibiotherapy did not cover *Legionellosis*, and probably led to the patient's death.

Extrapulmonary legionellosis is a very challenging diagnosis and might involve many different organs[15-18]. In patients with immunocompromising conditions, *L. pneumophila* can cause septic arthritis, endocarditis, myocarditis, myositis or cutaneous involvement, including panniculitis, exanthema, subcutaneous nodules, pustules or even abscesses. Other *Legionella* species include, among others, *L. bozemanii*, and *L. micdadei*[2]. These other species, much rarer than *L. pneumophila*, can also exceptionally cause pneumonia with pleural empyema, which seems to be overrepresented compared to *L. pneumophila*[19,20]. *Mycoplasma pneumonia*, another intracellular bacteria known to cause pneumonia, has also been reported a few times as the causative agent of pleural empyema[21].

CONCLUSION

Although uncommon, pleural empyema caused by *L. pneumophila* is associated with a poor outcome, and is therefore a very challenging diagnosis. We suggest that Legionnaire's disease should be considered in patients with multiple risk factors and pleural empyema with negative bacteriological standard culture and unresponsive to conventional antibiotherapy.

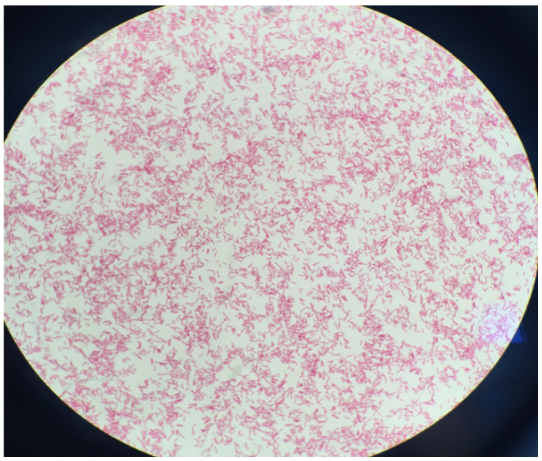


Figure 3 Gram staining of pleural culture confirmed gram-negative bacillus, consistent with *Legionella pneumophila*.

ACKNOWLEDGEMENTS

The authors would like to thank Laetita Beraud, from the French National Reference Center for Legionella, for her work in the identification of serogroup 1 *Legionella pneumophila*.

REFERENCES

1 **Fraser DW**, Tsai TR, Orenstein W, Parkin WE, Beecham HJ, Sharrar RG, Harris J, Mallison GF, Martin SM, McDade JE, Shepard CC, Brachman PS. Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med* 1977; **297**: 1189-1197 [PMID: 335244 DOI: 10.1056/NEJM197712012972201]
2 **Khodr A**, Kay E, Gomez-Valero L, Ginevra C, Doublet P, Buchrieser C, Jarraud S. Molecular epidemiology, phylogeny and evolution of Legionella. *Infect Genet Evol* 2016; **43**: 108-122 [PMID: 27180896 DOI: 10.1016/j.meegid.2016.04.033]
3 **Burillo A**, Pedro-Botet ML, Bouza E. Microbiology and Epidemiology of Legionnaire's Disease. *Infect Dis Clin North Am* 2017; **31**: 7-27 [PMID: 28159177 DOI: 10.1016/j.idc.2016.10.002]
4 **Sakai F**, Tokuda H, Goto H, Tateda K, Johkoh T, Nakamura H, Matsuoka T, Fujita A, Nakamori Y, Aoki S, Ohdama S. Computed tomographic features of Legionella pneumophila pneumonia in 38 cases. *J Comput Assist Tomogr* 2007; **31**: 125-131 [PMID: 17259844 DOI: 10.1097/01.rct.0000233129.06056.65]
5 **Poirier R**, Rodrigue J, Villeneuve J, Lacasse Y. Early Radiographic and Tomographic Manifestations of Legionnaires' Disease. *Can Assoc Radiol J* 2017; **68**: 328-333 [PMID: 28479105 DOI: 10.1016/j.carj.2016.10.005]
6 **Ribera E**, Ferrer A, Gelabert R, Xercavins M, Martínez-Vázquez JM. Pleural empyema caused by Legionella pneumophila. *Med Clin (Barc)* 1989; **92**: 605-607 [PMID: 2747322]
7 **Ferrufino E**, Mejía C, Ortiz de la Tabla V, Chiner E. Empyema caused by Legionella pneumophila. *Arch Bronconeumol* 2012; **48**: 102-103 [PMID: 22153580 DOI: 10.1016/j.arbres.2011.10.005]
8 **Muder RR**, Stout JE, Yee YC. Isolation of Legionella pneumophila serogroup 5 from empyema following esophageal perforation. Source of the organism and mode of transmission. *Chest* 1992; **102**: 1601-1603 [PMID: 1424901 DOI: 10.1378/chest.102.5.1601]
9 **Gómez J**, Cuesta F, Zamorano C, García Lax F. Pleural empyema in Legionella pneumophila nosocomial pneumonia in a patient with systemic lupus erythematosus. *Med Clin (Barc)* 1992; **99**: 358-359 [PMID: 1435013]
10 **Zamarrón Sanz C**, Novoa García D, Fernández Vázquez E, Sánchez Guisande D, Pérez del Molino M, Gómez Ruiz D. Pulmonary abscess and pleural empyema caused by Legionella pneumophila in kidney transplant recipient. *An Med Interna* 1993; **10**: 547-548 [PMID: 8117870]
11 **Winn WC**, Myerowitz RL. The pathology of the Legionella pneumonias. A review of 74 cases and the literature. *Hum Pathol* 1981; **12**: 401-422 [PMID: 6166529 DOI: 10.1016/s0046-8177(81)80021-4]
12 **Randolph KA**, Beekman JF. Legionnaires' disease presenting with empyema. *Chest* 1979; **75**: 404-406 [PMID: 421592 DOI: 10.1378/chest.75.3.404]
13 **Romay-Lema E**, Corredoira-Sánchez J, Ventura-Valcárcel P, Iñiguez-Vázquez I, García Pais MJ, García-Garrote F, Rabuñal Rey R. Community acquired pneumonia by Legionella pneumophila: Study of 136 cases. *Med Clin (Barc)* 2018; **151**: 265-269 [PMID: 29705157 DOI: 10.1016/j.medcli.2018.03.011]
14 **Zhang Z**, Smischney NJ, Zhang H, Van Poucke S, Tsirigotis P, Rello J, Honore PM, Sen Kuan W, Ray JJ, Zhou J, Shang Y, Yu Y, Jung C, Robba C, Taccone FS, Caironi P, Grimaldi D, Hofer S, Dimopoulos G, Leone M, Hong SB, Bahloul M, Argaud L, Kim WY, Spapen HD, Rocco JR. AME evidence series 001-The Society for Translational Medicine: clinical practice guidelines for diagnosis and early identification of sepsis in the hospital. *J Thorac Dis* 2016; **8**: 2654-2665 [PMID: 27747021 DOI: 10.21037/jtd.2016.08.03]
15 **Thurneysen C**, Boggian K. Legionella pneumophila serogroup 1 septic arthritis with probable endocarditis in an immunodeficient patient. *J Clin Rheumatol* 2014; **20**: 297-298 [PMID: 25057741 DOI: 10.1097/RHU.0000000000000128]
16 **Samuel V**, Bajwa AA, Cury JD. First case of Legionella pneumophila native valve endocarditis. *Int J*

Infect Dis 2011; **15**: e576-e577 [PMID: 21641261 DOI: 10.1016/j.ijid.2011.04.007]
17 **Chitasombat MN**, Ratchatanawin N, Visessiri Y. Disseminated extrapulmonary Legionella pneumophila infection presenting with panniculitis: case report and literature review. *BMC Infect Dis* 2018; **18**: 467 [PMID: 30223775 DOI: 10.1186/s12879-018-3378-0]
18 **Barigou M**, Cavalie L, Daviller B, Dubois D, Mantion B, Delobel P, Debard A, Prere MF, Marchou B, Martin-Blondel G. Isolation on Chocolate Agar Culture of Legionella pneumophila Isolates from Subcutaneous Abscesses in an Immunocompromised Patient. *J Clin Microbiol* 2015; **53**: 3683-3685 [PMID: 26292305 DOI: 10.1128/JCM.01116-15]
19 **Halberstam M**, Isenberg HD, Hilton E. Abscess and empyema caused by Legionella micdadei. *J Clin Microbiol* 1992; **30**: 512-513 [PMID: 1537927]
20 **Taviot B**, Gueyffier F, Pacheco Y, Boniface E, Coppere B, Perrin-Fayolle M. [Purulent pleurisy due to Legionella bozemanii]. *Rev Mal Respir* 1987; **4**: 47-48 [PMID: 3589108]
21 **Shuvy M**, Rav-Acha M, Izhar U, Ron M, Nir-Paz R. Massive empyema caused by Mycoplasma pneumoniae in an adult: a case report. *BMC Infect Dis* 2006; **6**: 18 [PMID: 16451727 DOI: 10.1186/1471-2334-6-18]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2019 November 19; 8(7): 106-134

Published by Baishideng Publishing Group Inc

WJCCM

World Journal of Critical Care Medicine

Contents Irregular Volume 8 Number 7 November 19, 2019

ORIGINAL ARTICLE

Basic Study

Retrospective Cohort Study

Observational Study

Contents

World Journal of Critical Care Medicine

Volume 8 Number 7 November 19, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Malbrain Malbrain, MD, PhD, Chief Doctor, Professor, Department of Intensive Care Medicine, University Hospital Brussels (UZB), Vrije Universiteit Brussel (VUB), Brussels 1090, Brussels, Belgium

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, infection and anti-infection treatment, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, severe infection, and shock and multiple organ dysfunction syndrome.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Mei-Yi Liu*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

EDITORIAL OFFICE
Jia-Ping Yan, Director

PUBLICATION DATE
November 19, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 November 19; 8(7): 106-119

DOI: 10.5492/wjccm.v8.i7.106

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Basic Study

Minocycline fails to improve neurologic and histologic outcome after ventricular fibrillation cardiac arrest in rats

Andreas Janata, Ingrid AM Magnet, Kristin L Schreiber, Caleb D Wilson, Jason P Stezoski, Keri Janesko-Feldman, Patrick M Kochanek, Tomas Drabek

ORCID number: Andreas Janata (0000-0001-6098-8581); Ingrid AM Magnet (0000-0002-7577-9712); Kristin L Schreiber (0000-0002-7361-2214); Caleb D Wilson (0000-0001-6258-3836); Jason P Stezoski (0000-0002-2121-2251); Keri Janesko-Feldman (0000-0003-3970-3013); Patrick M Kochanek (0000-0002-2627-913X); Tomas Drabek (0000-0002-5702-4498).

Author contributions: Janata A, Magnet IAM, Drabek T, and Kochanek PM designed the study; Janata A, Magnet IAM, and Drabek T conducted the study and collected the data; Janata A, Magnet IAM, Drabek T, Schreiber KL, Wilson CD, and Janesko-Feldman K analyzed the data; Janata A, Magnet IAM, Drabek T, Schreiber KL, Wilson CD, Stezoski JP, and Janesko-Feldman K prepared the manuscript; Stezoski JP performed the experiments and collected the biochemical and neurobehavioral data; Janesko-Feldman K prepared the histological slides; Kochanek PM coordinated the research.

Supported by the Laerdal Foundation for Acute Medicine to Janata A; the Erwin Schroedinger Stipend by the Austrian Science Fund (#J 2931-818) to Janata A; Medical Student Anesthesia Research Foundation Award from the International Anesthesia Research Society to Wilson CD; Seed Grant from The Department of Anesthesiology, University of Pittsburgh to Drabek T; Starter

Andreas Janata, Ingrid AM Magnet, Kristin L Schreiber, Caleb D Wilson, Jason P Stezoski, Keri Janesko-Feldman, Patrick M Kochanek, Tomas Drabek, Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine, Pittsburgh, PA 15224, United States

Andreas Janata, Jason P Stezoski, Keri Janesko-Feldman, Patrick M Kochanek, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, United States

Andreas Janata, Emergency Department, KA Rudolfstiftung, Vienna 1030, Austria

Ingrid AM Magnet, Department of Emergency Medicine, Vienna General Hospital, Medical University of Vienna, Vienna 1090, Austria

Kristin L Schreiber, Jason P Stezoski, Tomas Drabek, Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, United States

Kristin L Schreiber, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, United States

Caleb D Wilson, Wyoming Otolaryngology, Wyoming Medical Center, Casper, WY 82604, United States

Corresponding author: Tomas Drabek, MD, PhD, Associate Professor, Research Scientist, FASA, Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine, 4401 Penn Avenue, Pittsburgh, PA 15224, United States. drabekt@anes.upmc.edu
Telephone: +1-412-6471687
Fax: +1-412-6240943

Abstract

BACKGROUND

Prolonged cardiac arrest (CA) produces extensive neuronal death and microglial proliferation and activation resulting in neuro-cognitive disabilities. Among other potential mechanisms, microglia have been implicated as triggers of neuronal death after hypoxic-ischemic insults. Minocycline is neuroprotective in some brain ischemia models, either by blunting the microglial response or by a direct effect on neurons.

AIM

To improve survival, attenuate neurologic deficits, neuroinflammation, and

Grant from the Society of Cardiovascular Anesthesiologists to Drabek T; the Laerdal Foundation for Acute Medicine to Drabek T.

Institutional review board statement: The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh on February 12, 2013 (Protocol #13021161).

Institutional animal care and use committee statement: The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh on February 12, 2013 (Protocol #13021161). Principal Investigator: Tomas Drabek. Protocol Title: Neuroinflammation after prolonged cardiac arrest.

Conflict-of-interest statement: Dr Drabek reports grants from Society of Cardiovascular Anesthesiolgists, grants from The Laerdal Foundation for Acute Medicine, grants from Department of Anesthesiology, University of Pittsburgh, during the conduct of the study.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

Manuscript source: Invited manuscript

Received: June 21, 2019
Peer-review started: June 26, 2019
First decision: August 2, 2019
Revised: September 17, 2019
Accepted: October 27, 2019
Article in press: October 27, 2019
Published online: November 19, 2019

P-Reviewer: Tiruvoipati R
S-Editor: Yan JP
L-Editor: A

histological damage after ventricular fibrillation (VF) CA in rats.

METHODS

Adult male isoflurane-anesthetized rats were subjected to 6 min VF CA followed by 2 min resuscitation including chest compression, epinephrine, bicarbonate, and defibrillation. After return of spontaneous circulation (ROSC), rats were randomized to two groups: (1) Minocycline 90 mg/kg intraperitoneally (i.p.) at 15 min ROSC, followed by 22.5 mg/kg i.p. every 12 h for 72 h; and (2) Controls, receiving the same volume of vehicle (phosphate-buffered saline). The rats were kept normothermic during the postoperative course. Neurologic injury was assessed daily using Overall Performance Category (OPC; 1 = normal, 5 = dead) and Neurologic Deficit Score (NDS; 0% = normal, 100% = dead). Rats were sacrificed at 72 h. Neuronal degeneration (Fluoro-Jade C staining) and microglia proliferation (anti-Iba-1 staining) were quantified in four selectively vulnerable brain regions (hippocampus, striatum, cerebellum, cortex) by three independent reviewers masked to the group assignment.

RESULTS

In the minocycline group, 8 out of 14 rats survived to 72 h compared to 8 out of 19 rats in the control group ($P = 0.46$). The degree of neurologic deficit at 72 h [median, (interquartile range)] was not different between survivors in minocycline *vs* controls: OPC 1.5 (1-2.75) *vs* 2 (1.25-3), $P = 0.442$; NDS 12 (2-20) *vs* 17 (7-51), $P = 0.328$) or between all studied rats. The number of degenerating neurons (minocycline *vs* controls, mean ± SEM: Hippocampus 58 ± 8 *vs* 76 ± 8; striatum 121 ± 43 *vs* 153 ± 32; cerebellum 20 ± 7 *vs* 22 ± 8; cortex 0 ± 0 *vs* 0 ± 0) or proliferating microglia (hippocampus 157 ± 15 *vs* 193 cortex 0 ± 0 *vs* 0 ± 0; 16; striatum 150 ± 22 *vs* 161 ± 23; cerebellum 20 ± 7 *vs* 22 ± 8; cortex 26 ± 6 *vs* 31 ± 7) was not different between groups in any region (all $P > 0.05$). Numerically, there were approximately 20% less degenerating neurons and proliferating microglia in the hippocampus and striatum in the minocycline group, with a consistent pattern of histological damage across the individual regions of interest.

CONCLUSION

Minocycline did not improve survival and failed to confer substantial benefits on neurologic function, neuronal loss or microglial proliferation across multiple brain regions in our model of rat VF CA.

Key words: Heart arrest/pathology; Cardiopulmonary resuscitation; Survival rate; Neurons/drug effects; Microglia/drug effects; Minocycline/pharmacology

Core tip: Prolonged cardiac arrest (CA) produces extensive neuronal death and neuroinflammation resulting in neuro-cognitive disabilities *via* ischemia-reperfusion injury. Minocycline was shown neuroprotective in some brain ischemia models, in part by blunting the microglial response or by a direct effect on neurons. In our established experimental CA model in adult rats, minocycline did not improve survival and failed to confer substantial benefits on survival, neurobehavioral outcome, neuronal loss or microglial proliferation across multiple brain regions.

Citation: Janata A, Magnet IA, Schreiber KL, Wilson CD, Stezoski JP, Janesko-Feldman K, Kochanek PM, Drabek T. Minocycline fails to improve neurologic and histologic outcome after ventricular fibrillation cardiac arrest in rats. *World J Crit Care Med* 2019; 8(7): 106-119
URL: https://www.wjgnet.com/2220-3141/full/v8/i7/106.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i7.106

INTRODUCTION

Currently, outcomes after cardiac arrest (CA) are poor, with an approximately 10% survival rate, and significant seuro-cognitive disabilities in survivors. No

E-Editor: Liu MY

pharmacological adjuncts have as yet been shown to improve outcomes after CA in a clinical setting. Exploration of novel strategies and compounds for neuroprotection thus has scientific merit.

Janata *et al*[1], Drabek *et al*[2], Uray *et al*[3], and others[4-6] have reported that experimental CA produces extensive neuronal death and microglial proliferation and activation. Among other potential mechanisms, microglial activation have been implicated as significantly contributing to neuronal death and cerebral edema after insults to the central nervous system (CNS). Minocycline is suggestive to be neuroprotective in multiple brain ischemia models including CA[4-9], in part by blunting the microglial response[6], or by a direct effect on neurons[10].

Minocycline is neuroprotective in chronic inflammation models and stroke, most likely *via* attenuation of microglial activation. Minocycline was effective in improving functional outcome and neuronal death in a pediatric asphyxial CA model, concurrent with decrease in microglial proliferation and CNS cytokine expression at 72 h[7].

We have previously reported that minocycline at sufficient doses had only modest effect in our prolonged deep hypothermic CA model[2]. We concluded that the expected salutary effects of minocycline might have been masked by the concomitant beneficial effects of hypothermia, leaving little space for the detection of benefits of minocycline. Thus, in the current study, we chose to test minocylcine's effects in our newly established model of normothermic ventricular fibrillation (VF) CA. We tested the hypothesis that minocycline would improve survival, functional and histological outcome after VF CA in rats. Primary outcomes were survival and functional outcome; secondary outcomes were histological damage (neuronal death and microglial activation) in multiple selectively vulnerable brain regions.

MATERIALS AND METHODS

Animal model

The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh (Protocol #13021161). We used our previously established model of VF CA[1].

Preparation phase

In brief, adult male Sprague-Dawley rats (350-400 g) were obtained from a licensed vendor (Hilltop Lab Animals, Scottdale, PA, United States) and housed under 12 h/12 h light/dark in a holding facility for at least two days prior to the experiment. Water was provided ad libitum until the experiment. Standard chow was removed 12 h prior to experiment. On the day of the experiment, rats were anesthetized with 4% isoflurane (Baxter, Deerfield, IL, United States) in FiO_2 1.0 in a plexiglass jar, intubated with a 14-gauge cannula (Becton Dickinson, Sandy, UT), and mechanically ventilated (Harvard Ventilator 683, Harvard Rodent Apparatus, South Natick, MA, United States) with tidal volume 8 mL/kg, PEEP 3 cm H_2O and respiratory rate 30-40/min to maintain normocapnia. Anesthesia was maintained with 2% isoflurane (FiO_2 of 0.5). Arterial (PE50) and venous (PE90) femoral lines were inserted *via* cut-downs for blood pressure monitoring and drug administration. Electrocardiogram (ECG), mean arterial pressure (MAP) and central venous pressure were continuously monitored and recorded (Polygraph, Grass Instruments, Quincy, MA, United States). Rectal temperature (Trec) was controlled at 37.0 ± 0.5 °C with a temperature controlled operating table, overhead heating lamp and a fan. After surgery, FiO_2 was reduced to 0.3 and isoflurane was weaned over 5 min. VF CA was induced by a 2 min impulse of 12 V/50 Hz alternating current and ensured by ECG readings and reduction in MAP.

Resuscitation phase

After 6 min CA, manual chest compressions were started at a rate approximately 275/min along with mechanical ventilation with FiO_2 1.0. Epinephrine (Abbott, Abbott Park, IL, United States) 20 mg/kg was given with start of compressions; additional epinephrine 10 mg/kg was given at 1 min resuscitation time (RT). Sodium bicarbonate (Abbott, Abbott Park, IL, United States) 1 mEq/kg was given at start of resuscitation. At 2 min RT, defibrillation was attempted with biphasic 10 J impulse (Zoll M series defibrillator; Zoll, Chelmsford, MA, United States). If unsuccessful, subsequent shocks were delivered every 30 s, with maximum 5 attempts over 4 min resuscitation effort.

ICU phase

A Mini-mitter probe (Mini-mitter Co. Inc., Bend, OR) was advanced into the peritoneal cavity *via* small laparotomy to allow postoperative temperature control using overhead heating lamp and fan and monitoring *via* advanced telemetry system.

Rats were weaned to spontaneous ventilation at 30 min RT. The rats were extubated and lines were removed at 60 min RT.

Postoperative care

Controlled normothermia (36.5-37.5 °C) was maintained for 12 h, followed by an additional 12 h monitoring period. Rats that did not resume eating/drinking were given D5W/0.9NS (Baxter, Deerfield, IL, United States) sq twice daily. Morphine 0.15 mg was given twice daily subcutaneously for pain/distress. Neurologic status was assessed daily using Overall Performance Category (OPC, 1 = normal, 5 = dead)[11] and Neurologic Deficit Score (NDS, 0-10% = normal, 100% max deficit)[12].

At 72 h, rats were deeply anesthetized with isoflurane and perfused transcardially with normal saline followed by 10% formalin. Fixed tissues were paraffin-embedded and standard coronal sections were performed at levels of aforementioned regions. Histological damage score was assessed in the striatum, hippocampus, cerebellum and cortex. Fluoro-Jade C was used to assess neuronal degeneration. Anti-Iba-1 staining was used to label activated microglia.

Experimental protocol

A randomization schedule was created prior to study commencement with balancing for each sequential groups of 4 rats, with two rats in each block assigned to receive minocycline and two rats assigned to receive vehicle treatment, in order to balance the number of rats allocated to each condition for each shipping container, thus reducing the possibility of bias and confounding. Rats that either did not achieve return of spontaneous circulation (ROSC), or died prior to the scheduled time-point of sacrifice were replaced at the end of the study following the same randomization protocol. The ongoing block was finished as originally designed. Minocycline (Sigma-Aldrich, Cat. No. M9511, St. Louis, MO) 90 mg/kg i.p. was administered at 15 min RT, followed by 22.5 mg/kg i.p. twice daily (6 am-6 pm) for 72 h. This regimen was based on prior studies which have demonstrated benefits[13]. In controls, vehicle (phosphate-buffered saline) was administered at the same time points and at the same volume.

Histology

The tissue samples were processed for embedding in paraffin. The resulting paraffin blocks were sequentially sectioned at 5 micrometer slices. All sections were stained with Fluoro-Jade C (Millipore, CA, United States) as a marker neuronal degeneration[14] and with anti-Iba-1 staining visualizing microglia. Iba-1 is a calcium-binding protein expressed specifically in activated microglia[15]. For the Iba-1 staining, sections were washed in tris-buffered saline and Tween 20 (TBST) (Biocare Medical, CA, United States), incubated in 0.3% H_2O_2 in TBST for 30 min to inhibit endogenous peroxidase activity, washed in TBST, and blocked in TBST containing 3% normal goat serum for 30 min. The sections were incubated with a rabbit anti-Iba1 polyclonal antibody (1:250, Wako, Richmond, VA, United States) overnight at 4 °C. The sections were then washed in TBST and incubated with a FITC-conjugated goat anti-rabbit IgG secondary antibody (Invitrogen, Carlsbad, CA, United States) for 1 h at room temperature. Sections were then washed and cover-slipped with Vectashield Mounting media containing 4',6-diamidino-2-phenylindole counterstain.

In addition, colorimetric visualization of Iba-1 immunostaining using diaminobenzamide (DAB) (Vector, CA, United States) was used as a secondary confirmatory method to visualize microglia. In short, sections were incubated with a primary antibody using a 1:250 dilution of anti-rabbit Iba-1 overnight at 4 °C. Sections were washed with TBST, incubated at RT for 1 h with a biotinylated secondary anti-rabbit IgG (Sigma-Aldrich Cat. No. 21537, St. Louis, MO, United States), followed by 1 h of avidin-biotin complex binding using an ABC kit (Vector, CA, United States). Sections were washed and incubated for 10 min with DAB followed by hematoxylin counterstaining. Tissue was dehydrated, cleared and cover-slipped for microscopic analysis. For control staining, normal rabbit IgG was used as the primary antibody.

A photograph of the representative section of the aforementioned regions of interest was taken under 10 × magnification (Nikon Eclipse 90i). The regions of interest were defined as follows: Hippocampus and cortex, bregma -3.2 mm; striatum, bregma +0.48 mm; and cerebellum, bregma -10.04 mm. Fluoro-Jade C positive neurons and Iba-1 positive activated microglia (characterized by ameboid cell body and retracted processes without thin ramifications)[16] were then quantitated morphometrically by three independent evaluators (KLS, CDW, KJ-F) masked to the treatment assignment using the National Institutes of Health Image-J software. No automated features of the software were used. Image-J was used solely to track the cell counts and provide a controlled feedback between the independent evaluators.

Statistical evaluation

The analysis was performed using IBM SPSS Statistics 24.0 software (International Business Machines Corporation, Armonk, United States). All data were expressed as the mean ± SD except stated otherwise. We have targeted n = 8 survivors in each group to allow for evaluation of neuronal death. This was based on power sample size calculation for a continuous parameter (neuronal count), using two independent sample analysis with alpha = 0.05, power = 0.8, to detect 20% reduction in neuronal death. Survival and favorable (OPC 1-2) *vs* unfavorable (OPC 3-5) outcome was evaluated with Fisher's exact test. Survival time was evaluated using a Kaplan-Meier survival analysis. Differences in OPC categories were evaluated with chi square test. NDS was evaluated with Mann-Whitney *U*-test. Differences in HDS and physiological and biochemical values between groups were evaluated with an independent samples *t*-test. Differences in physiological and biochemical parameters vs. respective baselines were evaluated by a paired samples *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 39 rats was used (Figure 1). Prolonged CA resulted in significant early biochemical derangements heralded by marked metabolic acidosis and significantly increased lactate levels that clearly indicated a severe insult. Post-resuscitation treatment with minocycline did not change survival rate or survival time, neurologic outcome or histological damage at 72 h that included marked neuronal degeneration and microglial activation in multiple selectively vulnerable brain regions.

Baseline and early resuscitation outcome

Three rats did not achieve ROSC. Three additional rats were excluded for technical complications (bleeding during cannulation or decannulation). ROSC was achieved after 155 ± 51 s in the control group *vs* 141 ± 16 s in the minocycline group, respectively (P = 0.492). The number of defibrillation shocks (median, interquartile range) did not differ between groups [control: 1.9 (0, 4) *vs* minocycline: 1.7 (1, 2); P = 0.779].

Biochemical and physiological profiles were similar between groups at baseline and in the early post-resuscitation period, characterized by transient marked increased in lactate and metabolic acidosis. These changes were mostly normalized by RT 60 min (Table 1).

Survival /neurological outcome

There were no differences in overall survival (8/19 in control group *vs* 8/14 in the minocycline group; Figure 2). The final NDS at 72 h was not different in all animals entering the study or in survivors only (Figure 3). Similarly, survival time was not different between groups (Figure 4). The weight of the rats did not different at baseline or on individual survival days. However, the overall weight decrease (baseline - D3) was greater in the control group (63 ± 19 g) *vs* minocycline group (42 ± 14 g; P = 0.04).

Histological outcome

Histological damage assessed in survivors showed similar degree of neuronal loss and microglia proliferation in hippocampus, striatum, cerebellum and cortex in both control and minocycline groups at 72 h. Despite a relatively lower number of degenerating neurons and proliferating microglia (approximately 20% decrease) in the minocycline group, histologic damage score was not different between groups (Figure 5). Hippocampal neuronal degeneration was limited to the CA1 region, which is known to be selectively vulnerable hypoxia-ischemia, and to neurons in dentate gyrus. In striatum, medium spiny neurons, comprising about 80% of striatal population, showed extensive neurodegeneration. Large Purkinje neurons in cerebellum were also affected. No evidence of neuronal degeneration was apparent in cortex in either group (Figure 6). Regions with extensive neurodegeneration were also hallmarked by extensive microglia activation and proliferation with thickened, shortened processes. Interestingly, signs of mild microglial activation and proliferation were present in the cortex even in the absence of neuronal death at this stage (Figure 7).

DISCUSSION

Our model of VF CA is characterized by extensive neuronal cell death and microglial

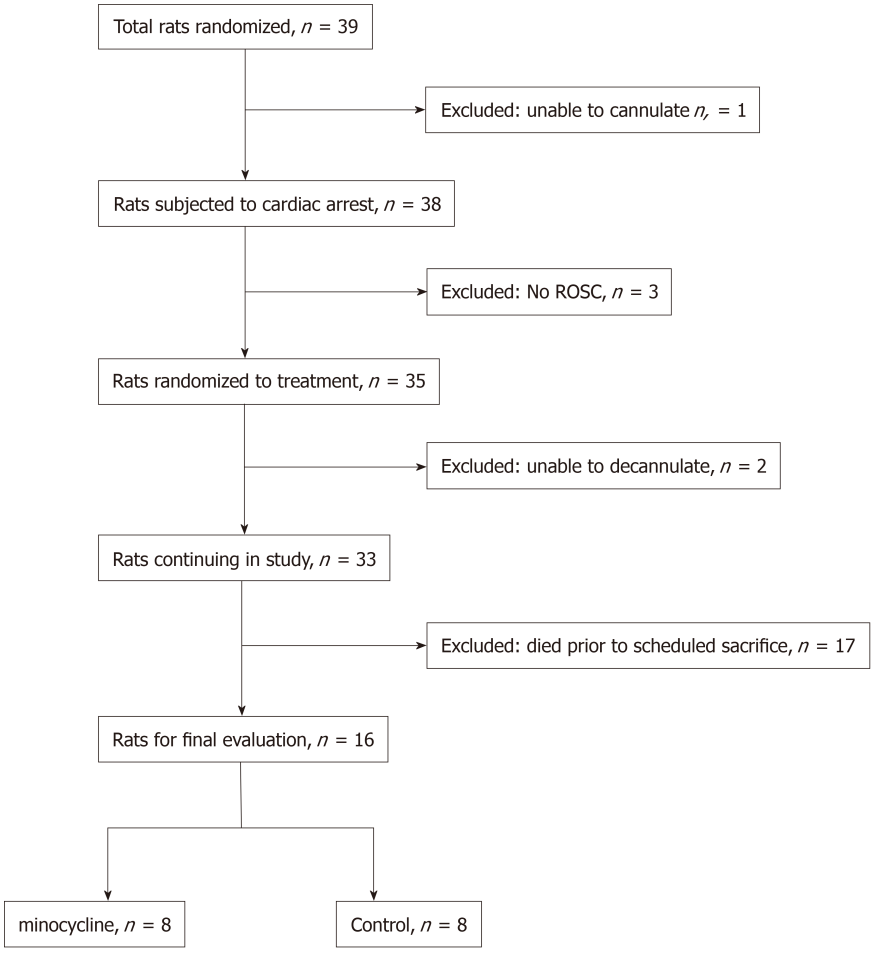


Figure 1 A flow-chart of the study. Please refer to the text for details on randomization protocol. ROSC: Return of spontaneous circulation.

activation across multiple brain regions. We have characterized in detail the temporal pattern of evolving neuronal death in this model previously[1], identifying several selectively vulnerable regions as potential therapeutical targets. In this study, minocycline did not improve survival and failed to confer substantial benefits on neurologic injury, neuronal loss or microglial proliferation in multiple brain regions in our rat model of VF CA. The relative lack of effect of minocycline in this normothermic VF CA model is consistent with our prior results from deep hypothermic CA[2], as well as with the previous work by others documenting limited effect of minocycline in asphyxial CA in adult rats[5]. In contrast, other groups have demonstrated sustained beneficial effects of minocycline on hippocampal cell death and neuro-behavioral cognitive tasks both after a single dose pretreatment of minocycline[17], or after once-daily treatment for 7 d[18]. It is possible that differences between our models and treatment regimens might have contributed to these conflicting results. Also, minocycline has previously showed benefits in immature rats subjected to asphyxial CA[7], suggesting significant age-dependent differences in neuroinflammation after CA.

Traditionally, microglia have been viewed as the resident immune cell of the CNS, which serve a role of immune surveillance. While the early brain injury in ischemia-reperfusion is caused by release of excitatory mediators resulting from energy failure, secondary damage could also be triggered by microglia, which transform into phagocytes, purportedly aggravating the injury. From a temporal standpoint, microglial activation starts immediately after ischemia and thus importantly precedes morphologically detectable neuronal damage.

Microglial activation has been suggested to be a major cause of delayed neuronal death, most likely through releasing neurotoxic substances, including reactive oxygen radicals, nitric oxide, and pro-inflammatory cytokines[19]. Microglial activation could contribute to neuronal death or microglial-mediated synaptic injury and/or neuronal dysfunction – which could mediate cognitive deficits even in the absence of overt neuronal death. After hypoxic-ischemic injury, inactive microglia and macrophages in

Table 1 Physiologic and biochemical profile after cardiac arrest

		BL	RT5	RT15	RT30	RT60	RT72H
HR (bpm)	Control	355 ± 21	335 ± 47	354 ± 20	378 ± 45	366 ± 26	N/A
	Minocycline	348 ± 20	335 ± 38	355 ± 21	369 ± 22	374 ± 28	N/A
MAP (mmHg)	Control	91 ± 5	98 ± 31	100 ± 20	89 ± 13	94 ± 19	N/A
	Minocycline	90 ± 9	98 ± 13	86 ± 11	94 ± 13	102 ± 9	N/A
pHa °	Control	7.39 ± 0.02	7.12 ± 0.06[c]	7.24 ± 0.08[c]	7.37 ± 0.05	7.41 ± 0.03	7.38 ± 0.15
	Minocycline	7.46 ± 0.13	7.14 ± 0.04[c]	7.27 ± 0.05[c]	7.39 ± 0.03	7.42 ± 0.02	7.46 ± 0.15
paO_2 (mmHg)	Control	136 ± 15	381 ± 56[c]	373 ± 41[c]	144 ± 36	136 ± 37	306 ± 187
	Minocycline	133 ± 14	378 ± 35[c]	384 ± 43[c]	145 ± 48	145 ± 38	427 ± 56[c]
$paCO_2$ (mmHg)	Control	39 ± 3	51 ± 2[c]	45 ± 2[c]	40 ± 4	45 ± 5[c]	41 ± 17
	Minocycline	40 ± 4	51 ± 5[c]	47 ± 4[c]	40 ± 2	41 ± 2	35 ± 15
BE (mEq/L)	Control	-1.3 ± 1.5[a]	-12.6 ± 1.3[c]	-8.1 ± 4.2[c]	-1.8 ± 3.3	2.7 ± 1.9[c]	-1.8 ± 5
	Minocycline	0.5 ± 1.6	-12.1 ± 1.3[c]	-5.9 ± 2.1[c]	-0.2 ± 1.5	1.9 ± 1.6	0.0±3.5
Lactate (mmol/L)	Control	1.7 ± 0.6	13.0 ± 2.6[c]	9.7 ± 2.8[c]	5.4 ± 2.0[c]	2.0 ± 1.2	3.9 ± 1.1[c]
	Minocycline	1.2 ± 0.4	12.5 ± 1.6[c]	8.7 ± 1.4[c]	4.6 ± 1.0[c]	1.9 ± 0.7[c]	3.0 ± 0.7[c]
Hct (%)	Control	39 ± 1[a]	38 ± 2	39 ± 2	39 ± 2	37 ± 3[a]	43 ± 5[c]
	Minocycline	40 ± 1	38 ± 3	39 ± 2	40 ± 3	40 ± 1	41 ± 6
Glucose (g/dL)	Control	218 ± 28	325 ± 31[c]	277 ± 44[c]	213 ± 41	134 ± 24[c]	243 ± 48
	Minocycline	223 ± 16	337 ± 19[c]	293 ± 18[c]	205 ± 41	162 ± 51[c]	183 ± 15[ac]

BL: Baseline; RT: Resuscitation time; HR: Heart rate; MAP: Mean arterial pressure; BE: Base excess; Hct: Hematocrit; N/A: Not assessed.
[a]$P < 0.05$ *vs* minocycline;
[c]$P < 0.05$ *vs* respective baseline.

the neurovasculature change expression patterns, producing active substances, affecting survival vs. apoptosis[20].

Minocycline is a widely used antibiotic with anti-inflammatory and anti-apoptotic properties, and has been tested in several models of neurologic injury, including global[21-23] and focal brain ischemia[24-27], traumatic brain injury[28,29], spinal cord injury[30,31] and intracerebral hemorrhage[32]. Most recently, minocycline has showed promise in a clinical trial in acute stroke patients[33]. Minocycline has been shown to penetrate the blood-brain barrier well[34], reduce tissue injury and also improve functional recovery[9,21,35]. On a molecular level, minocycline inhibits inflammatory cell migration and degranulation and formation of free oxygen radicals[36-38], leads to decreased expression of inducible nitric-oxide synthetase[39-42] and augments expression of cyclooxygenase-2[43]. It also suppresses both caspase-dependent[28,44-47] and caspase-independent apoptotic pathways[37,47] which are relevantly expressed in our deep hypothermic CA model and similar models described elsewhere[48-50]. The primary effect of minocycline is probably inhibition of activation of microglia[21,22,24,30,51]. A few studies suggest that minocycline may exert its effects independent of microglia inhibition[9,52]. Both motor and neurocognitive behavior have improved after treatment with minocycline, even when the initiation of treatment was delayed for several hours after the insult[8,9,25,28].

Several studies have previously disputed a neuroprotective role of minocycline[53,54] or showed only transient protection[5,52,55]. Surprisingly, minocycline ablated hypoxic-ischemic injury in neonatal rat models[21,56-58] but was detrimental in a neonatal mouse model[59]. A combination of drugs including minocycline, but not minocycline alone, targeting multiple mechanisms operating after hypoxic-ischemic injury seemed to be more effective than either drug alone[60].

We have demonstrated in prior studies that reperfusion after prolonged ischemia results in extensive region-specific neuroinflammatory response. Interleukin (IL)-1a, IL-1b and tumor necrosis factor (TNF)-α were the most prominent cytokines detected early after reperfusion[61,62]. One of the purported actions of minocycline includes blocking TNF-α release from activated microglia. In our hypothermic CA model, minocycline was able to attenuate the increase in TNF-α most prominently in the striatum, although this was not associated with improved early outcome (24 h)[10]. One important caveat may be that, in our model of VF CA, neurons rather than microglia appeared to be a major source of early TNF-a release[62]. This finding has been anecdotally reported earlier[63]. Direct protective effects of minocycline on neurons subjected to hypoxic-ischemic injury might be associated with the mitigation of

	Control	Minocycline
OPC 5 Death / brain death	••••••••••••	••••••
OPC 4 Severe disability		
OPC 3 Moderate disability	•••	••
OPC 2 Mild disability	•••	••
OPC 1 Normal	••	••••

Figure 2 Overall performance categories after cardiac arrest. Each dot represents one rat. No difference between groups. OPC: Overall performance category.

neuronal excitability, glutamate release, Ca(2+) overloading, and neuroinflammation[64,65].

In this study, we eliminated hypothermia as a confounding factor, and extended the window of observation from 24 h to 72 h, in order to allow a more sensitive detection of potential benefits of minocycline. Our treatment protocol was based on prior studies[55]. Intraperitoneal administration of minocycline results in a bioavailability of 10%-80% with variable serum concentrations. Peak concentrations are achieved after 2.5 h, with half-life of 3 h. With this regard, we chose a more frequent dosing (b.i.d. rather than once daily) to ascertain adequate trough levels of the drug. It should be noted that minocycline penetrates blood-brain barrier well.

We chose a model with considerable mortality to allow for the tested drug to demonstrate its beneficial or detrimental effects. Most studies exploring neuronal death after brain ischemia have focused on neuronal death in the hippocampus, making this selectively vulnerable region a proxy for therapeutic efficacy. Hippocampal structure and neuronal circuits have been well defined but represent only one of the many selectively vulnerable regions with a unique cell population. However, prior reports have suggested that microglial activation is dominant in the striatum and neocortex rather than in the hippocampus[66]. This prompted us to broaden our histological damage assessment to other relevant selectively vulnerable brain regions with different neuronal populations, using various populations predominantly. For example, large pyramidal neurons in the CA1 sector of the hippocampus receive mostly glutamatergic input; Purkinje cells in the cerebellum are solely GABAergic; medium spiny neurons in the striatum are glutamatergic. Large pyramidal cells in cortical layer V use glutamate as the primary neurotransmitter; a smaller population of inhibitory interneurons with local projections and chandelier cells that make synaptic connections only to the axons protruding from other neurons, are also found in layer V, and are GABAergic. We acknowledge that neuronal death is a continuum and that individual brain regions may have different cell death trajectories, and thus our selection of regions of interest thus represents multiple types of neuronal cells across several brain regions. However, we did not observe a breakthrough effect of minocycline in any of these selectively vulnerable brain regions. In conclusion, in our experimental model of VF CA, minocycline did not confer benefits on neurologic outcomes or histological damage at 72 h.

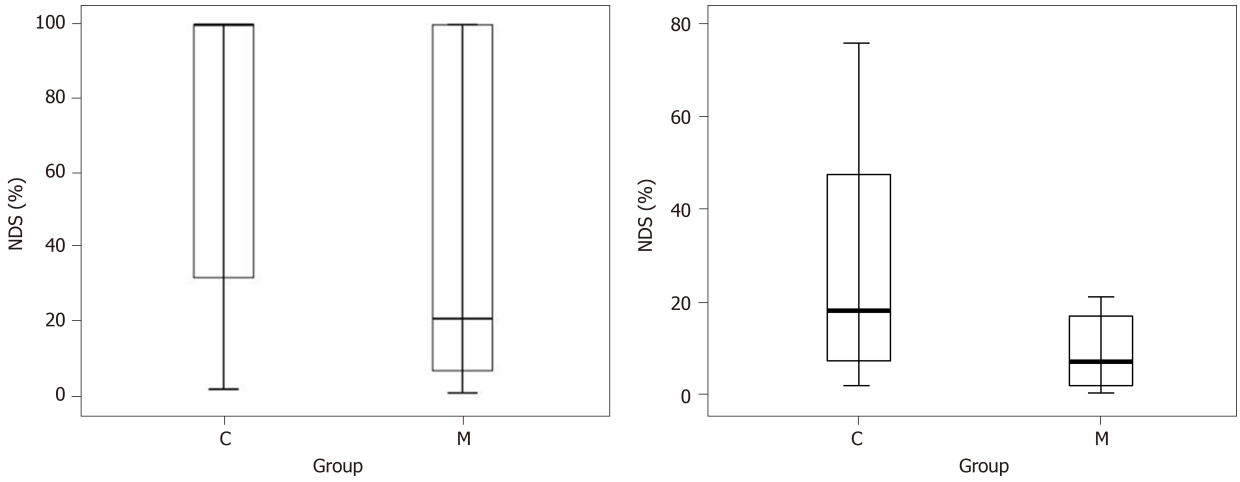


Figure 3 Neurologic deficit score at 72 h in all rats studied (left panel) and in survivors only (right panel). Boxes represent interquartile ranges. The line across each box indicates the median, and the whiskers are the highest and lowest values. No differences between groups. C: Control group; M: Minocycline group; NDS: Neurologic deficit score.

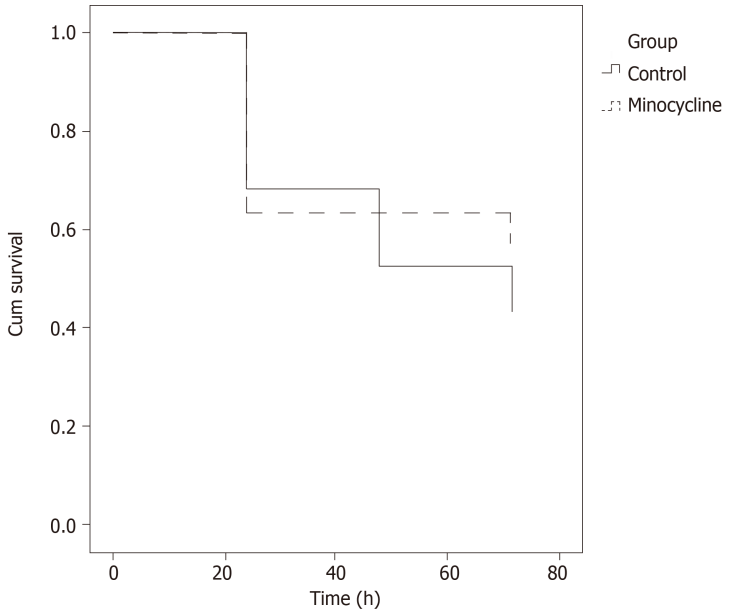


Figure 4 Kaplan-Maier survival plot. No differences between groups.

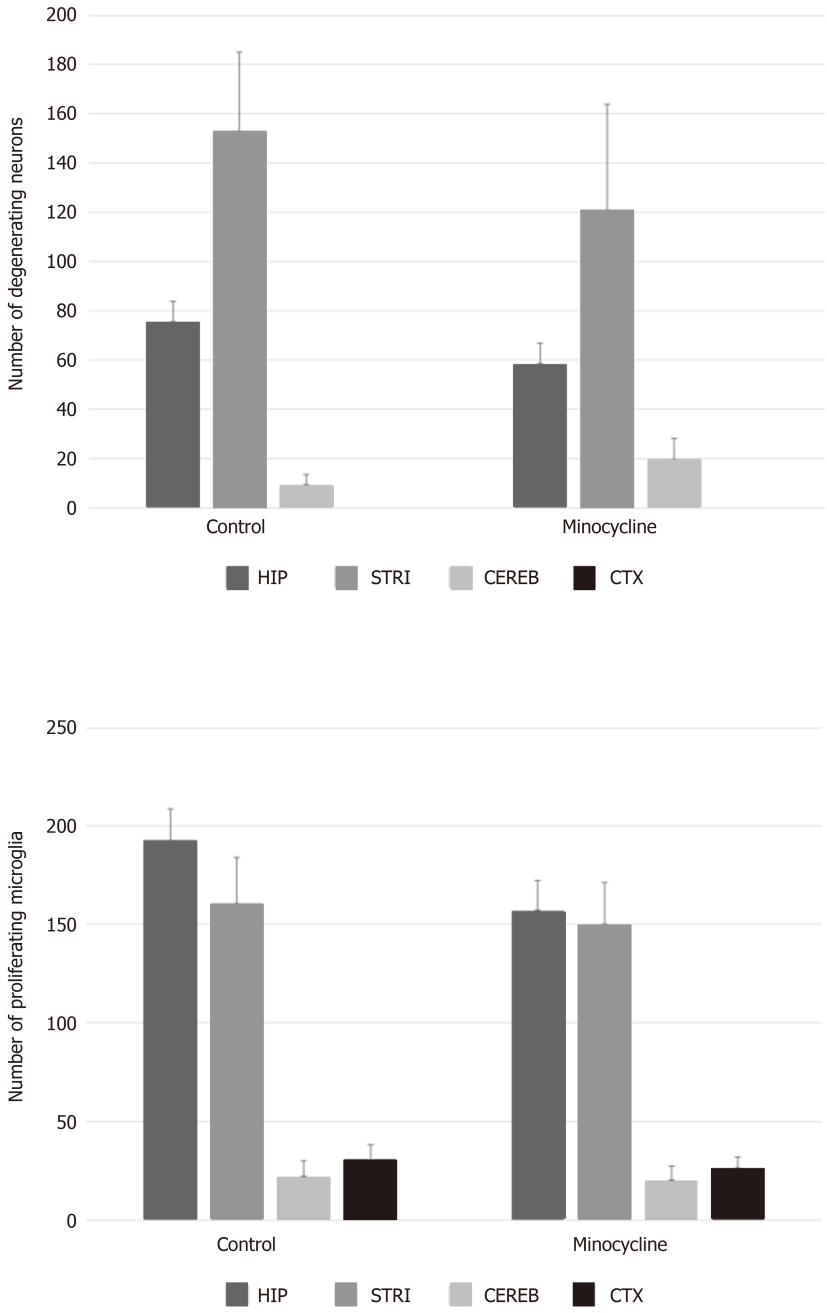


Figure 5 Regional neuronal degeneration (top) and microglial proliferation (bottom) after cardiac arrest. Regional neuronal loss and microglial proliferation after cardiac arrest in controls and rats treated with minocycline were not different between groups in any region at 72 h. HIP: Hippocampus; STRI: Striatum; CEREB: Cerebellum; CTX: Cortex. Mean ± SEM values are displayed.

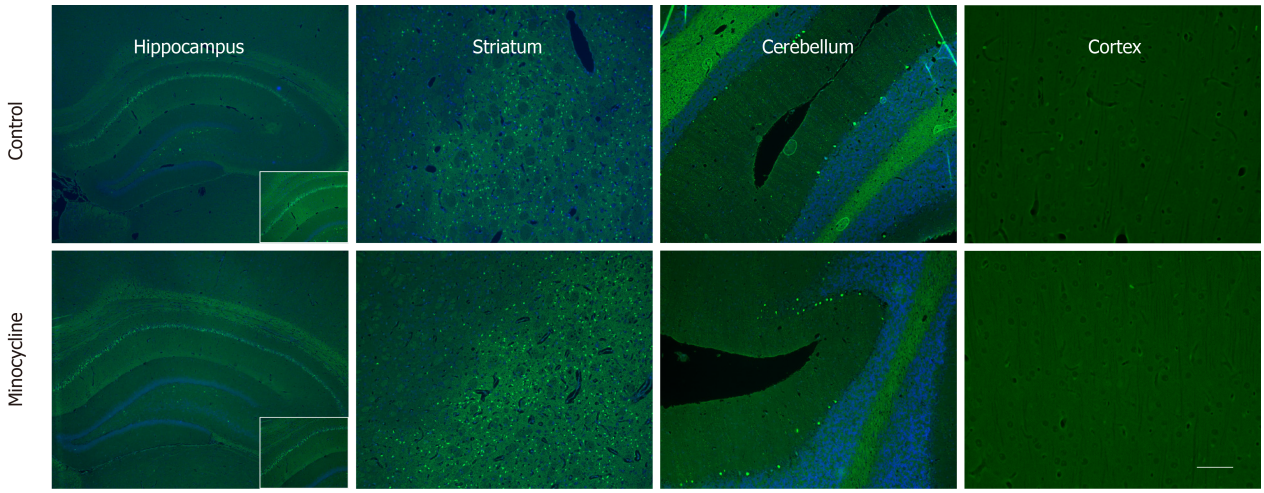


Figure 6 Representative samples of neuronal degeneration after 6 min ventricular fibrillation cardiac arrest at 72 h. Blue staining is 4',6-diamidino-2-phenylindole, visualizing neurons, and green staining is Fluoro-Jade C, visualizing degenerating neurons. Hippocampal neuronal loss is visible in the cardiac arrest 1 sector and in hilar region of the dentate gyrus. The inset shows the mid-section of cardiac arrest 1 in closer detail. Marked neuronal degeneration of the medium spiny neurons is seen in the striatum. Selectively vulnerable neuronal loss of Purkinje neurons visualized in the cerebellum. No neurodegeneration is observed in the cortex. Magnification × 10 except the panoramic view of the hippocampus, magnification × 4. The scale bars in the far left and far right lower panels represent 10 μm.

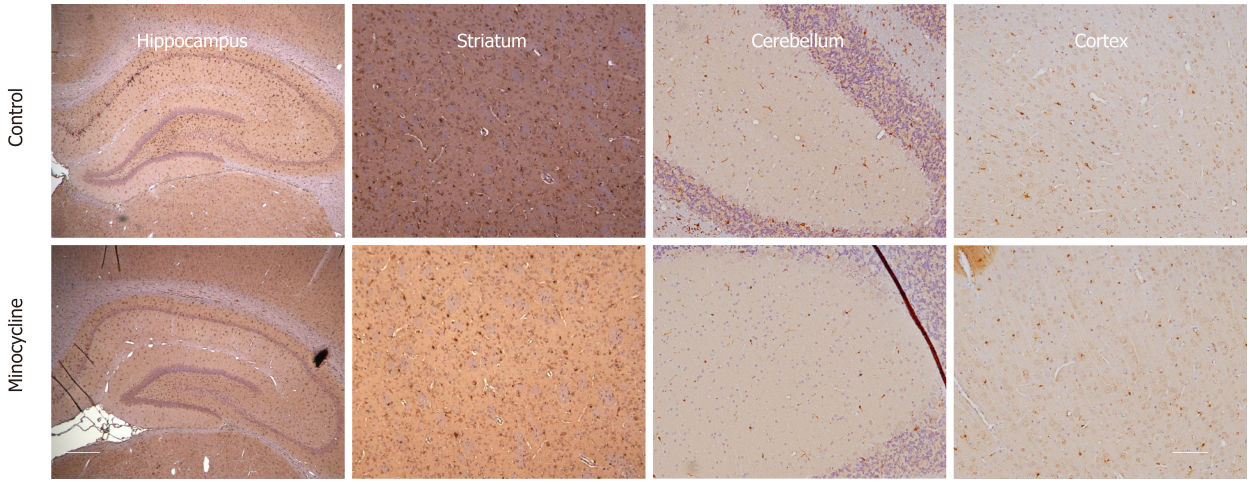


Figure 7 Representative samples of microglial activation and proliferation after 6 min ventricular fibrillation cardiac arrest at 72 h. Sections are stained with hematoxylin. Brown staining is anti-Iba-1 staining, visualizing microglia, counterstained with diaminobenzamide. Magnification × 10. The scale bars in the far left and far right lower panels represent 10 μm.

ARTICLE HIGHLIGHTS

Research background

Outcomes from cardiac arrest (CA) are suboptimal and survivors are often left with significant neuro-cognitive disabilities. No pharmacological adjuncts have been shown to improve outcomes after CA in a clinical setting. Exploration of novel therapeutical adjuncts for neuroprotection in clinically relevant animal models is thus warranted.

Research motivation

Minocycline has been shown to be neuroprotective in several models of ischemia-reperfusion, attenuating microglial activation as a dominant effect. Minocycline seemed a promising candidate to be tested in an experimental CA model that is characterized by extensive neuronal degeneration and microglial activation.

Research objectives

We tested the hypothesis that early treatment with minocycline at a sufficient dose would improve survival rate, survival time, neurologic outcome and histological damage in adult male rats subjected to prolonged CA.

Research methods

Rats were subjected to CA and randomized to either minocycline treatment or control group, treated with vehicle, for 72 h. Minocycline treatment regimen was selected based on prior studies that demonstrated benefits.

Research results
Minocycline did not improve survival rate, survival time, neurologic outcome or histological damage (neuronal degeneration or microglial proliferation) in multiple selectively vulnerable brain regions.

Research conclusions
Minocycline did not provide a breakthrough beneficial effect on neurologic injury or histological damage resulting from prolonged experimental CA.

Research perspectives
Alternative pharmacological strategies should be explored to augment the outcome from CA.

ACKNOWLEDGEMENTS

The abstract of this work was awarded "Best of Category" Abstract for the Critical Care, Trauma and Resuscitation and "Best of Meeting" Abstract Finalist at the International Anesthesia Research Society, Montreal, Canada.

REFERENCES

1 **Janata A**, Drabek T, Magnet IA, Stezoski JP, Janesko-Feldman K, Popp E, Garman RH, Tisherman SA, Kochanek PM. Extracorporeal versus conventional cardiopulmonary resuscitation after ventricular fibrillation cardiac arrest in rats: a feasibility trial. *Crit Care Med* 2013; **41**: e211-e222 [PMID: 23666097 DOI: 10.1097/CCM.0b013e318287f51e]
2 **Drabek T**, Tisherman SA, Beuke L, Stezoski J, Janesko-Feldman K, Lahoud-Rahme M, Kochanek PM. Deep hypothermia attenuates microglial proliferation independent of neuronal death after prolonged cardiac arrest in rats. *Anesth Analg* 2009; **109**: 914-923 [PMID: 19690267 DOI: 10.1213/ane.0b013e3181b0511e]
3 **Uray T**, Lamade A, Elmer J, Drabek T, Stezoski JP, Missé A, Janesko-Feldman K, Garman RH, Chen N, Kochanek PM, Dezfulian C, Callaway CW, Doshi AA, Frisch A, Guyette FX, Reynolds JC, Rittenberger JC; University of Pittsburgh Post-Cardiac Arrest Service. Phenotyping Cardiac Arrest: Bench and Bedside Characterization of Brain and Heart Injury Based on Etiology. *Crit Care Med* 2018; **46**: e508-e515 [PMID: 29533310 DOI: 10.1097/CCM.0000000000003070]
4 **Neigh GN**, Karelina K, Glasper ER, Bowers SL, Zhang N, Popovich PG, DeVries AC. Anxiety after cardiac arrest/cardiopulmonary resuscitation: exacerbated by stress and prevented by minocycline. *Stroke* 2009; **40**: 3601-3607 [PMID: 19762688 DOI: 10.1161/STROKEAHA.109.564146]
5 **Keilhoff G**, Schweizer H, John R, Langnaese K, Ebmeyer U. Minocycline neuroprotection in a rat model of asphyxial cardiac arrest is limited. *Resuscitation* 2011; **82**: 341-349 [PMID: 21168947 DOI: 10.1016/j.resuscitation.2010.11.011]
6 **Wang W**, Lu R, Feng DY, Liang LR, Liu B, Zhang H. Inhibition of microglial activation contributes to propofol-induced protection against post-cardiac arrest brain injury in rats. *J Neurochem* 2015; **134**: 892-903 [PMID: 26016627 DOI: 10.1111/jnc.13179]
7 **Tang M**, Alexander H, Clark RS, Kochanek PM, Kagan VE, Bayir H. Minocycline reduces neuronal death and attenuates microglial response after pediatric asphyxial cardiac arrest. *J Cereb Blood Flow Metab* 2010; **30**: 119-129 [PMID: 19756023 DOI: 10.1038/jcbfm.2009.194]
8 **Wang QY**, Sun P, Zhang Q, Yao SL. Minocycline attenuates microglial response and reduces neuronal death after cardiac arrest and cardiopulmonary resuscitation in mice. *J Huazhong Univ Sci Technolog Med Sci* 2015; **35**: 225-229 [PMID: 25877356 DOI: 10.1007/s11596-015-1415-4]
9 **Hewlett KA**, Corbett D. Delayed minocycline treatment reduces long-term functional deficits and histological injury in a rodent model of focal ischemia. *Neuroscience* 2006; **141**: 27-33 [PMID: 16690215 DOI: 10.1016/j.neuroscience.2006.03.071]
10 **Drabek T**, Janata A, Wilson CD, Stezoski J, Janesko-Feldman K, Tisherman SA, Foley LM, Verrier JD, Kochanek PM. Minocycline attenuates brain tissue levels of TNF-α produced by neurons after prolonged hypothermic cardiac arrest in rats. *Resuscitation* 2014; **85**: 284-291 [PMID: 24513126 DOI: 10.1016/j.resuscitation.2013.10.015]
11 **Carrillo P**, Takasu A, Safar P, Tisherman S, Stezoski SW, Stolz G, Dixon CE, Radovsky A. Prolonged severe hemorrhagic shock and resuscitation in rats does not cause subtle brain damage. *J Trauma* 1998; **45**: 239-248; discussion 248-249 [PMID: 9715179 DOI: 10.1097/00005373-199808000-00007]
12 **Neumar RW**, Bircher NG, Sim KM, Xiao F, Zadach KS, Radovsky A, Katz L, Ebmeyer E, Safar P. Epinephrine and sodium bicarbonate during CPR following asphyxial cardiac arrest in rats. *Resuscitation* 1995; **29**: 249-263 [PMID: 7667556 DOI: 10.1016/0300-9572(94)00827-3]
13 **Cho KO**, Kim SK, Cho YJ, Sung KW, Kim SY. Regional differences in the neuroprotective effect of minocycline in a mouse model of global forebrain ischemia. *Life Sci* 2007; **80**: 2030-2035 [PMID: 17408699 DOI: 10.1016/j.lfs.2007.03.005]
14 **Schmued LC**, Hopkins KJ. Fluoro-Jade B: a high affinity fluorescent marker for the localization of neuronal degeneration. *Brain Res* 2000; **874**: 123-130 [PMID: 10960596 DOI: 10.1016/s0006-8993(00)02513-0]
15 **Ito D**, Imai Y, Ohsawa K, Nakajima K, Fukuuchi Y, Kohsaka S. Microglia-specific localisation of a novel calcium binding protein, Iba1. *Brain Res Mol Brain Res* 1998; **57**: 1-9 [PMID: 9630473 DOI: 10.1016/S0169-328X(98)00040-0]
16 **Koshinaga M**, Suma T, Fukushima M, Tsuboi I, Aizawa S, Katayama Y. Rapid microglial activation

induced by traumatic brain injury is independent of blood brain barrier disruption. *Histol Histopathol* 2007; **22**: 129-135 [PMID: 17149685 DOI: 10.14670/HH-22.129]
17 **Naderi Y**, Sabetkasaei M, Parvardeh S, Moini Zanjani T. Neuroprotective effects of pretreatment with minocycline on memory impairment following cerebral ischemia in rats. *Behav Pharmacol* 2017; **28**: 214-222 [PMID: 28257293 DOI: 10.1097/FBP.0000000000000297]
18 **Naderi Y**, Sabetkasaei M, Parvardeh S, Zanjani TM. Neuroprotective effect of minocycline on cognitive impairments induced by transient cerebral ischemia/reperfusion through its anti-inflammatory and anti-oxidant properties in male rat. *Brain Res Bull* 2017; **131**: 207-213 [PMID: 28454931 DOI: 10.1016/j.brainresbull.2017.04.010]
19 **Gehrmann J**, Banati RB, Wiessner C, Hossmann KA, Kreutzberg GW. Reactive microglia in cerebral ischaemia: an early mediator of tissue damage? *Neuropathol Appl Neurobiol* 1995; **21**: 277-289 [PMID: 7494596 DOI: 10.1111/j.1365-2990.1995.tb01062.x]
20 **Barakat R**, Redzic Z. The Role of Activated Microglia and Resident Macrophages in the Neurovascular Unit during Cerebral Ischemia: Is the Jury Still Out? *Med Princ Pract* 2016; **25** Suppl 1: 3-14 [PMID: 26303836 DOI: 10.1159/000435858]
21 **Fan LW**, Lin S, Pang Y, Rhodes PG, Cai Z. Minocycline attenuates hypoxia-ischemia-induced neurological dysfunction and brain injury in the juvenile rat. *Eur J Neurosci* 2006; **24**: 341-350 [PMID: 16836639 DOI: 10.1111/j.1460-9568.2006.04918.x]
22 **Yrjänheikki J**, Keinänen R, Pellikka M, Hökfelt T, Koistinaho J. Tetracyclines inhibit microglial activation and are neuroprotective in global brain ischemia. *Proc Natl Acad Sci U S A* 1998; **95**: 15769-15774 [PMID: 9861045 DOI: 10.1073/pnas.95.26.15769]
23 **Arvin KL**, Han BH, Du Y, Lin SZ, Paul SM, Holtzman DM. Minocycline markedly protects the neonatal brain against hypoxic-ischemic injury. *Ann Neurol* 2002; **52**: 54-61 [PMID: 12112047 DOI: 10.1002/ana.10242]
24 **Yrjänheikki J**, Tikka T, Keinänen R, Goldsteins G, Chan PH, Koistinaho J. A tetracycline derivative, minocycline, reduces inflammation and protects against focal cerebral ischemia with a wide therapeutic window. *Proc Natl Acad Sci U S A* 1999; **96**: 13496-13500 [PMID: 10557349 DOI: 10.1073/pnas.96.23.13496]
25 **Liu Z**, Fan Y, Won SJ, Neumann M, Hu D, Zhou L, Weinstein PR, Liu J. Chronic treatment with minocycline preserves adult new neurons and reduces functional impairment after focal cerebral ischemia. *Stroke* 2007; **38**: 146-152 [PMID: 17122429 DOI: 10.1161/01.STR.0000251791.64910.cd]
26 **Wang CX**, Yang T, Shuaib A. Effects of minocycline alone and in combination with mild hypothermia in embolic stroke. *Brain Res* 2003; **963**: 327-329 [PMID: 12560140 DOI: 10.1016/s0006-8993(02)04045-3]
27 **Wang CX**, Yang T, Noor R, Shuaib A. Delayed minocycline but not delayed mild hypothermia protects against embolic stroke. *BMC Neurol* 2002; **2**: 2 [PMID: 11960560 DOI: 10.1186/1471-2377-2-2]
28 **Sanchez Mejia RO**, Ona VO, Li M, Friedlander RM. Minocycline reduces traumatic brain injury-mediated caspase-1 activation, tissue damage, and neurological dysfunction. *Neurosurgery* 2001; **48**: 1393-9; discussion 1399-401 [PMID: 11383749 DOI: 10.1097/00006123-200106000-00051]
29 **Bye N**, Habgood MD, Callaway JK, Malakooti N, Potter A, Kossmann T, Morganti-Kossmann MC. Transient neuroprotection by minocycline following traumatic brain injury is associated with attenuated microglial activation but no changes in cell apoptosis or neutrophil infiltration. *Exp Neurol* 2007; **204**: 220-233 [PMID: 17188268 DOI: 10.1016/j.expneurol.2006.10.013]
30 **Stirling DP**, Khodarahmi K, Liu J, McPhail LT, McBride CB, Steeves JD, Ramer MS, Tetzlaff W. Minocycline treatment reduces delayed oligodendrocyte death, attenuates axonal dieback, and improves functional outcome after spinal cord injury. *J Neurosci* 2004; **24**: 2182-2190 [PMID: 14999069 DOI: 10.1523/JNEUROSCI.5275-03.2004]
31 **Festoff BW**, Ameenuddin S, Arnold PM, Wong A, Santacruz KS, Citron BA. Minocycline neuroprotects, reduces microgliosis, and inhibits caspase protease expression early after spinal cord injury. *J Neurochem* 2006; **97**: 1314-1326 [PMID: 16638021 DOI: 10.1111/j.1471-4159.2006.03799.x]
32 **Power C**, Henry S, Del Bigio MR, Larsen PH, Corbett D, Imai Y, Yong VW, Peeling J. Intracerebral hemorrhage induces macrophage activation and matrix metalloproteinases. *Ann Neurol* 2003; **53**: 731-742 [PMID: 12783419 DOI: 10.1002/ana.10553]
33 **Lampl Y**, Boaz M, Gilad R, Lorberboym M, Dabby R, Rapoport A, Anca-Hershkowitz M, Sadeh M. Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. *Neurology* 2007; **69**: 1404-1410 [PMID: 17909152 DOI: 10.1212/01.wnl.0000277487.04281.db]
34 **Saivin S**, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet* 1988; **15**: 355-366 [PMID: 3072140 DOI: 10.2165/00003088-198815060-00001]
35 **Yenari MA**, Xu L, Tang XN, Qiao Y, Giffard RG. Microglia potentiate damage to blood-brain barrier constituents: improvement by minocycline in vivo and in vitro. *Stroke* 2006; **37**: 1087-1093 [PMID: 16497985 DOI: 10.1161/01.STR.0000206281.77178.ac]
36 **Golub LM**, Ramamurthy NS, McNamara TF, Greenwald RA, Rifkin BR. Tetracyclines inhibit connective tissue breakdown: new therapeutic implications for an old family of drugs. *Crit Rev Oral Biol Med* 1991; **2**: 297-321 [PMID: 1654139 DOI: 10.1177/10454411910020030201]
37 **Morimoto N**, Shimazawa M, Yamashima T, Nagai H, Hara H. Minocycline inhibits oxidative stress and decreases in vitro and in vivo ischemic neuronal damage. *Brain Res* 2005; **1044**: 8-15 [PMID: 15862784 DOI: 10.1016/j.brainres.2005.02.062]
38 **Lin S**, Wei X, Xu Y, Yan C, Dodel R, Zhang Y, Liu J, Klaunig JE, Farlow M, Du Y. Minocycline blocks 6-hydroxydopamine-induced neurotoxicity and free radical production in rat cerebellar granule neurons. *Life Sci* 2003; **72**: 1635-1641 [PMID: 12551752 DOI: 10.1016/S0024-3205(02)02442-6]
39 **Du Y**, Ma Z, Lin S, Dodel RC, Gao F, Bales KR, Triarhou LC, Chernet E, Perry KW, Nelson DL, Luecke S, Phebus LA, Bymaster FP, Paul SM. Minocycline prevents nigrostriatal dopaminergic neurodegeneration in the MPTP model of Parkinson's disease. *Proc Natl Acad Sci USA* 2001; **98**: 14669-14674 [PMID: 11724929 DOI: 10.1073/pnas.251341998]
40 **Lin S**, Zhang Y, Dodel R, Farlow MR, Paul SM, Du Y. Minocycline blocks nitric oxide-induced neurotoxicity by inhibition p38 MAP kinase in rat cerebellar granule neurons. *Neurosci Lett* 2001; **315**: 61-64 [PMID: 11711215 DOI: 10.1016/S0304-3940(01)02324-2]
41 **Tomás-Camardiel M**, Rite I, Herrera AJ, de Pablos RM, Cano J, Machado A, Venero JL. Minocycline reduces the lipopolysaccharide-induced inflammatory reaction, peroxynitrite-mediated nitration of proteins, disruption of the blood-brain barrier, and damage in the nigral dopaminergic system. *Neurobiol Dis* 2004; **16**: 190-201 [PMID: 15207276 DOI: 10.1016/j.nbd.2004.01.010]
42 **Ryu JK**, McLarnon JG. Minocycline or iNOS inhibition block 3-nitrotyrosine increases and blood-brain

barrier leakiness in amyloid beta-peptide-injected rat hippocampus. *Exp Neurol* 2006; **198**: 552-557 [PMID: 16480717 DOI: 10.1016/j.expneurol.2005.12.016]

43 **Attur MG**, Patel RN, Patel PD, Abramson SB, Amin AR. Tetracycline up-regulates COX-2 expression and prostaglandin E2 production independent of its effect on nitric oxide. *J Immunol* 1999; **162**: 3160-3167 [PMID: 10092766 DOI: 10.1042/bj3130617]

44 **Chen M**, Ona VO, Li M, Ferrante RJ, Fink KB, Zhu S, Bian J, Guo L, Farrell LA, Hersch SM, Hobbs W, Vonsattel JP, Cha JH, Friedlander RM. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. *Nat Med* 2000; **6**: 797-801 [PMID: 10888929 DOI: 10.1038/77528]

45 **Teng YD**, Choi H, Onario RC, Zhu S, Desilets FC, Lan S, Woodard EJ, Snyder EY, Eichler ME, Friedlander RM. Minocycline inhibits contusion-triggered mitochondrial cytochrome c release and mitigates functional deficits after spinal cord injury. *Proc Natl Acad Sci U S A* 2004; **101**: 3071-3076 [PMID: 14981254 DOI: 10.1073/pnas.0306239101]

46 **Kelly KJ**, Sutton TA, Weathered N, Ray N, Caldwell EJ, Plotkin Z, Dagher PC. Minocycline inhibits apoptosis and inflammation in a rat model of ischemic renal injury. *Am J Physiol Renal Physiol* 2004; **287**: F760-F766 [PMID: 15172883 DOI: 10.1152/ajprenal.00050.2004]

47 **Wang X**, Zhu S, Drozda M, Zhang W, Stavrovskaya IG, Cattaneo E, Ferrante RJ, Kristal BS, Friedlander RM. Minocycline inhibits caspase-independent and -dependent mitochondrial cell death pathways in models of Huntington's disease. *Proc Natl Acad Sci U S A* 2003; **100**: 10483-10487 [PMID: 12930891 DOI: 10.1073/pnas.1832501100]

48 **Sato Y**, Laskowitz DT, Bennett ER, Newman MF, Warner DS, Grocott HP. Differential cerebral gene expression during cardiopulmonary bypass in the rat: evidence for apoptosis? *Anesth Analg* 2002; **94**: 1389-1394, table of contents [PMID: 12031994 DOI: 10.1213/00000539-200206000-00003]

49 **Hindman BJ**, Moore SA, Cutkomp J, Smith T, Ross-Barta SE, Dexter F, Brian JE. Brain expression of inducible cyclooxygenase 2 messenger RNA in rats undergoing cardiopulmonary bypass. *Anesthesiology* 2001; **95**: 1380-1388 [PMID: 11748396 DOI: 10.1097/00000542-200112000-00017]

50 **Zhang TJ**, Hang J, Wen DX, Hang YN, Sieber FE. Hippocampus bcl-2 and bax expression and neuronal apoptosis after moderate hypothermic cardiopulmonary bypass in rats. *Anesth Analg* 2006; **102**: 1018-1025 [PMID: 16551891 DOI: 10.1213/01.ane.0000199221.96250.8c]

51 **Fan LW**, Pang Y, Lin S, Rhodes PG, Cai Z. Minocycline attenuates lipopolysaccharide-induced white matter injury in the neonatal rat brain. *Neuroscience* 2005; **133**: 159-168 [PMID: 15893639 DOI: 10.1016/j.neuroscience.2005.02.016]

52 **Fox C**, Dingman A, Derugin N, Wendland MF, Manabat C, Ji S, Ferriero DM, Vexler ZS. Minocycline confers early but transient protection in the immature brain following focal cerebral ischemia-reperfusion. *J Cereb Blood Flow Metab* 2005; **25**: 1138-1149 [PMID: 15874975 DOI: 10.1038/sj.jcbfm.9600121]

53 **Sriram K**, Miller DB, O'Callaghan JP. Minocycline attenuates microglial activation but fails to mitigate striatal dopaminergic neurotoxicity: role of tumor necrosis factor-alpha. *J Neurochem* 2006; **96**: 706-718 [PMID: 16405514 DOI: 10.1111/j.1471-4159.2005.03566.x]

54 **Cornet S**, Spinnewyn B, Delaflotte S, Charnet C, Roubert V, Favre C, Hider H, Chabrier PE, Auguet M. Lack of evidence of direct mitochondrial involvement in the neuroprotective effect of minocycline. *Eur J Pharmacol* 2004; **505**: 111-119 [PMID: 15556143 DOI: 10.1016/j.ejphar.2004.10.039]

55 **Elewa HF**, Hilali H, Hess DC, Machado LS, Fagan SC. Minocycline for short-term neuroprotection. *Pharmacotherapy* 2006; **26**: 515-521 [PMID: 16553511 DOI: 10.1592/phco.26.4.515]

56 **Carty ML**, Wixey JA, Colditz PB, Buller KM. Post-insult minocycline treatment attenuates hypoxia-ischemia-induced neuroinflammation and white matter injury in the neonatal rat: a comparison of two different dose regimens. *Int J Dev Neurosci* 2008; **26**: 477-485 [PMID: 18387771 DOI: 10.1016/j.ijdevneu.2008.02.005]

57 **Buller KM**, Carty ML, Reinebrant HE, Wixey JA. Minocycline: a neuroprotective agent for hypoxic-ischemic brain injury in the neonate? *J Neurosci Res* 2009; **87**: 599-608 [PMID: 18831005 DOI: 10.1002/jnr.21890]

58 **Cikla U**, Chanana V, Kintner DB, Covert L, Dewall T, Waldman A, Rowley P, Cengiz P, Ferrazzano P. Suppression of microglia activation after hypoxia-ischemia results in age-dependent improvements in neurologic injury. *J Neuroimmunol* 2016; **291**: 18-27 [PMID: 26857490 DOI: 10.1016/j.jneuroim.2015.12.004]

59 **Tsuji M**, Wilson MA, Lange MS, Johnston MV. Minocycline worsens hypoxic-ischemic brain injury in a neonatal mouse model. *Exp Neurol* 2004; **189**: 58-65 [PMID: 15296836 DOI: 10.1016/j.expneurol.2004.01.011]

60 **Yu IC**, Kuo PC, Yen JH, Paraiso HC, Curfman ET, Hong-Goka BC, Sweazey RD, Chang FL. A Combination of Three Repurposed Drugs Administered at Reperfusion as a Promising Therapy for Postischemic Brain Injury. *Transl Stroke Res* 2017; **8**: 560-577 [PMID: 28624878 DOI: 10.1007/s12975-017-0543-5]

61 **Drabek T**, Wilson CD, Janata A, Stezoski JP, Janesko-Feldman K, Garman RH, Tisherman SA, Kochanek PM. Unique brain region-dependent cytokine signatures after prolonged hypothermic cardiac arrest in rats. *Ther Hypothermia Temp Manag* 2015; **5**: 26-39 [PMID: 25423415 DOI: 10.1089/ther.2014.0013]

62 **Janata A**, Magnet IA, Uray T, Stezoski JP, Janesko-Feldman K, Tisherman SA, Kochanek PM, Drabek T. Regional TNFα mapping in the brain reveals the striatum as a neuroinflammatory target after ventricular fibrillation cardiac arrest in rats. *Resuscitation* 2014; **85**: 694-701 [PMID: 24530249 DOI: 10.1016/j.resuscitation.2014.01.033]

63 **Liu T**, Clark RK, McDonnell PC, Young PR, White RF, Barone FC, Feuerstein GZ. Tumor necrosis factor-alpha expression in ischemic neurons. *Stroke* 1994; **25**: 1481-1488 [PMID: 8023366 DOI: 10.1161/01.STR.25.7.1481]

64 **González JC**, Egea J, Del Carmen Godino M, Fernandez-Gomez FJ, Sánchez-Prieto J, Gandía L, García AG, Jordán J, Hernández-Guijo JM. Neuroprotectant minocycline depresses glutamatergic neurotransmission and Ca(2+) signalling in hippocampal neurons. *Eur J Neurosci* 2007; **26**: 2481-2495 [PMID: 17986028 DOI: 10.1111/j.1460-9568.2007.05873.x]

65 **Huang WC**, Qiao Y, Xu L, Kacimi R, Sun X, Giffard RG, Yenari MA. Direct protection of cultured neurons from ischemia-like injury by minocycline. *Anat Cell Biol* 2010; **43**: 325-331 [PMID: 21267407 DOI: 10.5115/acb.2010.43.4.325]

66 **Liu J**, Bartels M, Lu A, Sharp FR. Microglia/macrophages proliferate in striatum and neocortex but not in hippocampus after brief global ischemia that produces ischemic tolerance in gerbil brain. *J Cereb Blood Flow Metab* 2001; **21**: 361-373 [PMID: 11323522 DOI: 10.1097/00004647-200104000-00005]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 November 19; 8(7): 120-126

DOI: 10.5492/wjccm.v8.i7.120

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Machine learning in data abstraction: A computable phenotype for sepsis and septic shock diagnosis in the intensive care unit

Prabij Dhungana, Laura Piccolo Serafim, Arnaldo Lopez Ruiz, Danette Bruns, Timothy J Weister, Nathan Jerome Smischney, Rahul Kashyap

ORCID number: Prabij Dhungana (0000-0001-5565-6013); Laura Piccolo Serafim (0000-0002-1829-9042); Arnaldo Lopez Ruiz (0000-0002-8950-2087); Danette Bruns (0000-0001-7291-1725); Timothy J Weister (0000-0003-1485-2338); Nathan Jerome Smischney (0000-0003-1051-098X); Rahul Kashyap (0000-0002-4383-3411).

Author contributions: All listed authors provided intellectual contribution and made critical revisions of this paper; Kashyap R, Lopes Ruiz A and Smischney NJ contributed to study conception and design; Dhungana P, Piccolo Serafim L, BrunsD and Weister TJ contributed to data acquisition; Dhungana P, Piccolo Serafim L, Smischney NJ and Kashyap R contributed to data analysis; all authors approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Mayo Clinic Institutional Review Board.

Informed consent statement: Retrospective study was exempt from need for informed consent.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and

Prabij Dhungana, Nathan Jerome Smischney, Rahul Kashyap, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN 55905, United States

Prabij Dhungana, Laura Piccolo Serafim, Arnaldo Lopez Ruiz, Nathan Jerome Smischney, Rahul Kashyap, Multidisciplinary Epidemiology and Translational Research in Intensive Care, Mayo Clinic, Rochester, MN 55905, United States

Laura Piccolo Serafim, Arnaldo Lopez Ruiz, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Danette Bruns, Timothy J Weister, Anesthesia Clinical Research Unit, Mayo Clinic, MN 55905, United States

Corresponding author: Rahul Kashyap, MBBS, Assistant Professor, MBA, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. kashyap.rahul@mayo.edu
Telephone: +1-507-2557196

Abstract

BACKGROUND

With the recent change in the definition (Sepsis-3 Definition) of sepsis and septic shock, an electronic search algorithm was required to identify the cases for data automation. This supervised machine learning method would help screen a large amount of electronic medical records (EMR) for efficient research purposes.

AIM

To develop and validate a computable phenotype via supervised machine learning method for retrospectively identifying sepsis and septic shock in critical care patients.

METHODS

A supervised machine learning method was developed based on culture orders, Sequential Organ Failure Assessment (SOFA) scores, serum lactate levels and vasopressor use in the intensive care units (ICUs). The computable phenotype was derived from a retrospective analysis of a random cohort of 100 patients admitted to the medical ICU. This was then validated in an independent cohort of 100 patients. We compared the results from computable phenotype to a gold standard by manual review of EMR by 2 blinded reviewers. Disagreement was resolved by a critical care clinician. A SOFA score ≥ 2 during the ICU stay with a

revised according to the STROBE Statement-checklist of items.

Manuscript source: Invited manuscript

Received: April 23, 2019
Peer-review started: May 8, 2019
First decision: August 2, 2019
Revised: August 21, 2019
Accepted: October 27, 2019
Article in press: October 27, 2019
Published online: November 19, 2019

P-Reviewer: Zhang ZH
S-Editor: Yan JP
L-Editor: A
E-Editor: Liu MY

culture 72 h before or after the time of admission was identified. Sepsis versions as V1 was defined as blood cultures with SOFA ≥ 2 and Sepsis V2 was defined as any culture with SOFA score ≥ 2. A serum lactate level ≥ 2 mmol/L from 24 h before admission till their stay in the ICU and vasopressor use with Sepsis-1 and-2 were identified as Septic Shock-V1 and-V2 respectively.

RESULTS
In the derivation subset of 100 random patients, the final machine learning strategy achieved a sensitivity-specificity of 100% and 84% for Sepsis-1, 100% and 95% for Sepsis-2, 78% and 80% for Septic Shock-1, and 80% and 90% for Septic Shock-2. An overall percent of agreement between two blinded reviewers had a k = 0.86 and 0.90 for Sepsis 2 and Septic shock 2 respectively. In validation of the algorithm through a separate 100 random patient subset, the reported sensitivity and specificity for all 4 diagnoses were 100%-100% each.

CONCLUSION
Supervised machine learning for identification of sepsis and septic shock is reliable and an efficient alternative to manual chart review.

Key words: Machine learning; Computable phenotype; Critical care; Sepsis; Septic shock

Core tip: This study presents and validates a supervised machine learning model for the identification of sepsis and septic shock cases using electronic medical records as an alternative to manual chart review. This method showed to be an efficient, fast and reliable option for retrospective data abstraction, with the potential to be applied to other clinical conditions.

Citation: Dhungana P, Serafim LP, Ruiz AL, Bruns D, Weister TJ, Smischney NJ, Kashyap R. Machine learning in data abstraction: A computable phenotype for sepsis and septic shock diagnosis in the intensive care unit. *World J Crit Care Med* 2019; 8(7): 120-126
URL: https://www.wjgnet.com/2220-3141/full/v8/i7/120.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i7.120

INTRODUCTION

Septicemia was identified as one of the most costly in-hospital conditions in the United States[1]. The incidence and burden of Systematic Inflammatory Response Syndrome in the acutely ill is around 35% and almost half of all patients hospitalized develop this condition at least once during their stay[2]. It also contributes to as many as half of all hospital deaths[3]. These statistics outline the overall burden of sepsis as a leading cause of critical illness associated with significant mortality and morbidity[4,5]. The Third International Consensus Definition for Sepsis and Septic Shock defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection[6]. The identification of cases of sepsis in the intensive care unit (ICU) is important to further gain knowledge on the subject and improve outcomes.

The use of electronic medical records (EMR's) as a tool to reduce cost and improve safety has been increasing over the years in both clinical practice and health care research[7]. Despite increasing use, there is a lack of structured search strategies and data capturing to identify cases of sepsis or septic shock. With the change in definition of sepsis and septic shock, a search phenotype is useful to identify cases and help additional studies related to sepsis. Machine learning methods to identify comorbidities, post-operative complications, and extubation failure have been developed and validated[8-10]. These algorithms are valuable in research to identify conditions of interest with a sensitivity and specificity approaching and improving on manual review.

The objective of the study was to develop and validate a computable phenotype *via* supervised machine learning method for retrospectively identifying sepsis and septic shock in the ICU based on the Sepsis-3 criteria using information available from the EMR. Identification of these cases is necessary for improving research related to this

condition, and also as a stepping stone to design machine learning models for real-time sepsis detection. Our secondary aim was to validate the results obtained from the computable phenotype by comparing it with a gold standard (*i.e.*, manual review) performed by two independent blinded reviewers.

MATERIALS AND METHODS

The study was approved by the Mayo Clinic Institutional Review Board for the use of existing medical records of patients who gave prior research authorization. The guidelines of the STROBE statement have been adopted.

Study population

The study population consisted of patients above 18 years of age admitted to the medical ICU at Mayo Clinic, Rochester, with prior research authorization. A random subset of 100 patients each was used for derivation and validation of the computable phenotype (Figure 1). The selection of 200 total patients for the study population was to be able to have a comparable sample size between the two cohorts while keeping the time and effort for manual review reasonable.

Manual data abstraction for Gold Standard

The medical records of the derivation and validation cohort were manually reviewed by two independent blinded reviewers. The data obtained from the two reviewers were compared to each other and disagreements were reviewed by a third reviewer. The final set obtained from this process was taken as the gold standard for the study (Figure 1). The reviewers collected data for cultures, Sequential Organ Failure Assessment (SOFA) scores, serum lactate levels, and vasopressor use for the cohorts during their ICU admission. Serum lactate and Cultures were abstracted within 24 h and 72 h before or after ICU admission date respectively, while the other parameters were abstracted during the entire period of their ICU stay.

Automated electronic search strategy

Data for the retrospective study was used from Mayo Clinic ICU DataMart and Unified Data Platform, which are extensive data warehouses containing a near real-time normalized replica of Mayo Clinic's EMR. These databases contain patient information along with their laboratory test results, clinical and pathological information from sources within the institution and have been previously validated. A web-based software tool set (Advanced Cohort Explorer) was used for data access.

The data for cultures, SOFA scores, serum lactate levels and vasopressor use was abstracted and cases were identified as having or not having sepsis and septic shock. The computable phenotype was refined continuously in several iterations to improve the sensitivity and specificity of the derivation subset to more than 90%. The phenotype algorithm was validated using sensitivity and specificity calculated by comparing the results to the gold standard obtained by manual review (Figure 1). The machine learning model for the cohort was done under supervision of an independent critical care researcher.

Sepsis 1 and 2 was defined as blood culture and any culture drawn within 72 h of ICU admission and SOFA score ≥ 2 on any ICU admission days 1-7 respectively. Septic Shock 1 and 2 was defined as Sepsis 1 or 2 criteria plus a serum lactate ≥ 2 mmol/L and at least one vasopressor infusion during ICU admission respectively.

Statistical analysis

Sensitivity and specificity of the computable phenotype was calculated by comparing the results to the gold standard obtained by manual review of the charts using JMP statistical software, SAS 13.0, Cary, North Carolina.

RESULTS

In the initial derivation cohort, the supervised machine learning model achieved a sensitivity of 100% for sepsis (Table 1) and 80% for septic shock (Table 2). There were 4 disagreements between the manual review and the computable phenotype in the dataset. The disagreements were reviewed and it was identified that 2 of the disagreements were due to the results being obtained at a time before the patient was admitted to the ICU. The 2 other disagreements were due to the sample culture sent. The reviewers identified the cases as not being septic even though a culture was sent for the cases and fulfilling sepsis-3 criteria. The supervised machine-learning

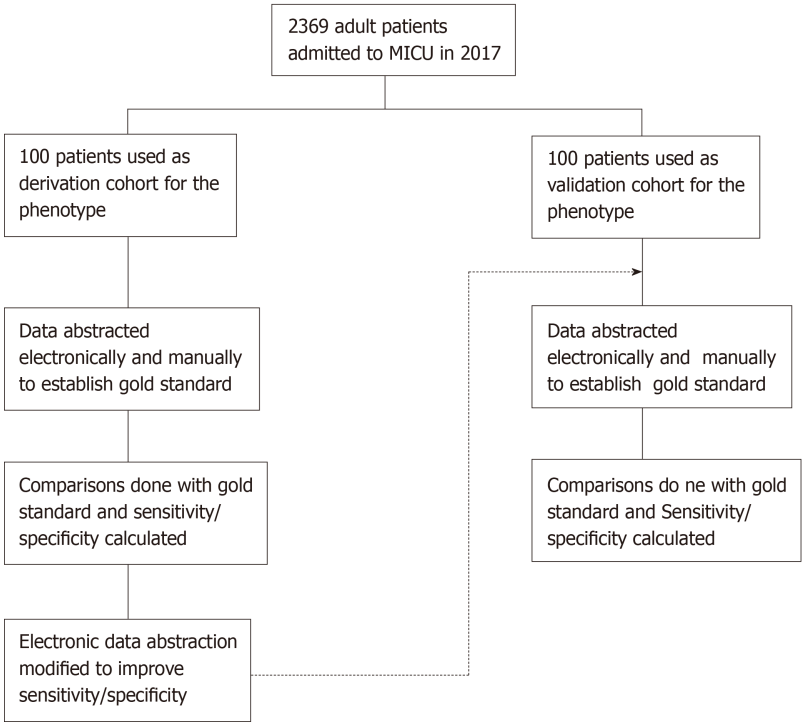


Figure 1 Flow chart of study derivation and validation cohorts. MICU: Medical intensive care unit.

phenotype algorithm was refined and the results compared to obtain a final derivation sensitivity-specificity of 100%-100% for sepsis (Table 1) and 90%-100% for septic shock (Table 2). Correction was then made for the timing of the lactate data and data was abstracted for the validation cohort by both manual review and the computable phenotype. The sensitivity-specificity for the validation cohort was found to be 100%-100% for both sepsis and septic shock (Tables 1 and 2).

DISCUSSION

The results of the study demonstrate that the development of an automated phenotype algorithm (computable phenotype) based on supervised machine learning is an effective and reliable method when compared to manual review. It is also faster than manual review and the sensitivity-specificity achieved in this study provides a highly effective method for reliable retrospective data extraction. Computable phenotypes via machine learning methods have been used as alternatives to manual chart review[8-13]; however, to date, it has never been employed for sepsis and the new sepsis-3 criteria, representing a novel application of this technology.

With widespread use of EMRs, the emphasis on "big data" has increased. The accumulation of vast amounts of data opens doors for opportunities to improve the processes of care and treatment by conducting studies on the available data. Time might be a constraining factor when trying to identify the correct study population through manual review as it takes significant time. Traditional billing searches for conditions may not be completely accurate[9] and changes in coding guidelines make them even less reliable.

The study has several strengths. It allows for a quick and reliable way to retrospectively identify cases of sepsis and septic shock based on the Sepsis-3 guidelines. This provides strong support to the educational and research activity at our institution and demonstrates a simple, yet effective, method that can be applied to other clinical conditions and institutions. It also demonstrates the capability of an algorithm to identify cases based on data stream and hence is an important step towards algorithm/model for real time detection of sepsis.

The limitation of our study is that we used ICU DataMart and Advanced Cohort Explorer systems for electronic data abstraction which are specific to Mayo Clinic. This reduces the generalizability of supervised machine learning model for sepsis and septic shock. The computable phenotype however used laboratory, culture and medication data which are well recorded through various EMR systems and therefore should be easy to recreate with modification based on the institutions' database. Our

Table 1 Machine learning model's sensitivity and specificity for sepsis

	Sepsis-V1[1]		Sepsis-V2[2]	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Initial derivation cohort	100	84.2	100	94.7
Final derivation cohort	100	100	100	100
Validation cohort	100	100	100	100

[1]Version 1;
[2]Version 2.

machine learning model also offers an opportunity for other researchers and institutions to build additional phenotype algorithms to identify conditions/cases objectively to further the improvement in care and knowledge of the medical community.

In conclusion, computable phenotypes based on machine learning are able to correctly identify sepsis and septic shock with high sensitivity and specificity in a cohort of retrospective data. This method can help expedite clinical research by reducing cost and time required for cohort identification. It will also allow the use of larger cohorts thereby enabling the researcher to perform larger studies to ultimately improve clinical outcomes. Finally, the supervised machine learning model can be incorporated into a near real time identification tool to pick up cases of sepsis and septic shock and aid clinical practice as part of a sniffer system.

Table 2 Machine learning model's sensitivity and specificity for septic shock

	Septic shock-V1[1]		Septic shock-V2[2]	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Initial derivation cohort	78	80	80	90
Final derivation cohort	87	100	91	100
Validation cohort	100	100	100	100

[1]Version 1;
[2]Version 2.

ARTICLE HIGHLIGHTS

Research background

With the recent change in the definition (Sepsis-3 Definition) of sepsis and septic shock, an electronic search algorithm was required to identify the cases for data automation.

Research motivation

This supervised machine learning method would help screen a large amount of electronic medical records (EMR) for efficient research purposes.

Research objectives

The main objective was to develop and validate a computable phenotype via supervised machine learning method for retrospectively identifying sepsis and septic shock in critical care patients.

Research methods

A supervised machine learning method was developed based on culture orders, Sequential Organ Failure Assessment (SOFA) scores, serum lactate levels and vasopressor use in the intensive care units (ICUs). The computable phenotype was derived from a retrospective analysis of a random cohort of 100 patients admitted to the medical ICU. This was then validated in an independent cohort of 100 patients. We compared the results from computable phenotype to a gold standard by manual review of EMR by 2 blinded reviewers. Disagreement was resolved by a critical care clinician. A SOFA score ≥ 2 during the ICU stay with a culture 72 h before or after the time of admission was identified. Sepsis versions as V1 was defined as blood cultures with SOFA ≥ 2 and Sepsis V2 was defined as any culture with SOFA score ≥ 2. A serum lactate level ≥ 2 mmol/L from 24 h before admission till their stay in the ICU and vasopressor use with Sepsis-1 and-2 were identified as Septic Shock-V1 and-V2 respectively.

Research results

In the derivation subset of 100 random patients, the final machine learning strategy achieved a sensitivity-specificity of 100% and 84% for Sepsis-1, 100% and 95% for Sepsis-2, 78% and 80% for Septic Shock-1, and 80% and 90% for Septic Shock-2. An overall percent of agreement between two blinded reviewers had a k = 0.86 and 0.90 for Sepsis 2 and Septic shock 2 respectively. In validation of the algorithm through a separate 100 random patient subset, the reported sensitivity and specificity for all 4 diagnoses were 100%-100% each.

Research conclusions

Supervised machine learning for identification of sepsis and septic shock is reliable and an efficient alternative to manual chart review.

Research perspectives

This study presents and validates a supervised machine learning model for the identification of sepsis and septic shock cases using EMRs as an alternative to manual chart review. This method showed to be an efficient, fast and reliable option for retrospective data abstraction, with the potential to be applied to other clinical conditions.

REFERENCES

1 **Torio CM**, Andrews RM. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011: Statistical Brief #160. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville, MD, United States. 2006 [PMID: 24199255]
2 **Churpek MM**, Zadravecz FJ, Winslow C, Howell MD, Edelson DP. Incidence and Prognostic Value of the Systemic Inflammatory Response Syndrome and Organ Dysfunctions in Ward Patients. *Am J Respir Crit Care Med* 2015; **192**: 958-964 [PMID: 26158402 DOI: 10.1164/rccm.201502-0275OC]
3 **Liu V**, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, Iwashyna TJ. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA* 2014; **312**: 90-92 [PMID: 24838355 DOI:

10.1001/jama.2014.5804]
4 **Fleischmann C**, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K; International Forum of Acute Care Trialists. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med* 2016; **193**: 259-272 [PMID: 26414292 DOI: 10.1164/rccm.201504-0781OC]
5 **Vincent JL**, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njimi H, Jimenez E, Sakr Y; ICON investigators. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *Lancet Respir Med* 2014; **2**: 380-386 [PMID: 24740011 DOI: 10.1016/S2213-2600(14)70061-X]
6 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]
7 **Zlabek JA**, Wickus JW, Mathiason MA. Early cost and safety benefits of an inpatient electronic health record. *J Am Med Inform Assoc* 2011; **18**: 169-172 [PMID: 21292703 DOI: 10.1136/jamia.2010.007229]
8 **Rishi MA**, Kashyap R, Wilson G, Hocker S. Retrospective derivation and validation of a search algorithm to identify extubation failure in the intensive care unit. *BMC Anesthesiol* 2014; **14**: 41 [PMID: 24891838 DOI: 10.1186/1471-2253-14-41]
9 **Singh B**, Singh A, Ahmed A, Wilson GA, Pickering BW, Herasevich V, Gajic O, Li G. Derivation and validation of automated electronic search strategies to extract Charlson comorbidities from electronic medical records. *Mayo Clin Proc* 2012; **87**: 817-824 [PMID: 22958988 DOI: 10.1016/j.mayocp.2012.04.015]
10 **Tien M**, Kashyap R, Wilson GA, Hernandez-Torres V, Jacob AK, Schroeder DR, Mantilla CB. Retrospective Derivation and Validation of an Automated Electronic Search Algorithm to Identify Post Operative Cardiovascular and Thromboembolic Complications. *Appl Clin Inform* 2015; **6**: 565-576 [PMID: 26448798 DOI: 10.4338/ACI-2015-03-RA-0026]
11 **Amra S**, O'Horo JC, Singh TD, Wilson GA, Kashyap R, Petersen R, Roberts RO, Fryer JD, Rabinstein AA, Gajic O. Derivation and validation of the automated search algorithms to identify cognitive impairment and dementia in electronic health records. *J Crit Care* 2017; **37**: 202-205 [PMID: 27969571 DOI: 10.1016/j.jcrc.2016.09.026]
12 **Guru PK**, Singh TD, Passe M, Kashani KB, Schears GJ, Kashyap R. Derivation and Validation of a Search Algorithm to Retrospectively Identify CRRT Initiation in the ECMO Patients. *Appl Clin Inform* 2016; **7**: 596-603 [PMID: 27437064 DOI: 10.4338/ACI-2015-12-RA-0183]
13 **Smischney NJ**, Velagapudi VM, Onigkeit JA, Pickering BW, Herasevich V, Kashyap R. Derivation and validation of a search algorithm to retrospectively identify mechanical ventilation initiation in the intensive care unit. *BMC Med Inform Decis Mak* 2014; **14**: 55 [PMID: 24965680 DOI: 10.1186/1472-6947-14-55]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 November 19; 8(7): 127-134

DOI: 10.5492/wjccm.v8.i7.127

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Observational Study

Assessment of quadriceps muscle thickness using bedside ultrasonography by nurses and physicians in the intensive care unit: Intra- and inter-operator agreement

Rohit Kumar, Tajamul Hussain Shah, Vijay Hadda, Pawan Tiwari, Saurabh Mittal, Karan Madan, Maroof Ahmad Khan, Anant Mohan

ORCID number: Rohit Kumar (0000-0003-2853-543X); Tajamul Hussain Shah (0000-0002-6770-9108); Vijay Hadda (0000-0001-5820-3685); Pawan Tiwari (0000-0002-5136-4221); Saurabh Mittal (0000-0003-1430-5799); Karan Madan (0000-0002-5330-6391); Maroof Ahmad Khan (0000-0001-9449-6518); Anant Mohan (0000-0002-2383-9437).

Author contributions: Kumar R and Shah TH contributed equally in performance of the acquisition and analysis of the ultrasonography images; Hadda V designed the study, performed acquisition and analysis of the ultrasonography images, and wrote the manuscript; Tiwari P, Mittal S, Madan K and Mohan A contributed in critical appraisal of the study design, literature search, and editing of the manuscript; Khan MA performed the statistical analysis.

Institutional review board statement: The study protocol was approved by the institutional ethics committee of All India Institute of Medical Sciences, New Delhi, India (Ref. No. IEC-435/02.09.2016, RP-52/2016).

Informed consent statement: All study participants or their legal guardians provided written informed consent prior to participation in the study.

Conflict-of-interest statement: All

Rohit Kumar, Tajamul Hussain Shah, Vijay Hadda, Pawan Tiwari, Saurabh Mittal, Karan Madan, Anant Mohan, Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences, New Delhi 110029, India

Maroof Ahmad Khan, Department of Biostatistics, All India Institute of Medical Sciences, New Delhi 110029, India

Corresponding author: Vijay Hadda, MD, Assistant Professor, Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. vijayhadda@yahoo.com
Telephone: +91-11-26546347
Fax: +91-11-26548663

Abstract

BACKGROUND

Data regarding the agreement among multiple operators for measurement of quadriceps muscle thickness by bedside ultrasonography (USG) are sparse.

AIM

To statistically assess the agreement among 5 operators for measurement of quadriceps muscle thickness on bedside USG.

METHODS

This was a cross-sectional observational study. The 5 operators of varied experience (comprised of 1 critical care consultant, 2 fellows, and 2 nurses) independently measured quadriceps muscle thickness in triplicate for 45 critically ill patients each, using USG. Intra- and interrater agreement rates among the 5 operators were assessed using intraclass correlation coefficient (ICC) and expressed with 95% confidence interval (CI).

RESULTS

The 5 operators produced a total of 135 readings and 675 observations for ICC calculations to determine the intraoperator and interoperator variations respectively. For intraoperator agreement, the overall ICC (95%CI) was 0.998 (0.997, 0.999) for operator 1, 0.998 (0.997, 0.999) for operator 2, 0.997 (0.995, 0.999) for operator 3, 0.999 (0.998, 0.999) for operator 4, and 0.998 (0.997, 0.999) for

authors state they have no conflicts of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

Manuscript source: Unsolicited manuscript

Received: December 28, 2018
Peer-review started: December 29, 2018
First decision: June 7, 2019
Revised: August 29, 2019
Accepted: October 27, 2019
Article in press: October 27, 2019
Published online: November 19, 2019

P-Reviewer: Fiaccadori E, Li CH, Valek V
S-Editor: Yan JP
L-Editor: A
E-Editor: Liu MY

operator 5. For interoperator agreement, the overall ICC (95%CI) was 0.977 (0.965, 0.986; $P < 0.001$) for reading 1, 0.974 (0.960, 0.984; $P < 0.001$) for reading 2, and 0.975 (0.961, 0.985; $P < 0.001$) for reading 3.

CONCLUSION
USG measurement of quadriceps muscle thickness was not dependent on clinical experience, supporting training for nurses in it.

Key words: Agreement; Intensive care unit; Critical illness; Muscle thickness; Quadriceps muscle; Ultrasonography

Core tip: Ultrasonography-measured quadriceps muscle thickness may be an early marker of adverse outcome among patients in the intensive care unit (ICU). However, while the technological approach is available for routine bedside use in the ICU, its application in daily care can increase the workload of ICU physicians. In this study, we found that quadriceps muscle thickness measurement by using ultrasonography can be done reliably by nurses, to a degree that is comparable to that of ICU fellows and a critical care consultant. These results suggest that nurses may be trained easily and used for ultrasonography measurement of quadriceps muscle thickness.

Citation: Kumar R, Shah TH, Hadda V, Tiwari P, Mittal S, Madan K, Khan MA, Mohan A. Assessment of quadriceps muscle thickness using bedside ultrasonography by nurses and physicians in the intensive care unit: Intra- and inter-operator agreement. *World J Crit Care Med* 2019; 8(7): 127-134
URL: https://www.wjgnet.com/2220-3141/full/v8/i7/127.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i7.127

INTRODUCTION

Patients admitted to intensive care units (ICUs) exhibit significant loss of muscle mass and function during their hospital stay[1,2]. Inactivity of muscles, poor nutrition, and various proinflammatory cytokines associated with the systemic inflammatory response may be responsible for these losses[1,2]. The loss of muscle mass, in particular, has been associated with various adverse clinical outcomes among the ICU patient population, including prolonged mechanical ventilation, reintubation, mortality, and increased cost of care[2,3].

Accurate assessment of muscle functions and timely diagnosis of muscle dysfunction, together, are crucial for effective preventive or therapeutic interventions. The Medical Research Council (MRC) grading system and anthropometry are commonly applied to clinically assess the muscle mass and functions. The MRC grading requires patients to be fully alert, while anthropometry assessment requires only normal hydration status. Since the majority of critically ill patients have depressed mental status and altered hydration, both of these tools are insensitive and unreliable for assessment of the muscle mass and functions in the ICU patients[4,5]. Researchers have, however, shown that muscle thickness correlates with muscle function[6]. Muscle thickness can be measured accurately using tools such as dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), and computer tomography (CT)[3,7]. Thus, data obtained through these scans provide information regarding muscle functions independent of patients' level of alertness, effort, and hydration status. However, these tools remain of limited use for critically ill patients on multiple life-support therapies.

Recently, ultrasonography (USG) has been proposed as a promising tool for the assessment of skeletal muscle thickness[8-10]. USG has the advantage of being a bedside technology, appropriate for single-time measurement, and useful for studying trends in a patient's status. Importantly, there is also no risk of radiation exposure with USG. The quadriceps muscles are bulky muscle tissue, usually free of clinical monitoring devices and intravenous lines, and can be used for thickness assessment by USG. Preliminary data from others have also suggested that USG-measured quadriceps muscle thickness can be an early marker of adverse outcome among critically ill

patients[9]. Thus, it is likely that the role of USG in assessment of muscle functions will expand among the critically ill patient population. However, addition of USG to daily care in the ICU is also likely to increase the workload of the treating physicians. If the paramedical staff, especially nurses, can perform the USG assessment of muscle thickness, it will help to counter this hindering factor. Before asking nurses to use USG for this purpose though, the reliability of their measurements, as compared to the more highly expert staff, should be established. This study was hence designed to assess intra- and interoperator reliability of measurements of quadriceps muscle thickness using USG data obtained by 2 nurses and 3 physicians who practice in the ICU.

MATERIALS AND METHODS

This study was conducted following good clinical practices proposed for biomedical research involving human subjects[11]. Prior approval of the study protocol was sought from the institute's ethics committee for research protocols (Ref. No. IEC-435/02.09.2016, RP-52/2016). All patients provided a written informed consent for participation in the study.

Study design and patients

This cross-sectional study included critically ill adult patients (age > 18 years) admitted under the Pulmonary Medicine Services of a tertiary care teaching institute between July 2016 and June 2017. Exclusion criteria were primary neuromuscular diseases (*i.e*., myopathy, neuropathy, stroke, *etc*.), an amputated limb, and refusal of participation in the study.

Equipment

The measurements were made using B-mode USG with a 5.0–13.0 MHz linear array probe (VF 13-5) on an ACUSON X300™ ultrasound (Siemens Healthineers, Erlangen, Germany).

Operators

There were 5 operators who independently assessed the quadriceps muscle thickness on USG. These operators represented faculty (a critical care consultant; n = 1), fellows (n = 2), and nurses (n = 2). The faculty member (VH) had an experience of > 5 years. Both fellows (RK, THS) were trained and actively using USG in the ICU for > 2 years. Both nurses were naïve to USG, and as such were given a short training regarding image acquisition and measurement of muscle thickness on 5-10 patients, prior to start of the study.

Muscle thickness measurements

Quadriceps muscle thickness measurements were done following the previously published protocol[9,12,13]. All measurements were carried out on the right thigh, with the patient in supine position and having the knee extended and toes facing the ceiling. The posture was maintained until all images were acquired. A circumferential mark was put at the midway between the tip of the greater trochanter and the lateral joint line of the knee. The linear ultrasound probe was placed on this circumferential line, perpendicular to the skin, and the probe was moved along the line until a suitable image was obtained. Then, the point corresponding to the center of the probe was marked with a vertical line. This point was used as the reference point for all subsequent measurements. The thickness of the quadriceps muscle group (vastus lateralis, rectus femoris, and vastus medialis) between the superficial fat-muscle interface and the femur was measured anteriorly. Each of the 5 operators took three measurements, independently. None of the 5 operators was aware of the muscle thickness measurement values obtained by any of the 4 others.

Statistical analysis

The intraclass correlation coefficient (ICC) was calculated for intra- and interoperator variability among the 5 operators. For intraoperator variation, the ICC was calculated for the three pairs of measurements (1st and 2nd, 1st and 3rd, and 2nd and 3rd) made by each operator. Interoperator variation was assessed using ICC for 10 possible pairs of operators for each observation. The ICCs were expressed with 95% confidence intervals. A P value of < 0.05 was considered significant. Mean [± standard deviation (SD)] was applied as appropriate. All statistical analyses were performed on SPSS for Windows software (version 24; IBM Corp., Armonk, NY, United States).

RESULTS

Baseline characteristics

This study included 45 critically ill patients admitted to the pulmonary medicine ward or ICU. There were 30 males (66.6%). The mean (± SD) age of participants was 54.95 (± 15.97) years and that of Acute Physiology and Chronic Health Evaluation score and Simplified Acute Physiology Score was 14.66 (± 4.57) and 2.6 (± 1.37) respectively.

Muscle thickness measurements

Each of the 5 operators took three readings of quadriceps muscle thickness, which varied from 17.11 mm to 17.87 mm. The measurements taken by operator 3 (Fellow: TS) had the highest values. The collective mean (± SD) quadriceps thickness measurements obtained by all operators on three different attempts are shown in Table 1.

Intraoperator reliability

For each operator, there were 135 (3 × 45) readings for calculation of ICC to assess the intraoperator variation. The resultant ICCs for all of the three possible pairs (1st and 2nd, 1st and 3rd, and 2nd and 3rd) of quadriceps muscle thickness measurements taken by each operator were close to 1 (lowest being 0.997, to highest of 0.999); similarly, the overall ICC was excellent for each operator's intraoperator reliability separately (Table 2).

Interoperator reliability

There were a total 675 observations for analysis of ICC of interoperator variation. The minimum value of ICC for interoperator variation was 0.955, while the maximum value was 0.988. The results of pairwise and overall ICCs for interoperator variation are shown in Table 3.

DISCUSSION

Our study results demonstrate an excellent intra- and interoperator agreement for quadriceps muscle thickness measured on bedside USG by 2 nurses and 3 ICU physicians, representing varied clinical experience levels. The excellent intra- and interoperator agreement rates found indicate that nurses may be utilized for assessment of quadriceps muscle thickness in this setting.

Availability of USG in general has increased the precision and reduced the complication rates of various procedures carried out in the ICU setting[14,15]. Indeed, USG was recently proposed to be a useful tool for assessment of muscle mass in the form of muscle thickness[8-10]. It seems reasonable to include bedside USG in daily care for assessment of muscle thickness among patients in the ICU; however, inclusion of USG assessment for muscle thickness will also serve to increase the workload of the critical care fellows and consultants. Nurses working in the ICU contribute immensely to the provision of care given to the critically ill patient population in this setting; yet, the services of these highly-skilled workers likely remain underutilized.

Nurses represent potential manpower that can be readily trained for the measurement of quadriceps muscle thickness on USG. In consideration of this and the fact that USG measurements are operator-dependent (with potential for significant variation), our results support the notion that nurses can measure quadriceps muscle thickness to a similar excellent degree of the more highly trained physician-level staff in our facility. It should be noted, here, that both of our nurses were naïve to USG and both received only a short training course involving 5-10 patients prior to study participation. Thus, only a short training was required for our nurses to carry out appropriate assessment of quadriceps muscle thickness using USG; we suggest that this may be the case with the ICU nursing staff of other critical care hospitals and departments. The importance of expanding our finding to other facilities is highlighted by the observation that quadriceps muscle thickness may be an early predictor of adverse outcome among critically ill patients[9].

The comparison of measurements taken by operators naïve to USG (2 nurses) with those of experienced operators (consultant and fellows) is the greatest strength of our study. This design provided data from a real-time scenario, when a clinically-trained but USG-naïve operator was asked to take measurement after a short training course; the data from the experienced operator verified the reproducibility of the measurements obtained by the former. There have been other studies which have shown minimal variability when > 1 operator assessed the quadriceps muscle thickness on USG[10,13]. Also, in our study, the quadriceps muscle thicknesses were

Table 1 Quadriceps thickness measured by 5 operators in a critical care setting

Operator		Thickness measured on three different attempts, mean (± SD) mm		
ID	Level	1st	2nd	3rd
1	Consultant	17.14 (± 6.64)	17.49 (± 6.83)	17.44 (± 6.82)
2	Fellow	17.23 (± 6.81)	17.28 (± 6.92)	17.17 (± 6.81)
3	Fellow	17.82 (± 6.73)	17.87 (± 6.81)	17.80 (± 6.77)
4	Nurse	17.11 (± 6.54)	17.28 (± 6.49)	17.35 (± 6.57)
5	Nurse	17.52 (± 6.64)	17.42 (± 6.67)	17.52 (± 6.71)

SD: Standard deviation.

measured in all patients by each of the 5 operators, allowing for direct comparative analysis of all observations. Moreover, all measurements by all 5 operators were taken independently, without each operator being aware of the results of measurement by the other 4 operators. The blinding of operators from each other's results at the time of measurement further added to the reliability of the measurement data obtained by each.

There are certainly a few limitations to our study design that must be considered in the generalization of our findings. First, there was no radiologist included as an operator. Such might have helped in assessing the agreement of nonradiologist operators with the most experienced operator of USG. It is undebatable that radiologists are the most experienced staff to operate USG; however, they are not available round the clock in the ICU. Hence, results related to operators who stay in the ICU on a regular schedule, and are likely to use USG in this setting, are more useful for a day-to-day care point of view. In our ICU there is no dedicated radiologist available round the clock, which laid beneath our decision to not include a radiologist as an operator for this study. Second, there was no "gold-standard" used to check the accuracy of the measurement of muscle thicknesses taken by our 5 operators. Quadriceps muscle thickness measurements using CT, MRI or DEXA scan are considered "gold-standard", but many patients admitted to the ICU are too sick to be physically shifted for these investigations. Therefore, all these tools are of no use in this setting. Data have shown, however, that measurements obtained by USG have good correlation with those obtained by CT, MRI or DEXA scan[16]. Importantly, USG can be carried out at the bedside, bolstering the relevance of our findings in this setting.

In conclusion, quadriceps muscle thickness can be measured by nurses, with excellent reproducibility of measurements compared with readings taken by a critical care consultant and fellows. These results suggest that nurses may be trained for measurement of quadriceps muscle thickness on USG in the critical care setting.

Table 2 Intraclass correlation coefficient for intraoperator variation among five operators

Operator		Measurements	ICC (95%CI); *P* value	Cronbach's alpha
ID	Level			
1	Consultant	1st *vs* 2nd	0.997 (0.992-0.999); < 0.0001	0.998
		1st *vs* 3rd	0.997 (0.993-0.998); < 0.0001	0.997
		2nd *vs* 3rd	0.998 (0.996-0.999); < 0.0001	0.998
		Overall	0.998 (0.997-0.999); < 0.0001	0.997
2	Fellow	1st *vs* 2nd	0.997 (0.995-0.998); < 0.0001	0.997
		1st *vs* 3rd	0.997 (0.995-0.997); < 0.0001	0.997
		2nd *vs* 3rd	0.997 (0.995-0.998); < 0.0001	0.997
		Overall	0.998 (0.997-0.999); < 0.0001	0.998
3	Fellow	1st *vs* 2nd	0.997 (0.995-0.999); < 0.0001	0.997
		1st *vs* 3rd	0.997 (0.995-0.999); < 0.0001	0.997
		2nd *vs* 3rd	0.998 (0.996-0.998); < 0.0001	0.998
		Overall	0.997 (0.995-0.999); < 0.0001	0.998
4	Nurse	1st *vs* 2nd	0.998 (0.996-0.999); < 0.0001	0.998
		1st *vs* 3rd	0.997 (0.995-0.999); < 0.0001	0.998
		2nd *vs* 3rd	0.999 (0.998-0.999); < 0.0001	0.999
		Overall	0.999 (0.998-0.999); < 0.0001	0.999
5	Nurse	1st *vs* 2nd	0.998 (0.996-0.999); < 0.0001	0.998
		1st *vs* 3rd	0.997 (0.995-0.998); < 0.0001	0.997
		2nd *vs* 3rd	0.998 (0.996-0.999); < 0.0001	0.998
		Overall	0.998 (0.997-0.999); < 0.0001	0.998

CI: Confidence interval; ICC: Intraclass correlation coefficient.

Table 3 Intraclass correlation coefficients for intraoperator variation among five operators for interoperator variation among 5 operators

Operator[1] comparison	ICC (95%CI); *P* value		
	1st measurement	2nd measurement	3rd measurement
1 *vs* 2	0.979 (0.961, 0.988); < 0.001	0.976 (0.956, 0.987); < 0.001	0.977 (0.958, 0.987); < 0.001
1 *vs* 3	0.978 (0.960, 0.988); < 0.001	0.978 (0.960, 0.988); < 0.001	0.977 (0.959, 0.987); < 0.001
1 *vs* 4	0.965 (0.938, 0.981); < 0.001	0.955 (0.920, 0.975); < 0.001	0.962 (0.932, 0.979); < 0.001
1 *vs* 5	0.979 (0.963, 0.989); < 0.001	0.967 (0.942, 0.982); < 0.001	0.971 (0.948, 0.984); < 0.001
2 *vs* 3	0.988 (0.979, 0.994); < 0.001	0.984 (0.971, 0.991); < 0.001	0.982 (0.967, 0.990); < 0.001
2 *vs* 4	0.966(0.938, 0.981); < 0.001	0.963 (0.933, 0.979); < 0.001	0.966 (0.939, 0.981); < 0.001
2 *vs* 5	0.980(0.964, 0.989); < 0.001	0.975 (0.956, 0.986); < 0.001	0.978 (0.960, 0.988); < 0.001
3 *vs* 4	0.966 (0.939, 0.981); < 0.001	0.969 (0.945, 0.983); < 0.001	0.968 (0.942, 0.982); < 0.001
3 *vs* 5	0.983 (0.969, 0.991); < 0.001	0.979 (0.962, 0.988); < 0.001	0.980 (0.964, 0.989); < 0.001
4 *vs* 5	0.988 (0.978, 0.993); < 0.001	0.989 (0.980, 0.994); < 0.001	0.985 (0.973, 0.992); < 0.001
Overall	0.977 (0.965, 0.986); < 0.001	0.974 (0.960, 0.984); < 0.001	0.975 (0.961, 0.985); < 0.001

[1]1: Consultant; 2 and 3: Fellow; 4 and 5: Nurse. CI: Confidence interval; ICC: Intraclass correlation coefficient.

ARTICLE HIGHLIGHTS

Research background

Nurses can measure quadriceps muscle thickness using ultrasonography (USG). However, the data regarding the reliability of such measurements are sparse.

Research motivation

The inclusion of USG for assessment of quadriceps muscle thickness on a daily basis would add, remarkably, to the workload on intensive care unit (ICU) physicians. Reliable measurement of quadriceps muscle thickness by USG from nurse operators would reduce the workload of

physicians working in the ICU.

Research objectives
To evaluate the reliability of measurements of quadriceps muscle thickness using USG data obtained by critical care-setting nurses.

Research methods
In this cross-sectional observational study, 5 operators (comprised of 1 critical care consultant, 2 fellows, and 2 nurses) independently measured quadriceps muscle thickness on ICU patients by using USG. The experience of using USG was variable among the 5 operators. The consultant and 2 fellows had experience of > 5 years and 2 years, respectively. Both nurses were naïve to USG, and they were provided a short training course involving 5-10 patients before the actual start of the study. Each operator took three readings of each patient's quadriceps muscles thickness on USG, independently. Assessment of agreement for measurements taken by all 5 operators was done by computing the intraclass correlation coefficient (ICC) and expressed with the corresponding 95% confidence interval (CI).

Research results
We included 45 critically ill patients in this study. The quadriceps muscle thickness measured by the 2 nurses closely resembled those obtained by the critical care consultant and 2 fellows. The overall ICC (95%CI) for interoperator agreement for the 1st, 2nd and 3rd readings were 0.977 (0.965, 0.986; $P < 0.001$), 0.974 (0.960, 0.984; $P < 0.001$) and 0.975 (0.961, 0.985; $P < 0.001$) respectively.

Research conclusions
Critical care nurses can measure quadriceps muscle thickness on bedside USG, with their measurements having excellent reliability when compared to those from a critical care consultant and fellows.

Research perspectives
The current study adds to the expanding body of literature on the use of bedside USG in critical care settings. The study's results suggest that nurses in the ICU setting may successfully perform USG assessment of quadriceps muscle thickness. Feasibility of a nurses-led assessment of quadriceps muscle thickness should be explored further in studies involving larger populations of staff and patients and more various critical care settings.

REFERENCES

1 **Kramer CL**. Intensive Care Unit-Acquired Weakness. *Neurol Clin* 2017; **35**: 723-736 [PMID: 28962810 DOI: 10.1016/j.ncl.2017.06.008]
2 **Jolley SE**, Bunnell AE, Hough CL. ICU-Acquired Weakness. *Chest* 2016; **150**: 1129-1140 [PMID: 27063347 DOI: 10.1016/j.chest.2016.03.045]
3 **Apostolakis E**, Papakonstantinou NA, Baikoussis NG, Papadopoulos G. Intensive care unit-related generalized neuromuscular weakness due to critical illness polyneuropathy/myopathy in critically ill patients. *J Anesth* 2015; **29**: 112-121 [PMID: 24981564 DOI: 10.1007/s00540-014-1875-x]
4 **Thomaes T**, Thomis M, Onkelinx S, Coudyzer W, Cornelissen V, Vanhees L. Reliability and validity of the ultrasound technique to measure the rectus femoris muscle diameter in older CAD-patients. *BMC Med Imaging* 2012; **12**: 7 [PMID: 22471726 DOI: 10.1186/1471-2342-12-7]
5 **Mourtzakis M**, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008; **33**: 997-1006 [PMID: 18923576 DOI: 10.1139/H08-075]
6 **Freilich RJ**, Kirsner RL, Byrne E. Isometric strength and thickness relationships in human quadriceps muscle. *Neuromuscul Disord* 1995; **5**: 415-422 [PMID: 7496175 DOI: 10.1016/0960-8966(94)00078-N]
7 **Kress JP**, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med* 2014; **370**: 1626-1635 [PMID: 24758618 DOI: 10.1056/NEJMra1209390]
8 **Parry SM**, El-Ansary D, Cartwright MS, Sarwal A, Berney S, Koopman R, Annoni R, Puthucheary Z, Gordon IR, Morris PE, Denehy L. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. *J Crit Care* 2015; **30**: 1151.e9-1151.14 [PMID: 26211979 DOI: 10.1016/j.jcrc.2015.05.024]
9 **Hadda V**, Kumar R, Khilnani GC, Kalaivani M, Madan K, Tiwari P, Mittal S, Mohan A, Bhalla AS, Guleria R. Trends of loss of peripheral muscle thickness on ultrasonography and its relationship with outcomes among patients with sepsis. *J Intensive Care* 2018; **6**: 81 [PMID: 30564367 DOI: 10.1186/s40560-018-0350-4]
10 **Sabatino A**, Regolisti G, Bozzoli L, Fani F, Antoniotti R, Maggiore U, Fiaccadori E. Reliability of bedside ultrasound for measurement of quadriceps muscle thickness in critically ill patients with acute kidney injury. *Clin Nutr* 2017; **36**: 1710-1715 [PMID: 27743614 DOI: 10.1016/j.clnu.2016.09.029]
11 **World Medical Association**. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191-2194 [PMID: 24141714 DOI: 10.1001/jama.2013.281053]
12 **Campbell IT**, Watt T, Withers D, England R, Sukumar S, Keegan MA, Faragher B, Martin DF. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. *Am J Clin Nutr* 1995; **62**: 533-539 [PMID: 7661114 DOI: 10.1093/ajcn/62.3.533]
13 **Hadda V**, Khilnani GC, Kumar R, Dhunguna A, Mittal S, Khan MA, Madan K, Mohan A, Guleria R. Intra- and Inter-observer Reliability of Quadriceps Muscle Thickness Measured with Bedside Ultrasonography by Critical Care Physicians. *Indian J Crit Care Med* 2017; **21**: 448-452 [PMID:

28808365 DOI: 10.4103/ijccm.IJCCM_426_16]
14 **Narasimhan M**, Koenig SJ, Mayo PH. A Whole-Body Approach to Point of Care Ultrasound. *Chest* 2016; **150**: 772-776 [PMID: 27568582 DOI: 10.1016/j.chest.2016.07.040]
15 **Vignon P**, Repessé X, Vieillard-Baron A, Maury E. Critical care ultrasonography in acute respiratory failure. *Crit Care* 2016; **20**: 228 [PMID: 27524204 DOI: 10.1186/s13054-016-1400-8]
16 **Dupont AC**, Sauerbrei EE, Fenton PV, Shragge PC, Loeb GE, Richmond FJ. Real-time sonography to estimate muscle thickness: comparison with MRI and CT. *J Clin Ultrasound* 2001; **29**: 230-236 [PMID: 11323778 DOI: 10.1002/jcu.1025]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2019 December 20; 8(8): 135-147

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Irregular Volume 8 Number 8 December 20, 2019

SYSTEMATIC REVIEWS

Contents

World Journal of Critical Care Medicine

Volume 8 Number 8 December 20, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Kyoung Hoon Lim, MD, Assistant Professor, Director of Traumatic Intensive Care Unit, Division of Trauma, Department of Surgery, Kyungpook National University Hospital, Daegu 41944, South Korea

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, infection and anti-infection treatment, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, severe infection, and shock and multiple organ dysfunction syndrome.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Mei-Yi Liu*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

EDITORIAL OFFICE
Jia-Ping Yan, Director

PUBLICATION DATE
December 20, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2019 December 20; 8(8): 135-147

DOI: 10.5492/wjccm.v8.i8.135

ISSN 2220-3141 (online)

SYSTEMATIC REVIEWS

Extra-corporeal membrane oxygenation in aortic surgery and dissection: A systematic review

Massimo Capoccia, Marc O Maybauer

ORCID number: Massimo Capoccia (0000-0002-2351-9994); Marc O Maybauer (0000-0003-2406-655X).

Author contributions: Capoccia M and Maybauer MO contributed equally to the work; Capoccia M and Maybauer MO conceptualized and designed the review; Capoccia M and Maybauer MO carried out the analysis; Capoccia M drafted the initial manuscript; Capoccia M and Maybauer MO reviewed and approved the submitted manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Manuscript source: Invited

Massimo Capoccia, Department of Aortic and Cardiac Surgery, Royal Brompton Hospital, Royal Brompton and Harefield NHS Foundation Trust, London SW3 6NP, United Kingdom

Marc O Maybauer, Department of Anaesthesia, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester M13 9WL, United Kingdom

Marc O Maybauer, Department of Anaesthesiology and Intensive Care Medicine, Phillips University, Marburg 35037, Germany

Marc O Maybauer, Critical Care Research Group, The Prince Charles Hospital and The University of Queensland, Brisbane QLD 4032, Queensland, Australia

Marc O Maybauer, Advanced Critical Care and Transplant Institute, Integris Baptist Medical Centre, Oklahoma City, OK 73112, United States

Corresponding author: Massimo Capoccia, MD, MSc, Surgeon, Senior Aortic Fellow, Department of Aortic and Cardiac Surgery, Royal Brompton Hospital, Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, Chelsea, London SW3 6NP, United Kingdom. capoccia@doctors.org.uk
Telephone: +44-20-73528121

Abstract

BACKGROUND

Very little is known about the role of extracorporeal membrane oxygenation (ECMO) for the management of patients undergoing major aortic surgery with particular reference to aortic dissection.

AIM

To review the available literature to determine if there was any evidence.

METHODS

A systematic literature search through PubMed and EMBASE was undertaken according to specific key words.

RESULTS

The search resulted in 29 publications relevant to the subject: 1 brief communication, 1 surgical technique report, 1 invited commentary, 1 retrospective case review, 1 observational study, 4 retrospective reviews, 13 case reports and 7 conference abstracts. A total of 194 patients were included in these publications of whom 77 survived.

Manuscript

Received: October 15, 2019
Peer-review started: October 15, 2019
First decision: October 25, 2019
Revised: November 28, 2019
Accepted: November 28, 2019
Article in press: November 28, 2019
Published online: December 20, 2019

P-Reviewer: Jha NK
S-Editor: Ma RY
L-Editor: A
E-Editor: Liu MY

CONCLUSION
Although there is no compelling evidence for or against the use of ECMO in major aortic surgery or dissection, it is enough to justify its use in this patient population despite current adverse attitude.

Key words: Aortic dissection; Aortic surgery; Extra-corporeal life support; Extracorporeal membrane oxygenation; Extracorporeal life support; Mechanical circulatory support

Core tip: The subject of our review remains controversial in the absence of clear evidence but mainly based on opinions and speculations. We believe that such a timely review may contribute to reconsider current thinking and address the subject with an open mind.

Citation: Capoccia M, Maybauer MO. Extra-corporeal membrane oxygenation in aortic surgery and dissection: A systematic review. *World J Crit Care Med* 2019; 8(8): 135-147
URL: https://www.wjgnet.com/2220-3141/full/v8/i8/135.htm
DOI: https://dx.doi.org/10.5492/wjccm.v8.i8.135

INTRODUCTION

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has become an established and widely used technique to provide circulatory support for critically ill patients with refractory cardiogenic shock and cardiac arrest[1-3] although an increased left ventricular (LV) afterload may affect the intended beneficial effects[4]. The impact of VA-ECMO on LV function can be explained in terms of pressure-volume (PV) loops and Starling curves[5] following simulations based on a previously developed model[6,7]. VA-ECMO does not affect LV function directly. When LV afterload is maintained constant at a specific systemic pressure, the Starling curve generated before VA-ECMO support predicts the filling pressure related to any target stroke volume (SV) at that systemic pressure. The mechanism by which that specific pressure is achieved does not change the relationship between filling pressure and native LV SV. A maintained Starling relationship during VA-ECMO support may help predict ventricular distension and optimise the balance between LV unloading and systemic perfusion[5]. Despite the outcome of the SHOCK II trial which remains against the use of the intra-aortic balloon pump (IABP) in cardiogenic shock[8-10], a combined use of VA-ECMO and IABP has shown reduced in-hospital mortality[11,12]. In addition, the combination of VA-ECMO and the Impella device has been shown to be a useful method to offload the left ventricle[13,14]. Quantitative evaluation based on a simulation approach has confirmed the beneficial effect of adding IABP or Impella during VA-ECMO support[15].

A recent retrospective multi-centre cohort study on post-cardiotomy VA-ECMO has identified age, previous cardiac surgery, preoperative acute neurological events, aortic arch surgery and increased arterial lactate as factors associated with increased risk of early mortality following the procedure although the experience of the centre may contribute to improved results[16]. Nevertheless, there is no real focus on critical patients experiencing post-cardiotomy failure after major aortic surgery for aneurysmal disease or dissection.

Diseases of the thoracic aorta carry a high mortality with an increasing prevalence worldwide at present in the context of long-standing controversy regarding its treatment[17-19]. Current evidence suggests that acute aortic syndromes are best treated in dedicated, high-volume aortic centres[20]. Preoperative malperfusion plays a major role on early and late outcome[21-23].

Therefore, we sought to review current attitude on the use of mechanical circulatory support (MCS) following major aortic surgery with a view that it may be an option for these critical patients. The analysis has considered adult patients only.

MATERIALS AND METHODS

This review has been undertaken according to a web-based literature search on PubMed and EMBASE using appropriately combined key words [extra-corporeal life support (ECLS) and aortic surgery; ECLS and aortic dissection; ECMO and aortic surgery; ECMO and aortic dissection]. The Participants, Intervention, Comparison, Outcome and Study Design (PICOS) approach for the selection of clinical studies following our systematic search has been used (Table 1). The PRISMA approach has also been considered whose main purpose is to help ensure the clarity and transparency of systematic reviews; it was developed using an evidence-based approach and is not intended as a quality assessment tool[24]. An extension of the PRISMA statement has been developed to specifically address the reporting of systematic reviews incorporating network meta-analyses[25]. PRISMA-P is intended to help the preparation and reporting of a robust protocol for a systematic review[26].

We selected all the articles including major aortic surgery involving the ascending aorta, arch, descending thoracic and abdominal aorta.

The aim of this systematic review was to determine current knowledge and experience with ECLS/ECMO support for aortic disease and whether it is appropriate for postcardiotomy failure following major aortic surgery with particular reference to aortic dissection.

RESULTS

The search gave the following results (Figure 1): ECMO and aortic surgery retrieved 906 publications in PubMed and 13 publications in EMBASE; ECMO and aortic dissection retrieved 61 publications in PubMed and 49 in EMBASE; ECLS and aortic surgery retrieved 67 publications in PubMed and no publications in EMBASE; ECLS and aortic dissection retrieved 5 publications in PubMed and 2 publications in EMBASE. The overall analysis revealed 29 publications related to the subject of investigation as follows (Table 2): 1 brief communication[27], 1 surgical technique report[28], 1 invited commentary[29], 1 retrospective case review[30], 1 observational study[31], 4 retrospective studies[32-35], 13 case reports[36-48] and 7 conference abstracts[49-55]. The articles had been published between 1994 and 2019. Four publications reported key data for this review[31-34]. A total number of 194 patients had been treated with ECMO support leading to 77 surviving patients. Three publications[31,35,54] did not specify how many patients survived following ECMO support; therefore, the number of surviving patients remains incomplete. Further analysis gives a breakdown of aetiology, procedures performed and cannulation site when available (Table 3).

DISCUSSION

ECMO has become increasingly available for the treatment of a diverse population of critically ill patients and recent reviews have highlighted its indications and the evidence basis to justify its use[1,56]. VA-ECMO is a suitable approach in the context of cardiac failure. Veno-venous (VV) ECMO is appropriate in the context of acute respiratory disease syndrome. More recently, ECMO has been considered in the setting of extracorporeal cardiopulmonary resuscitation. Despite increased application of the technique, overall survival rates have remained unchanged with a 50%-70% range for respiratory support and 40%-60% range for cardiac support[57,58]. Traditional configurations for ECMO support include the VV through the right internal jugular vein (Avalon cannula) and the veno-arterial (VA) either through the ascending aorta and the right atrium (central cannulation) or through the femoral vessels (peripheral cannulation)[3,59]. Hybrid ECMO configurations have been increasingly considered recently as an attempt to improve outcome. Triple cannulation such as veno-venous-arterial (VVA) or venous-arterial-venous (VAV) configurations may help with concomitant cardiac and respiratory failure. VVA ECMO consists of double venous cannulation through the right internal jugular vein and the right femoral vein for drainage with right femoral artery cannulation for perfusion. VAV ECMO consists of single venous drainage through the right femoral vein with right femoral artery and right internal jugular vein for perfusion. The VPa configuration through the insertion of a long venous cannula in the pulmonary artery, usually via the right internal jugular vein, may be a suitable option for patients with right heart failure[3].

Our literature search revealed a limited number of relevant articles as expected. ECMO support following major aortic surgery has not been usually recommended

Table 1 "Participants, Intervention, Comparison, Outcome and Study Design" approach for the selection of clinical studies following systematic search

Participants	Patients undergoing major aortic surgery for aneurysmal disease or dissection
Intervention	VA-ECMO in patients requiring major aortic surgery for aneurysmal disease or dissection
Comparison	Comparison with those who did not need ECMO support
Outcome	If ECMO support made a difference
Study design	Prospective and retrospective clinical studies; case series and case reports

ECMO: Extra-corporeal membrane oxygenation; VA-ECMO: Veno-arterial extracorporeal membrane oxygenation.

because of its potential to further exacerbate lesions of the aortic wall and increased bleeding with delayed thrombosis of the false lumen due to the use of anticoagulation[60-62]. Nevertheless, 3 retrospective studies[32-34] and 1 observational study[31] (Table 2) have shown the feasibility of ECMO support in patients undergoing major aortic surgery for aneurysmal disease and dissection in contrast to current scepticism[29]. In many countries the argument is to make for a balance between the costs involved in running ECMO support and select those patients who would benefit the most from a period of circulatory support following repair for acute aortic dissection. Monitoring the outcome of those patients who required ECMO support postoperatively and develop a specific database may be the way forward to shed further lights on the role of ECMO support in patients undergoing major aortic surgery. Although 1 retrospective study[34] has reported 88% mortality rate in 35 patients who underwent ECMO support following surgical treatment for type A aortic dissection, there is no mention about indications for ECMO support; profile and co-morbidities of these patients; cannulation site (peripheral or central); cause of death. Twenty-seven patients received ECMO support on the day of surgery and 8 patients required ECMO support on postoperative day 1 or later. Most unusual, 4 additional patients with type A aortic dissection underwent ECMO support without surgical intervention but none of them survived. The other two retrospective studies[32,33] are more detailed with more favourable outcome in line with the extra corporeal life support organization registry[57,58]. One study[33] included 36 patients who required VA-ECMO for post-cardiotomy failure following major aortic surgery. In-hospital mortality was 50% with multi-organ failure being the main cause of death. Preoperative levels of CK-MB > 100 IU/L and peak lactate levels > 20 mmol/L were considered relevant factors for in-hospital mortality. Retrograde flow cannulation was identified as another key factor for reduced survival compared to antegrade cannulation although the risk for early mortality is related to the preoperative clinical and haemodynamic status rather than the cannulation technique[62]. The other study[32] compared short- and long-term outcomes between patients who required ECMO support and those who did not. In-hospital mortality was higher in the ECMO group (65%) compared to the non-ECMO group (8.5%). Preoperative haemodynamic instability, aortic cross-clamp time and postoperative peak CK-MB were identified as predicting factors for postoperative ECMO support. ECMO survivors had younger age and less postoperative blood transfusion. Interestingly, those patients who survived after ECMO support following repair for acute type A aortic dissection showed a long-term survival rate comparable to patients who did not require ECMO support postoperatively. These findings were confirmed by a very detailed observational study[31] comparing patients with and without LV systolic dysfunction who underwent surgical intervention for acute type A aortic dissection. A total of 510 patients were considered: 86 with LV systolic dysfunction (group I) and 424 patients with preserved LV systolic function (group II). ECMO support was required in 7 patients from group I and in 10 patients from group II. The overall mortality was 79 patients out of 510: 20 from group I and 59 from group II. Multivariate analysis confirmed that a preoperative serum creatinine greater than 1.5 mg/dL and the requirement for ECMO support intra-operatively were significant independent predictors of in-hospital mortality but survival following ECMO support was not specified. Although patients with preoperative LV systolic dysfunction showed higher surgical risk for in-hospital mortality, their 3-year cumulative survival rate (77.8%) was comparable with those with preserved LV systolic function (82.1%). Serial echocardiographic assessment did not show further deterioration of LV systolic function during the 3-year follow-up.

To summarise the key factors related to the need for postoperative ECMO support and outcome, the following have been identified.

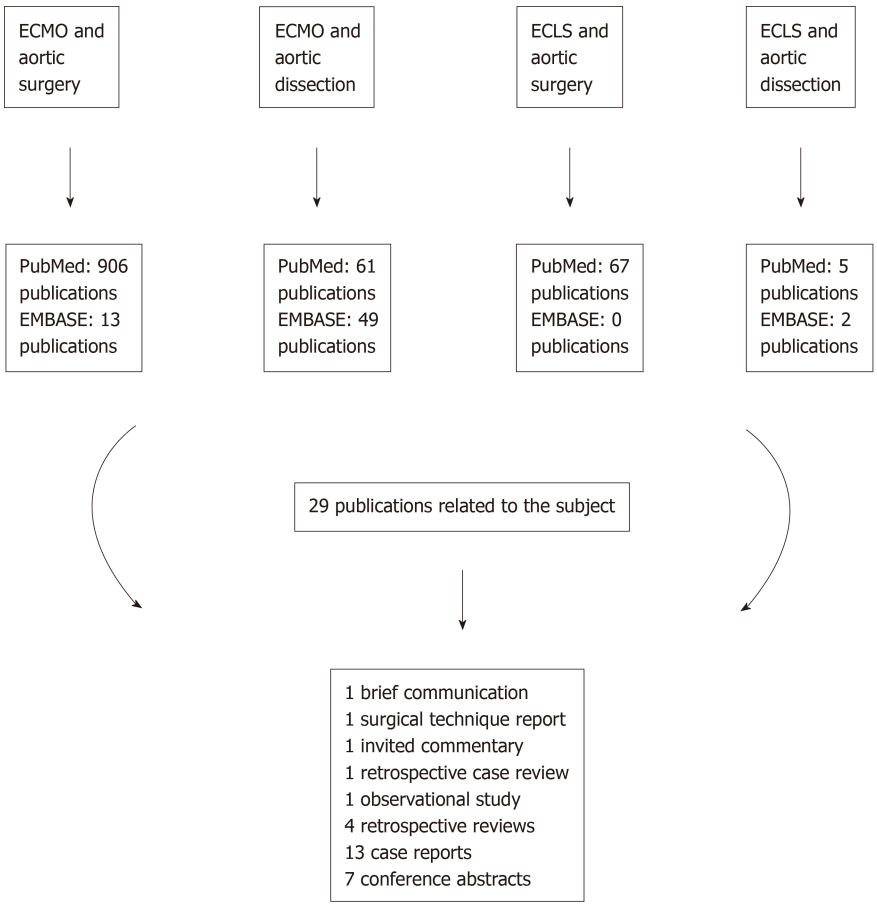


Figure 1 Summary of the steps followed during the literature search. ECLS: Extra-corporeal life support; ECMO: Extra-corporeal membrane oxygenation.

Factors predicting the need for postoperative ECMO support[31,32,34]: Preoperative haemodynamic instability; Myocardial infarction; Aortic cross-clamp time; Cardiopulmonary bypass time; Biventricular systolic dysfunction; Inadequate myocardial protection; Postoperative peak CK-MB; Propagation of the dissection into the coronary arteries.

Factors related with survival following ECMO support[32,33]: Younger age; Reduced postoperative blood transfusion; Lower level of preoperative CK-MB; Higher rate of antegrade cannulation; Lower lactate levels at 12 h; Lower rate of continuous renal replacement therapy; Longer intensive care stay.

Factors related with adverse outcome[31,33]: Retrograde flow cannulation; Peak lactate levels > 20 mmol/L; Preoperative CK-MB > 100 IU/L; Combined aortic arch replacement; Postoperative need of continuous renal replacement therapy; Prolonged inotropic support; Visceral ischaemia; Limb ischaemia.

In conclusion, although there is no compelling evidence in favour or against the use of ECMO support following major aortic surgery for aneurysmal disease or acute aortic dissection, it is enough to justify its use in those patients who develop haemodynamic instability refractory to inotropic support.

Table 2 Grading of manuscripts with key information and outcome

Ref.	Study design/level of evidence	ECMO patients	Outcome
Abouliatim *et al*[27], 2012	Brief Communication; Level 3	AAA repair on ECMO support in 2 patients after failed EVAR	Both patients were discharged 12 days postoperatively
Lorusso *et al*[28], 2019	Surgical Technique; Level 3	2 patients requiring elective aortic arch replacement and treated with minimally invasive central ECMO, which avoids re-sternotomy and maintains antegrade blood flow	Successful outcome for both patients. The technique is suitable only in those patients where a side-armed prosthetic graft had been used
Lazar *et al*[29], 2017	Invited commentary; Level 3	Comment to Sultan, 2017 with further considerations about ECMO in aortic dissection	
Guenther *et al*[30], 2014	Retrospective Case Review; Level 3	6 patients with acute type A aortic dissection involving the coronary arteries treated with ECMO support	Mortality 67% (4 patients)
Lin *et al*[31], 2018	Observational Study; Level 2-	510 patients with TAAD between 2007 and 2018 17 required ECMO postoperatively	Comparison between low LVEF and preserved LVEF
Lin *et al*[32], 2017	Retrospective Study; Level 2-	162 patients underwent TAAD repair between 2008 and 2015 20 patients required ECMO support postoperatively	Mortality: ECMO group 65%; non-ECMO group 8.5% Factors predicting postop ECMO: haemodynamic instability; aortic cross-clamp time; postop peak creat kinase-MB Younger age for ECMO survivors
Zhong *et al*[33], 2017	Retrospective Study; Level 2-	5637 patients underwent major aortic surgery between 2009 and 2016 36 patients required ECMO support: 20 with TAAD; 3 Type B; 12 with thoracic aortic aneurysm; 1 with CoA (aortic coarctation)	Mortality 50% Three main factors for in-hospital mortality: retrograde-flow cannulation; preop CK-MB level 100 IU/L; peak lactate level 20 mmol/L
Sultan *et al*[34], 2017	Retrospective Study; Level 2-	Database review between 2004 and 2014 35 patients with Type A Aortic Dissection (TAAD) underwent ECMO support	Overall mortality 88% There is no mention about indications for ECMO support; profile and co-morbidities of these patients; cannulation site (peripheral or central); cause of death
Guihaire *et al*[35], 2017	Retrospective Study; Level 2-	92 patients required ECMO support following valve surgery (66%), acute aortic dissection (10%) and CABG (9%)	Survival for patients with aortic dissection is not specified
Gennari *et al*[36], 2019	Case Report; Level 3	1 patient with iatrogenic type A aortic dissection requiring ECMO support	Successful weaning off ECMO after 4 days
Chatterjee *et al*[37], 2018	Case Report; Level 3	3 patients requiring ECMO support after thoraco-abdominal aneurysm repair	1 patient discharged after 128 days but died 2 months later 1 patient discharged after 35 days and alive at 3-year follow up 1 patient discharged after 19 days and alive at 6-month follow up
Beyrouti *et al*[38], 2018	Case Report; Level 3	1patient with aortic dissection involving the left main stem requiring ECLS and subsequently LVAD	Discharged after 27 days
Yukawa *et al*[39], 2018	Case Report; Level 3	Acute aortic dissection with out-of-hospital cardiac arrest requiring ECMO support	Discharged after 49 days
Stroehle *et al*[40], 2017	Case Report; Level 3	Traumatic aortic dissection treated with TEVAR on ECMO support	Discharged after 42 days to neuro-rehabilitation
Szczechowicz *et al*[41], 2016	Case Report; Level 3	2 patients with acute type A aortic dissection complicated by right ventricular failure requiring ECMO support	First patient discharged after 27 days; second patient discharged to the ward after 8 days in ITU but no mention about how many days before discharge

Ishida *et al*[42], 2015	Case Report; Level 3	Two-stage procedure on ECMO support in 1 patient who sustained type A acute aortic dissection in a background of chronic thrombo-embolic pulmonary hypertension	Prolonged hospital stay; no mention how many days before discharge
Yavuz *et al*[43], 2015	Case Report; Level 3	ECMO following TEVAR in 1 patient	No mention about outcome
Amako *et al*[44], 2013	Case Report; Level 3	1 patient with type A aortic dissection treated with ECMO support	ECMO weaned off after 65 hours uneventfully
Doguet *et al*[45], 2010	Case Report; Level 3	1 patient with acute type A aortic dissection involving the coronary arteries treated with ECMO support	Discharged after 29 days postoperatively
Koster *et al*[46], 2007	Case Report; Level 3	1 patient with acute type A aortic dissection requiring ECMO support who developed HIT treated successfully with bivalirudin	LV recovery during VA-ECMO support but RVAD required. Successful ECMO weaning; RVAD removed after 6 weeks
Fabricius *et al*[47], 2001	Case Report; Level 3	2 patients who sustained acute type A aortic dissection during pregnancy treated with ECMO support	Successful ECMO weaning
Yamashita *et al*[48], 1994	Case Report; Level 3	1 patient with acute aortic dissection treated with ECMO support	Successful ECMO weaning
Jorgensen *et al*[49], 2019	Conference Abstract; Level 3	Elective femoro-femoral VA-ECMO support for thoraco-abdominal aortic aneurysm repair in a 82-year-old patient	Discharged 11 days postoperatively
Heuts *et al*[50], 2017	Conference Abstract; Level 3	Surgical technique for ECMO insertion (the Maastricht Approach)	See Lorusso, 2019 in this table
Yang *et al*[51], 2017	Conference Abstract; Level 3	Retrospective analysis of 1695 patients who underwent surgery for aortic dissection between 2008 and 2015. 42 patients required VA-ECMO support	30 patients were successfully weaned off VA-ECMO and 19 patients were discharged. Higher lactate levels, pre-ECMO cardiac arrest, major haemorrhage and renal replacement therapy were related to in-hospital mortality
Goldberg *et al*[52], 2017	Conference Abstract; Level 3	185 patients requiring repair of acute type A aortic dissection between 2005 and 2016. 4 patients required VA-ECMO support.	All 4 patients survived to hospital discharge
Schmidt *et al*[53], 2016	Conference Abstract; Level 3	Acute type A aortic dissection presenting as acute coronary syndrome requiring ECMO support in the cath lab as a bridge to surgical intervention	Fatal outcome
Nierscher *et al*[54], 2012	Conference Abstract; Level 3	Observational study of patients undergoing cardiac surgery in 2008. 35 patients required ECMO support. Only one patient with aortic dissection is reported.	Survival not specified for the patient with aortic dissection
Shinar *et al*[55], 2011	Conference Abstract; Level 3	Observational study over a 14-mo period of ECMO support initiated by A&E physicians. The procedure was attempted in 19 patients	Four patients were discharged without neurological injury: 2 patients after MI, one after aortic dissection with cardiac tamponade and one after profound hypothermia

ECMO: Extra-corporeal membrane oxygenation; ECLS: Extra-corporeal life support; VA-ECMO: Veno-arterial extracorporeal membrane oxygenation.

Table 3 Aetiology, type of procedure and type of cannulation

Ref.	Study design/level of evidence	ECMO patients
Lin *et al*[31], 2018	Observational Study; Level 2-	510 patients with ATAAD between 2007 and 2018 Entry Tear Exclusion 73.1% Aortic Root Replacement 11.4% Ascending Aorta Replacement 65.9% Aortic Arch Replacement 25.3% Hemiarch 13.3% Total Arch 12.0% Frozen Elephant Trunk 8.2% Combined CABG 3.7% 17 required ECMO support but no procedure break down is available
Lin *et al*[32], 2017	Retrospective Study; Level 2-	162 patients underwent type A aortic dissection repair between 2008 and 2015 20 patients required ECMO support as follows: Ascending Aorta Interposition graft 6 Aortic Root/Valve Procedure 9 Aortic Arch Procedure 10 Combined CABG 5 Combined Mitral Replacement/Repair 1 Combined Femoro-femoral crossover 1
Zhong *et al*[33], 2017	Retrospective Study; Level 2-	5637 patients underwent major aortic surgery between 2009 and 2016 36 patients required ECMO support as follows: Type A aortic dissection 20 Type B aortic dissection 3 Thoracic aortic aneurysm 12 Aortic coarctation 1 Emergency surgery 9 Second operation 7 Ascending aorta replacement 34 Arch replacement 21 Descending aorta atenting 17 Thoraco-abdominal aorta replacement 2 Combined valve replacement 21 Combined CABG 16 Central ECMO cannulation 7 Peripheral ECMO cannulation 29 Femoro-femoral 20 Femoral vein to right axillary artery 7 Femoro-femoral + right axillary artery 2 IABP 9
Sultan *et al*[34], 2017	Retrospective Study; Level 2-	Database review between 2004 and 2014 35 patients with type A aortic dissection underwent ECMO support No procedure and cannulation break down is available
Guihaire *et al*[35], 2017	Retrospective Study; Level 2-	92 patients underwent ECMO support between January 2005 and December 2014 for post-cardiotomy cardiogenic shock as follows: Valve surgery 66% Acute Aortic Dissection 10% CABG 9% Break down of procedures and cannulation is not available

Nierscher *et al*[54], 2012	Conference Abstract; Level 3	35 patients underwent ECMO support in 2008 following CABG (7), valve procedure (8), heart transplant (8), LVAD insertion (1), combined procedure (10), aortic dissection (1). Cannulation was peripheral (23), central (7), subclavian artery (5).
Gennari *et al*[36], 2019	Case Report; Level 3	1 patient with iatrogenic type A aortic dissection requiring ECMO support through peripheral cannulation. Ascending aorta replacement including right coronary sinus with interposition graft and single-vessel coronary artery bypass grafting.
Jorgensen *et al*[49], 2019	Conference Abstract; Level 3	1 patient with thoraco-abdominal aortic aneurysm requiring ECMO support through peripheral cannulation. A multi-branched Gelweave Dacron graft was used.
Chatterjee *et al*[37], 2018	Case Report; Level 3	3 patients requiring ECMO support after thoraco-abdominal aneurysm repair. 2 patients had previous type A aortic dissection repair; 1 patient had ascending aorta and hemiarch replacement for type A aortic dissection and subsequent TEVAR procedure. ECMO cannulation between left axillary artery and femoral vein (1 patient), femoro-femoral (2 patients).
Beyrouti *et al*[38], 2018	Case Report; Level 3	1 patient with aortic dissection involving the left main stem treated with ascending aorta interposition graft and CABG requiring ECLS through central cannulation and subsequently LVAD
Yukawa *et al*[39], 2018	Case Report; Level 3	Acute aortic dissection with out-of-hospital cardiac arrest requiring ECMO support through peripheral percutaneous femoral cannulation and treated with ascending aorta replacement using an interposition graft
Yang *et al*[51], 2017	Conference Abstract; Level 3	1695 patients underwent repair for aortic dissection between 2008 and 2015. 42 patients required ECMO support. Procedure and cannulation break down is not available
Goldberg *et al*[52], 2017	Conference Abstract; Level 3	185 patients underwent surgical intervention for acute type A aortic dissection between January 2005 and May 2016. 4 patients required VA-ECMO support. Break down of procedures, concomitant procedures and type of cannulation are not available
Stroehle *et al*[40], 2017	Case Report; Level 3	Traumatic aortic dissection treated with TEVAR on ECMO support
Schmidt *et al*[53], 2016	Conference Abstract; Level 3	Emergency ECMO insertion in the Cath Lab with findings of type A acute aortic dissection resulting in fatal outcome
Szczechowicz *et al*[41], 2016	Case Report; Level 3	2 patients with acute type A aortic dissection complicated by right ventricular failure requiring ECMO support
Ishida *et al*[42], 2015	Case Report; Level 3	Two-stage procedure on ECMO support in 1 patient who sustained acute type A aortic dissection in a background of chronic thrombo-embolic pulmonary hypertension
Yavuz *et al*[43], 2015	Case Report; Level 3	ECMO following TEVAR in 1 patient
Guenther *et al*[30], 2014	Retrospective Case Review; Level 3	6 patients with acute type A aortic dissection involving the coronary arteries treated with ECMO support
Amako *et al*[44], 2013	Case Report; Level 3	1 patient with acute type A aortic dissection treated with ECMO support
Abouliatim *et al*[27], 2012	Brief Communication; Level 3	AAA repair on ECMO support in 2 patients after failed EVAR
Shinar *et al*[55], 2011	Conference Abstract; Level 3	19 cases of ECMO insertion in Accident & Emergency Department through percutaneous cannulation of the femoral vessels

Doguet *et al*[45], 2010	Case Report; Level 3	1 patient with acute type A aortic dissection involving the coronary arteries treated with peripheral ECMO support through femoro-femoral cannulation. CABG as concomitant procedure.
Koster *et al*[46], 2007	Case Report; Level 3	1 patient with acute type A aortic dissection requiring ECMO support using bivalirudin
Fabricius *et al*[47], 2001	Case Report; Level 3	2 patients who sustained acute type A aortic dissection during pregnancy treated with ECMO support
Yamashita *et al*[48], 1994	Case Report ; Level 3	1 patient with acute aortic dissection treated with ECMO support

ATAAD: Acute type A aortic dissection; ECMO: Extra-corporeal membrane oxygenation; TEVAR: Thoracic endo-vascular aortic repair; AAA: Abdominal aortic aneurysm; EVAR: Endo-vascular aortic repair.

ARTICLE HIGHLIGHTS

Research background

Extra-corporeal membrane oxygenation (ECMO) support following major aortic surgery with particular reference to aortic dissection remains controversial without clear direction. We aim to shed some lights on the subject in order to make an impact and give a clear view that may well lead to further studies.

Research motivation

We believe that a clear direction based on evidence may change current attitude.

Research objectives

Although ECMO support is not perfect, it does work when appropriately considered and performed. We believe it may become an additional option in aortic surgery.

Research methods

The methods have been already described in the article.

Research results

The results are promising and may lead to further studies to improve outcomes.

Research conclusions

There is enough evidence to support our statement although we would like to think that further studies can be pursued to confirm our initial findings.

Research perspectives

There is potential to support further studies in the future.

REFERENCES

1 **Ng GW**, Yuen HJ, Sin KC, Leung AK, Au Yeung KW, Lai KY. Clinical use of venoarterial extracorporeal membrane oxygenation. *Hong Kong Med J* 2017; **23**: 282-290 [PMID: 28473653 DOI: 10.12809/hkmj166096]

2 **Khorsandi M**, Dougherty S, Bouamra O, Pai V, Curry P, Tsui S, Clark S, Westaby S, Al-Attar N, Zamvar V. Extra-corporeal membrane oxygenation for refractory cardiogenic shock after adult cardiac surgery: a systematic review and meta-analysis. *J Cardiothorac Surg* 2017; **12**: 55 [PMID: 28716039 DOI: 10.1186/s13019-017-0618-0]

3 **Brasseur A**, Scolletta S, Lorusso R, Taccone FS. Hybrid extracorporeal membrane oxygenation. *J Thorac Dis* 2018; **10**: S707-S715 [PMID: 29732190 DOI: 10.21037/jtd.2018.03.84]

4 **Meani P**, Gelsomino S, Natour E, Johnson DM, Rocca HB, Pappalardo F, Bidar E, Makhoul M, Raffa G, Heuts S, Lozekoot P, Kats S, Sluijpers N, Schreurs R, Delnoij T, Montalti A, Sels JW, van de Poll M, Roekaerts P, Poels T, Korver E, Babar Z, Maessen J, Lorusso R. Modalities and Effects of Left Ventricle Unloading on Extracorporeal Life support: a Review of the Current Literature. *Eur J Heart Fail* 2017; **19** Suppl 2: 84-91 [PMID: 28470925 DOI: 10.1002/ejhf.850]

5 **Dickstein ML**. The Starling Relationship and Veno-Arterial ECMO: Ventricular Distension Explained. *ASAIO J* 2018; **64**: 497-501 [PMID: 29076945 DOI: 10.1097/MAT.0000000000000660]

6 **Santamore WP**, Burkhoff D. Hemodynamic consequences of ventricular interaction as assessed by model analysis. *Am J Physiol* 1991; **260**: H146-H157 [PMID: 1992793 DOI: 10.1152/ajpheart.1991.260.1.H146]

7 **Burkhoff D**, Tyberg JV. Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis. *Am J Physiol* 1993; **265**: H1819-H1828 [PMID: 8238596 DOI: 10.1152/ajpheart.1993.265.5.H1819]

8 **Thiele H**, Schuler G, Neumann FJ, Hausleiter J, Olbrich HG, Schwarz B, Hennersdorf M, Empen K, Fuernau G, Desch S, de Waha S, Eitel I, Hambrecht R, Böhm M, Kurowski V, Lauer B, Minden HH, Figulla HR, Braun-Dullaeus RC, Strasser RH, Rochor K, Maier SK, Möllmann H, Schneider S, Ebelt H, Werdan K, Zeymer U. Intraaortic balloon counterpulsation in acute myocardial infarction complicated by

cardiogenic shock: design and rationale of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial. *Am Heart J* 2012; **163**: 938-945 [PMID: 22709745 DOI: 10.1016/j.ahj.2012.03.012]

9 **Thiele H**, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, de Waha A, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Lauer B, Böhm M, Ebelt H, Schneider S, Werdan K, Schuler G; Intraaortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) trial investigators. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet* 2013; **382**: 1638-1645 [PMID: 24011548 DOI: 10.1016/S0140-6736(13)61783-3]

10 **Thiele H**, Zeymer U, Thelemann N, Neumann FJ, Hausleiter J, Abdel-Wahab M, Meyer-Saraei R, Fuernau G, Eitel I, Hambrecht R, Böhm M, Werdan K, Felix SB, Hennersdorf M, Schneider S, Ouarrak T, Desch S, de Waha-Thiele S; IABPSHOCK II Trial (Intraaortic Balloon Pump in Cardiogenic Shock II) Investigators. Intraaortic Balloon Pump in Cardiogenic Shock Complicating Acute Myocardial Infarction: Long-Term 6-Year Outcome of the Randomized IABP-SHOCK II Trial. *Circulation* 2018 [PMID: 30586721 DOI: 10.1161/CIRCULATIONAHA.118.038201]

11 **Li Y**, Yan S, Gao S, Liu M, Lou S, Liu G, Ji B, Gao B. Effect of an intra-aortic balloon pump with venoarterial extracorporeal membrane oxygenation on mortality of patients with cardiogenic shock: a systematic review and meta-analysis†. *Eur J Cardiothorac Surg* 2019; **55**: 395-404 [PMID: 30252028 DOI: 10.1093/ejcts/ezy304]

12 **Chen K**, Hou J, Tang H, Hu S. Concurrent initiation of intra-aortic balloon pumping with extracorporeal membrane oxygenation reduced in-hospital mortality in postcardiotomy cardiogenic shock. *Ann Intensive Care* 2019; **9**: 16 [PMID: 30673888 DOI: 10.1186/s13613-019-0496-9]

13 **Cheng A**, Swartz MF, Massey HT. Impella to unload the left ventricle during peripheral extracorporeal membrane oxygenation. *ASAIO J* 2013; **59**: 533-536 [PMID: 23995997 DOI: 10.1097/MAT.0b013e31829f0e52]

14 **Patel SM**, Lipinski J, Al-Kindi SG, Patel T, Saric P, Li J, Nadeem F, Ladas T, Alaiti A, Phillips A, Medalion B, Deo S, Elgudin Y, Costa MA, Osman MN, Attizzani GF, Oliveira GH, Sareyyupoglu B, Bezerra HG. Simultaneous Venoarterial Extracorporeal Membrane Oxygenation and Percutaneous Left Ventricular Decompression Therapy with Impella Is Associated with Improved Outcomes in Refractory Cardiogenic Shock. *ASAIO J* 2019; **65**: 21-28 [PMID: 29489461 DOI: 10.1097/MAT.0000000000000767]

15 **Donker DW**, Brodie D, Henriques JPS, Broomé M. Left Ventricular Unloading During Veno-Arterial ECMO: A Simulation Study. *ASAIO J* 2019; **65**: 11-20 [PMID: 29517515 DOI: 10.1097/MAT.0000000000000755]

16 **Biancari F**, Dalén M, Fiore A, Ruggieri VG, Saeed D, Jónsson K, Gatti G, Zipfel S, Perrotti A, Bounader K, Loforte A, Lechiancole A, Pol M, Spadaccio C, Pettinari M, Ragnarsson S, Alkhamees K, Mariscalco G, Welp H; PC-ECMO Study Group. Multicenter study on postcardiotomy venoarterial extracorporeal membrane oxygenation. *J Thorac Cardiovasc Surg* 2019 [PMID: 31358340 DOI: 10.1016/j.jtcvs.2019.06.039]

17 **Bonser RS**, Ranasinghe AM, Loubani M, Evans JD, Thalji NM, Bachet JE, Carrel TP, Czerny M, Di Bartolomeo R, Grabenwöger M, Lonn L, Mestres CA, Schepens MA, Weigang E. Evidence, lack of evidence, controversy, and debate in the provision and performance of the surgery of acute type A aortic dissection. *J Am Coll Cardiol* 2011; **58**: 2455-2474 [PMID: 22133845 DOI: 10.1016/j.jacc.2011.06.067]

18 **Bottle A**, Mariscalco G, Shaw MA, Benedetto U, Saratzis A, Mariani S, Bashir M, Aylin P, Jenkins D, Oo AY, Murphy GJ; UK Aortic Forum. Unwarranted Variation in the Quality of Care for Patients With Diseases of the Thoracic Aorta. *J Am Heart Assoc* 2017; **6** [PMID: 28292748 DOI: 10.1161/JAHA.116.004913]

19 **Mariscalco G**, Bilal H, Catarino P, Hadjinikolaou L, Kuduvalli M, Field M, Mascaro J, Oo AY, Quarto C, Kuo J, Tsang G; UK Aortic Group. Reflection From UK Aortic Group: Frozen Elephant Trunk Technique as Optimal Solution in Type A Acute Aortic Dissection. *Semin Thorac Cardiovasc Surg* 2019; **31**: 686-690 [PMID: 30980933 DOI: 10.1053/j.semtcvs.2019.03.010]

20 **Mariscalco G**, Maselli D, Zanobini M, Ahmed A, Bruno VD, Benedetto U, Gherli R, Gherli T, Nicolini F. Aortic centres should represent the standard of care for acute aortic syndrome. *Eur J Prev Cardiol* 2018; **25**: 3-14 [PMID: 29708034 DOI: 10.1177/2047487318764963]

21 **Girdauskas E**, Kuntze T, Borger MA, Falk V, Mohr FW. Surgical risk of preoperative malperfusion in acute type A aortic dissection. *J Thorac Cardiovasc Surg* 2009; **138**: 1363-1369 [PMID: 19733865 DOI: 10.1016/j.jtcvs.2009.04.059]

22 **Czerny M**, Schoenhoff F, Etz C, Englberger L, Khaladj N, Zierer A, Weigang E, Hoffmann I, Blettner M, Carrel TP. The Impact of Pre-Operative Malperfusion on Outcome in Acute Type A Aortic Dissection: Results From the GERAADA Registry. *J Am Coll Cardiol* 2015; **65**: 2628-2635 [PMID: 26088302 DOI: 10.1016/j.jacc.2015.04.030]

23 **Narayan P**, Rogers CA, Benedetto U, Caputo M, Angelini GD, Bryan AJ. Malperfusion rather than merely timing of operative repair determines early and late outcome in type A aortic dissection. *J Thorac Cardiovasc Surg* 2017; **154**: 81-86 [PMID: 28420536 DOI: 10.1016/j.jtcvs.2017.03.041]

24 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; **62**: e1-34 [PMID: 19631507 DOI: 10.1016/j.jclinepi.2009.06.006]

25 **Hutton B**, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gøtzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; **162**: 777-784 [PMID: 26030634 DOI: 10.7326/M14-2385]

26 **Moher D**, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; **4**: 1 [PMID: 25554246 DOI: 10.1186/2046-4053-4-1]

27 **Abouliatim I**, Paramythiotis A, Harmouche M, Ternisien E, Verhoye JP. Extracorporeal membrane oxygenation support for abdominal aortic aneurysms surgery in high-risk patients. *Interact Cardiovasc Thorac Surg* 2012; **14**: 215-216 [PMID: 22159237 DOI: 10.1093/icvts/ivr031]

28 **Lorusso R**, Bidar E, Natour E, Heuts S. Minimally invasive management of central ECMO after ascending aortic surgery. *J Card Surg* 2019; **34**: 131-133 [PMID: 30625246 DOI: 10.1111/jocs.13974]

29 **Lazar HL**. The use of extracorporeal membrane oxygenation in type A aortic dissections-Long run for a short slide? *J Card Surg* 2017; **32**: 826 [PMID: 29169213 DOI: 10.1111/jocs.13248]

30 **Guenther SP**, Peterss S, Reichelt A, Born F, Fischer M, Pichlmaier M, Hagl C, Khaladj N. Diagnosis of coronary affection in patients with AADA and treatment of postcardiotomy myocardial failure using extracorporeal life support (ECLS). *Heart Surg Forum* 2014; **17**: E253-E257 [PMID: 25367237 DOI: 10.1532/HSF98.2014397]

31 **Lin CY**, Lee KT, Ni MY, Tseng CN, Lee HA, Su IL, Ho HP, Tsai FC. Impact of reduced left ventricular function on repairing acute type A aortic dissection: Outcome and risk factors analysis from a single institutional experience. *Medicine (Baltimore)* 2018; **97**: e12165 [PMID: 30170461 DOI: 10.1097/MD.0000000000012165]

32 **Lin TW**, Tsai MT, Hu YN, Lin WH, Wang WM, Luo CY, Roan JN. Postoperative Extracorporeal Membrane Oxygenation Support for Acute Type A Aortic Dissection. *Ann Thorac Surg* 2017; **104**: 827-833 [PMID: 28267980 DOI: 10.1016/j.athoracsur.2017.01.059]

33 **Zhong Z**, Jiang C, Yang F, Hao X, Xing J, Wang H, Hou X. Veno-Arterial Extracorporeal Membrane Oxygenation Support in Patients Undergoing Aortic Surgery. *Artif Organs* 2017; **41**: 1113-1120 [PMID: 28718889 DOI: 10.1111/aor.12951]

34 **Sultan I**, Habertheuer A, Wallen T, Siki M, Szeto W, Bavaria JE, Williams M, Vallabhajosyula P. The role of extracorporeal membrane oxygenator therapy in the setting of Type A aortic dissection. *J Card Surg* 2017; **32**: 822-825 [PMID: 29216679 DOI: 10.1111/jocs.13245]

35 **Guihaire J**, Dang Van S, Rouze S, Rosier S, Roisne A, Langanay T, Corbineau H, Verhoye JP, Flécher E. Clinical outcomes in patients after extracorporeal membrane oxygenation support for post-cardiotomy cardiogenic shock: a single-centre experience of 92 cases. *Interact Cardiovasc Thorac Surg* 2017; **25**: 363-369 [PMID: 28575211 DOI: 10.1093/icvts/ivx155]

36 **Gennari M**, Polvani G, Agrifoglio M. Favorable outcome of mechanical support for iatrogenic aortic dissection. *Asian Cardiovasc Thorac Ann* 2019; **27**: 55-57 [PMID: 30482028 DOI: 10.1177/0218492318817660]

37 **Chatterjee S**, Mulvoy W, Preventza O, de la Cruz KI, LeMaire SA, Coselli JS. ECMO for Acute Respiratory Distress Syndrome After Thoracoabdominal Aortic Aneurysm Repair. *Ann Thorac Surg* 2018; **106**: e171-e172 [PMID: 29775606 DOI: 10.1016/j.athoracsur.2018.04.045]

38 **Beyrouti HE**, Kornberger A, Halloum N, Beiras-Fernandez A, Vahl CF. Early LVAD Implantation in a Patient with Left Ventricular Failure after Aortic Dissection with Left Main Stem Involvement. *Ann Thorac Cardiovasc Surg* 2018 [PMID: 29780073 DOI: 10.5761/atcs.cr.17-00236]

39 **Yukawa T**, Sugiyama K, Miyazaki K, Tanabe T, Ishikawa S, Hamabe Y. Treatment of a patient with acute aortic dissection using extracorporeal cardiopulmonary resuscitation after an out-of-hospital cardiac arrest: a case report. *Acute Med Surg* 2018; **5**: 189-193 [PMID: 29657734 DOI: 10.1002/ams2.324]

40 **Stroehle M**, Lederer W, Schmid S, Glodny B, Chemelli AP, Wiedermann FJ. Aortic stent graft placement under extracorporeal membrane oxygenation in severe multiple trauma. *Clin Case Rep* 2017; **5**: 1604-1607 [PMID: 29026554 DOI: 10.1002/ccr3.1127]

41 **Szczechowicz M**, Weymann A, Karck M, Szabo G. Right Ventricular Failure Following Acute Type A Aortic Dissection Successfully Treated with ECMO: Report of Two Cases. *J Clin Case Rep* 2016; **6**: 12

42 **Ishida K**, Masuda M, Ishizaka T, Matsumiya G. Successful staged operation for acute aortic dissection and chronic thromboembolic pulmonary hypertension. *Eur J Cardiothorac Surg* 2015; **47**: 575-577 [PMID: 24819361 DOI: 10.1093/ejcts/ezu194]

43 **Yavuz S**, Arikan AA, Ozbudak E, İrkil S, Hosten T, Gumustas S, Berki KT. Concomitant Persistent Atelectasis following TEVAR Due to a Descending Aortic Aneurysm: Hybrid Endovascular Repair and ECMO Therapy. *Heart Surg Forum* 2015; **18**: E188-E191 [PMID: 26509342 DOI: 10.1532/hsf.1265]

44 **Amako M**, Akasu K, Oda T, Zaima Y, Yasunaga H. A Case of Acute Aortic Dissection with Severe Aortic Regurgitation Successfully Treated by Postoperative Extracorporeal Membrane Oxygenation. *Jpn J Vasc Surg* 2013; **22**: 984-988

45 **Doguet F**, Vierne C, Leguillou V, Bessou JP. Place of extracorporeal membrane oxygenation in acute aortic dissection. *Interact Cardiovasc Thorac Surg* 2010; **11**: 708-710 [PMID: 20709696 DOI: 10.1510/icvts.2010.245167]

46 **Koster A**, Weng Y, Böttcher W, Gromann T, Kuppe H, Hetzer R. Successful use of bivalirudin as anticoagulant for ECMO in a patient with acute HIT. *Ann Thorac Surg* 2007; **83**: 1865-1867 [PMID: 17462416 DOI: 10.1016/j.athoracsur.2006.11.051]

47 **Fabricius AM**, Autschbach R, Doll N, Mohr W. Acute aortic dissection during pregnancy. *Thorac Cardiovasc Surg* 2001; **49**: 56-57 [PMID: 11243526 DOI: 10.1055/s-2001-9914]

48 **Yamashita T**, Kozawa S, Okada M, Ohta T, Ataka K, Kitade T. [A case of acute aortic dissection with aortic regurgitation successfully treated by postoperative ECMO]. *Kyobu Geka* 1994; **47**: 283-287 [PMID: 8152174]

49 **Jorgensen MS**, Farres H, Sorrells WS, Erben Y, Martin AK, Pham SM, Hakaim A. Utilization of Intraoperative Extracorporeal Membrane Oxygenation Bypass to Reduce Visceral Vessel Ischemia During Open Thoracoabdominal Aortic Aneurysm Repair. *J Vasc Surg* 2019; **69**: e118 [DOI: 10.1016/j.jvs.2019.04.140]

50 **Heuts S**, Gelsomino S, Natour E, Lozekoot P, Johnson D, Bidar E, Kats S, Sluijpers N, Makhoul M, Schreurs R, Gilbers M, Poels T, Weerwind P, Ganushchak Y, Korver E, Babar Z, Maessen J, Lorusso R, Meani P, Delnoij T, Sels JW, Van De Poll M, Montalti A, Roekaerts P. Minimally invasive central arterial cannulation management in ECMO patients after complex aortic surgery: The Maastricht approach. *Eur J Heart Fail* 2017; **19** Suppl 2: 11-12

51 **Yang F**, Hou D, Hou X. Venoarterial extracorporeal membrane oxygenation support for early refractory cardiogenic shock and cardiac arrest after aortic surgery. *Eur J Heart Fail* 2017; **19** Suppl 2: 7-8

52 **Goldberg JB**, Kai M, Malekan R, Tang G, Lansman SL, Spielvogel D. Extracorporeal membrane oxygenation after acute type a aortic dissection repair decreases the mortality rate and enhances survival. *Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery* 2017; **12**: S38

53 **Schmidt TR**, Baquero G, Hansen J, Mahidhar R. Ascending aortic dissection: A rare but fatal mechanism for anterior ST-elevation myocardial infarction. *J Am Coll Cardiol* 2016; **67**: 1157

54 **Nierscher FJ**, Zaludik J, Hiesmayr M, Lasnigg A, Ehrlich M. ECMO in cardiac surgery: Outcome, mortality and costs. *Appl Cardiopulm Pathophysiol* 2012; **16** Suppl I: 261-262

55 **Shinar Z**, Bellezzo J. Emergency physician initiated ECMO: Our experience. *Circulation* 2011; **124**: 2374 [DOI: 10.1161/CIR.0b013e31823c86a1]

56 **Squiers JJ**, Lima B, DiMaio JM. Contemporary extracorporeal membrane oxygenation therapy in adults: Fundamental principles and systematic review of the evidence. *J Thorac Cardiovasc Surg* 2016; **152**: 20-32 [DOI: 10.1016/j.jtcvs.2016.02.067]

57 **Clark JB**, Wang S, Palanzo DA, Wise R, Baer LD, Brehm C, Ündar A. Current techniques and outcomes in extracorporeal life support. *Artificial Organs* 2015; **39**: 926–930 [DOI: 10.1111/aor.12527]

58 Life support organization registry report, International summary, January 2015. Ann Arbor, MI: Extracorporeal Life Support Organization 2015: 1-26

59 **Pavlushkov E**, Berman M, Valchanov K. Cannulation techniques for extracorporeal life support. *Ann Transl Med* 2017; **5**: 70 [DOI: 10.21037/atm.2016.11.47]

60 **Easo J**, Weigang E, Hölzl PPF, Horst M, Hoffmann I, Blettner M, Dapunt OE. Influence of operative strategy for the aortic arch in DeBakey type I aortic dissection — analysis of the German Registry for Acute Aortic Dissection type A (GERAADA). *Ann Cardiothorac Surg* 2013; **2**: 175–180 [DOI: 10.3978/j.issn.2225-319X.2013.01.03]

61 **Rylski B**, Czerny M, Beyersdorf F, Kari FA, Siepe M, Adachi H, Yamaguchi A, Itagaki R, Kimura N. Is right axillary artery cannulation safe in type A aortic dissection with involvement of the innominate artery? *J Thorac Cardiovasc Surg* 2016; **152**: 801–807 [DOI: 10.1016/j.jtcvs.2016.04.092]

62 **Klotz S**, Bucsky BS, Richardt D, Petersen M, Sievers HH. Is the outcome in acute aortic dissection type A influenced by of femoral versus central cannulation? *Ann Cardiothorac Surg* 2016; **5**: 310–316 [DOI: 10.21037/acs.2016.07.09]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com