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EDITORIAL

New pharmacological approaches against chronic bowel and bladder problems in paralytics

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Abstract

Spinal cord injury (SCI) leads generally to an irreversible loss of sensory functions and voluntary motor control below injury level. Cures that could repair SCI and/or restore voluntary walking have not been yet developed nor commercialized. Beyond the well-known loss of walking capabilities, most SCI patients experience also a plethora of motor problems and health concerns including specific bladder and bowel dysfunctions. Indeed, chronic constipation and urinary retention, two significant life-threatening complications, are typically found in patients suffering of traumatic (*e.g.*, falls or car accidents) or non-traumatic SCI (*e.g.*, multiple sclerosis, spinal tumors). Secondary health concerns associated with these dysfunctions include hemorrhoids, abdominal distention, altered visceral sensitivity, hydronephrosis, kidney failure, urinary tract infections, sepsis and, in some cases, cardiac arrest. Consequently, individuals with chronic SCI are forced to regularly seek emergency and critical care treatments when some of these conditions occur or become intolerable. Increasing evidence supports the existence of a novel experimental approach that may be capable of preventing the occurrence or severity of bladder and bowel problems. Indeed, recent findings in animal models of SCI have revealed that, despite paraplegia or tetraplegia, it remains possible to elicit episodes of micturition and defecation by acting pharmacologically or electrically upon specialized lumbosacral neuronal networks, namely the spinal or sacral micturition center (SMC) and lumbosacral defecation center (LDC). Daily activation of SMC and LDC neurons could potentially become, new classes of minimally invasive treatments (*i.e.*, if orally active) against these dysfunctions and their many life-threatening complications.

Key words: Prevention of intensive care problems; Quality of care; Temporary recovery of vital functions; Micturition; Defecation; Spinal networks; Central pattern generators

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Core tip: This editorial is one of the first to describe

clearly the existence of an urgent medical need for new pharmacological products aimed at providing non-invasive solutions for those suffering chronically of constipation and urinary retention or detrusor-sphincter dyssynergia. Products combining several already known and safe active ingredients for new or synergistic effects acting upon specific central networks of neurons that normally control these functions are of particular interest.

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INTRODUCTION

Spinal cord injury (SCI) either traumatically (*e.g.*, falls, car or sport accidents) or non-traumatically induced (*e.g.*, multiple sclerosis, angioma, *etc.*) generally leads to an irreversible loss of sensory functions and voluntary motor control below injury level. In the United States and Canada, 1.3 million people (approximately 20-25 million worldwide) currently live with a traumatic SCI[1,2] which is a 5-fold increase (*i.e.*, attributed to improvements in acute emergency care) compared with prevalence values assessed previously. As such, SCI has thus progressively become the 2nd most important neurological problem in North America after Alzheimer's disease (*i.e.*, approximately 5 million patients)[2,3]. No therapy can repair SCI *per se*, cure paralysis or even significantly prevent related chronic complications, dysfunctions, multiple debilitating diseases and life-threatening problems (*i.e.*, cardiovascular problems, osteoporosis, muscular atrophy, anemia, spasticity, urinary tract infections, bed sores, pneumonia, sepsis, bladder and bowel problems, *etc.*)[4]. Only symptomatic drugs and biologics are currently used to minimize consequences (*e.g.*, aspirin for pain, antibiotics for infections, *etc.*)[5].

Urination, also called micturition or voiding, is the process of disposing urine from the urinary bladder through the urethra to the outside of the body. When urinary retention (UR) occurs, the bladder remains full which may cause complete anuria that is a medical emergency as the bladder distend (stretch) to enormous sizes. If the bladder distends enough it may become painful and tear. The increase in bladder pressure can also prevent urine entering from the ureters or even cause urine to back up and get into the kidneys, causing hydronephrosis, pyonephrosis, and kidney failure. It has been associated also with urinary tract infections, sepsis and cardiac arrest[6,7]. In chronic cases, UR may cause bladder stones, atrophy of the detrusor muscle, diverticula in the bladder wall and related infections. In cervical injured patients, bladder problems also impact autonomic responses that are affected by SCI, *e.g.*, a full bladder leads to autonomic dysreflexia, hypertension, severe headaches, stroke or cardiovascular failure.

Bowel problems such as diarrhea, fecal incontinence, irritable bowel syndrome (IBS) or constipation typically occur when the gastrointestinal (GI) tract does not work properly. More specifically, constipation is characterized clinically as difficult or infrequent (*i.e.*, < 3 times/wk) passage of stools[8]. In the general population, constipation is often caused by diet problems (*e.g.*, low fiber), lack of exercise, dairy products, stress, pregnancy, medicines such as laxatives, antacids, antidepressants, iron, pain killers or by structural abnormalities (*e.g.*, colon polyps, cancer, diverticula, anal problems, *etc.*)[9,10]. Related-secondary complications include fissures, fecal impaction, ulceration, abdominal distension, hemorrhoids, bleeding, pain and, occasionally, septic shock and death[11]. Chronic constipation is experienced overall by 60 M North Americans[10].

PATHOPHYSIOLOGY OF BLADDER AND BOWEL DYSFUNCTIONS IN PATIENTS WITH SCI

Normally, the process of urination (also called micturition) involves coordination between the central, autonomic and somatic nervous systems that is under voluntary control (brain). Specifically, muscles involved in micturition (*i.e.*, those activating bladder, urethra and pelvic floor) are essentially controlled by coordinated inputs from spinal or sacral micturition center (SMC) neurons[12]. Brain structures (*e.g.*, pontine micturition center) provide additional inputs mediated by SMC for facilitation or inhibition[13-15]. In brief, as the bladder fills, sensory receptors in the bladder wall trigger the micturition motor behaviour - a coordinated contraction of the detrusor and relaxation of the urethral and periurethral muscles[13]. When control over urination is abnormal, urinary incontinence generally occurs. However, for incompletely understood reasons, in patients with SCI and other related pathologies, the opposite problem occurs - that is UR and detrusor-sphincter dyssynergia that lead to improper capacity to empty bladder content is expressed in absence of descending brain inputs.

The gastrointestinal system is a 20 foot-long system comprising the stomach and intestine (bowel) that essentially releases hormones (*e.g.*, gastrin, secretin, melatonin, ghrelin, *etc.*) for local regulation of digestion, absorption and elimination[16]. However, to achieve that, it critically depends also on food transit (> 24 h/meal) that is ensured by rhythmic muscle contractions, *i.e.*, peristalsis, defined as cyclic rostrocaudal series of coordinated contractions and relaxations of GI smooth muscles mediated locally by two main sensorimotor reflexes using acetylcholine, noradrenaline, substance P, adenosine triphosphate, *etc.*[17-19]. In clear contrast with

causes and mechanisms underlying constipation in the general population, bowel problems after SCI (typically chronic constipation, *i.e.*, more than 12 wk/year) is specifically attributed to a dysfunctional control by the CNS of peristalsis and colorectal motility[20-24]. Defecation requires interactions between the somatic, autonomic and central nervous systems. Specifically, supraspinal networks (*e.g.*, pontine defecation center) that send inputs to lumbosacral defecation center (LDC) neurons and corresponding motoneurons (Onuf's nucleus) for control of autonomic and somatic systems (smooth muscles, sphincters) involved in colorectal motility and defecation[16,23,25,26]. Consequently, a failure of supraspinal inputs to modulate LDC neurons (*e.g.*, due SCI) may lead to reduced colorectal motility and increased constipatory problems[16,23,25].

CURRENTLY USED APPROACHES ARE UNACCEPTABLE OR UNSAFE

As of now, there are five (5) main approaches or tools used to control bladder problems after SCI[27-30]: (1) bladder drainage with chronic indwelling catheters or intermittent catheters but frequent hospitalizations, urinary tract infections, bladder and kidney damage and sepsis can be induced when chronically used; (2) drugs (sedatives, anticholinergic, alpha-adrenergic, cholinergic) with peripheral actions on the contraction of bladder muscles or relaxation of sphincters but constipation, dry mouth, blurred vision can also be induced; (3) electrostimulation of sacral anterior roots but it also impairs sexual function and is generally not considered as user-friendly; (4) diapers or condom sheaths can also be used although generally poorly accepted by patient mainly for self-esteem reasons; or (5) *Botox* injection (in bladder, *e.g.*, detrusor muscle) is sometime recommended but only for those specifically experiencing related mild incontinence rather than UR. In other words, UR remains considered as a poorly addressed medical need.

Regarding chronic constipation, SCI patients are currently bound to use nonspecific approaches to reduce the severity of this debilitating problem: (1) stool softeners and laxatives (*e.g.*, Fleet, Senokot, Metamucil, Dulcolax, Colace, Diocto, Exlax); (2) digital rectal stimulation or sacral root stimulation of reflexes; (3) digital evacuation by professionals; or (4) surgery (*e.g.*, ileostomy)[17,31-35]. Although some of the above-mentioned approaches may be suitable for occasional constipation, they are generally not recommended for repeated use. Indeed, when chronically used, they are associated with significantly reduced efficacy and increased side effects such as bloating, cramps, nausea, fever, vomiting, breathing trouble, fainting, flatulence, dependency, diarrhea, electrolyte imbalance, rectal bleeding, pain, nerve lesion, intestinal paralysis, IBS, renal failure, hernia, seizure, arrhythmia, and sepsis[35-39]. Therefore, chronic constipation after SCI or related disorders is still considered as a poorly addressed medical need that would benefit from novel, innovative and potent medicines[39].

EVIDENCE OF A NOVEL NON-INVASIVE AND SAFER APPROACH

Given the problematic described above, it is imperative that scientists attempt rapidly to identify user-friendly, safe and well-tolerated treatments that could specifically and selectively prevent and reduce SCI-related chronic constipation, UR/detrusor sphincter dyssynergia and related health concerns. In fact, some researchers have recently begun to obtain promising results towards that goal. Indeed, a few laboratories in France, Japan, United States, China and Canada have been exploring the feasibility and potential of modulating either SMC neurons or LDC neurons for acute induction of on-demand episodes of micturition or defecation after SCI.

In a rat model of paraplegia (spinal transection at thoracic level T10), Chinese and Americans found that serotonergic agonists of the 5-HT7 subclass, administered intravenously (*iv*) can augment voiding reflex efficacy suggesting SMC-facilitating actions (also called external urethral sphincter central pattern generator by some researchers) given the well-known expression of 5-HT7 receptors in that sacral area of the spinal cord[40]. This mechanism of action is also supported by similar effects obtained following intrathecal administration of 5-HT agonists[41]. Other receptors may be involved since activation (*iv* administration) of the 5-HT1A receptors in these conditions also induced similar effects[42].

A few years prior to those pharmacological studies, a promising role for specific sacral networks in micturition had been clearly shown by Americans who after stimulation at or immediately dorsal to the dorsal gray commissure at S(1) level observed strong (at least 20 mmHg) bladder contractions as well as strong (at least 40 mmHg) external urethral sphincter relaxation, resulting in bladder voiding in cats either intact or spinal cord-injured at the thoracic level[43].

In parallel, my own laboratory in Canada has undertaken extensive drug screening studies aimed at identifying brain permeable drugs that could powerfully elicit, within minutes, some episodes of voiding in chronic paraplegic mice. A few families of ligands including 5-HT1A, 5-HT2 and 5-HT1A/7 agonists were found to elicit within 30 min some significant micturition effects. However, among all tests performed, it was a drug combination composed of buspirone (5-HT1A agonist) and 8-OH-DPAT (5-HT1A/7 agonist) that ended up producing the best micturition-inducing effects upon subcutaneous (*sc*) administration[44]. Comparable effects were found also upon oral gavage suggesting that an orally active tablet comprising both active ingredients could become the first ever SMC-activating drug treatment against bladder dysfunction and related-secondary complications in patients with SCI and

comparable neurological disorders[45].

A comparable approach has been explored in recent years to determine the role of electrical stimulation or pharmacological ligands in LDC-mediated potent reflex defecation[46]. Japanese found that ghrelin receptor agonists such as capromorelin or CP464709 administered *sc* or *iv* (lumbosacral level) can increase fecal pellet production in SCI rats[47,48]. Indirectly, electrical stimulation of the pudendal nerve or of sacral roots can also trigger reflex defecation presumably by afferent-induced activation of LDC neurons given that comparable effects were found with intraspinal stimulation at S2 level[49-51].

As performed for micturition-inducing effects, we also conducted drug screening studies aimed at identify brain permeable drugs capable, within minutes, of inducing episodes of defecation in chronic paraplegic mice. Although, a few families of ligands were found to elicit some defecatory effects, it is a drug combination composed of buspirone (5-HT1A agonist) and neostigmine at low doses (cholinesterase inhibitor) that displayed the best defecation-inducing effects upon *sc* administration[52]. Again, comparable effects were found following oral gavage suggesting that an orally active tablet comprising both active ingredients could become the first ever LDC-activating drug treatment against chronic constipation and related-secondary complications in patients with SCI and comparable neurological disorders[53].

Since both technologies identified in our laboratory are already being developed, under contractual agreement, by a pharmaceutical company called Nordic Life Science Pipeline, it may be reasonably to expect that at least one of these therapies may be granted approval for commercialization in Canada, United States and Europe by 2022[54].

CONCLUSION

SCI is an increasing problem worldwide. It has recently become the second most important neurological problem after Alzheimer's disease. Beyond paralysis and loss of locomotion, several dysfunctions and life-threatening secondary complications associated with bladder and bower problems are often experienced by patients with SCI. Unfortunately, no safe or acceptable treatments have been found to control the occurrence or severity of these significant health concerns which, in turn, forces patients to seek emergency and critical care treatment on a regular basis. Pharmacological or electrical modulation of spinal command centers involved in controlling micturition and defecation behaviors may eventually constitute rather selective, specific and hence safe treatments against chronic constipation and UR after SCI.

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EDITORIAL

Optimizing the value of measuring inferior vena cava diameter in shocked patients

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Author contributions: Abu-Zidan FM had the idea, critically read the literature, supplied the images, wrote the paper, and approved its final version.

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Abstract

Point-of-care ultrasound has been increasingly used in evaluating shocked patients including the measurement of inferior vena cava (IVC) diameter. Operators should standardize their technique in scanning IVC. Relative changes are more important than absolute numbers. We advise using the longitudinal view (B mode) to evaluate the gross collapsibility, and the M mode to measure the IVC diameter. Combining the collapsibility and diameter size will increase the value of IVC measurement. This approach has been very useful in the resuscitation of shocked patients, monitoring their fluid demands, and predicting recurrence of shock. Pitfalls in measuring IVC diameter include increased intra-thoracic pressure by mechanical ventilation or increased right atrial pressure by pulmonary embolism or heart failure. The IVC diameter is not useful in cases of increased intra-abdominal pressure (abdominal compartment syndrome) or direct pressure on the IVC. The IVC diameter should be combined with focused echocardiography and correlated with the clinical picture as a whole to be useful.

Key words: Inferior vena cava diameter; Point-of-care ultrasound; Measurement

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Core tip: Bedside measurement of inferior vena cava is useful in evaluating and resuscitating shocked patients. To achieve that, the operator should be well-trained, use standardized techniques, understand ultrasound limitations, and finally correlate the findings with the clinical picture as a whole.

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INTRODUCTION

Point-of-care ultrasound has been increasingly used in

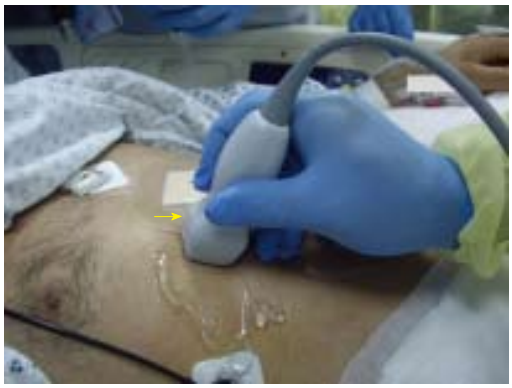

Figure 1 A figure demonstrating the technique to measure the inferior vena cava diameter longitudinally. A small print convex array probe with a frequency of 3-5 MHZ is located in the mid-clavicular line at 90 degrees perpendicular to the skin. The marker is pointing proximally towards the head (arrow).

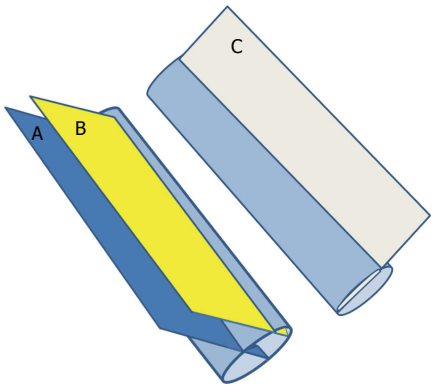

Figure 2 Three dimensional diagram showing the longitudinal ultrasound measurement of the antero-posterior diameter. Measurements depend on the site and angle at which it crosses the IVC. Section A is the proper one as it crosses the IVC vertically at the midpoint. Section B crosses the IVC vertically but peripherally and gives a false low measurement of the IVC diameter. Section C crosses the IVC obliquely and gives a false high measurement of the IVC diameter. IVC: Inferior vena cava.

evaluating shocked patients including the measurement of inferior vena cava diameter (IVC)[1-3]. Nevertheless, there have been conflicting results regarding its value[4-6]. It is important to highlight the technical and clinical difficulties that may be encountered in measuring the IVC diameter as these limit its use. There are four components that affect the outcome of ultrasound studies. These are the effectiveness and technical limitations of the ultrasound machine, the experience of the operator, the body built of the patient, and the pathology studied.

TECHNICAL CONSIDERATIONS

Operators should standardize their technique in scanning the IVC. IVC can be measured through different approaches including the subxiphoid or subcostal approach[7,8]. We prefer to measure the IVC directly through a transhepatic approach using a portable machine and a small print convex array probe with a frequency of 3-5 MHZ

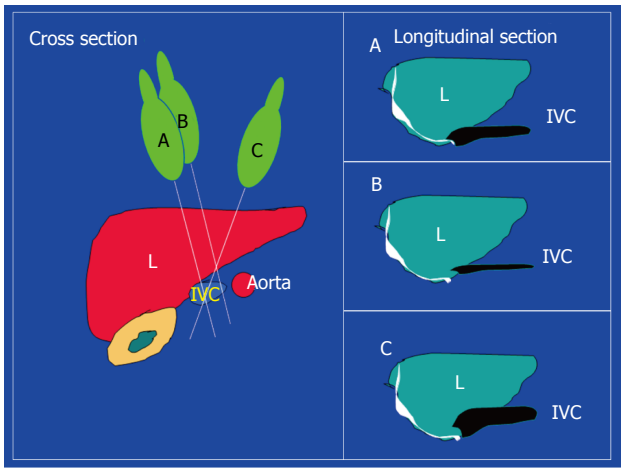

Figure 3 Cross section of the abdomen on the left side of the figure showing the liver, inferior vena cava, and aorta. The B mode longitudinal ultrasound image will depend on the angle between the plane of the ultrasound section and the IVC. Three different planes are shown on the cross section (A-B-C) and the corresponding longitudinal IVC images are shown to the right. Longitudinal section A is the proper one as it crosses the IVC vertically at the midpoint. Section B crosses the IVC vertically but peripherally and gives a false low measurement of the IVC diameter. Section C crosses the IVC obliquely and gives a false high IVC diameter measurement. IVC: Inferior vena cava.

while the patient is in supine position. The probe is located in the mid-clavicular line between the ribs of the right lower chest wall at 90 degrees perpendicular to the skin. The marker points proximally towards the head (Figure 1). The probe may be slightly directed towards the right to be parallel to the IVC. The probe is then shifted slowly transversely to get the best longitudinal perpendicular view. We think that this is better than the subxiphoid approach[7] as the IVC is located slightly to right and the diameter of the IVC may be overestimated by getting an oblique section (Figure 2).

The ultrasound cross section should be vertical to the IVC. Common pitfalls in measurement include measuring the IVC obliquely or peripherally (Figures 2 and 3). In general, it is advised to use the B mode to evaluate the gross collapsibility of the IVC and the M mode to accurately measure the changes in IVC diameter. The IVC can be measured in both longitudinal and transverse sections.

Pitfalls in measuring IVC include increased intra-thoracic pressure resulting from mechanical ventilation or increased right atrial pressure resulting from heart failure or pulmonary embolism. These conditions will increase the diameter of the abdominal IVC[3]. We have recently reported that IVC diameter was not useful in guiding resuscitation, and was even misleading in abdominal compartment syndrome[9]. The increased pressure in abdominal compartment syndrome will compress the IVC and reduce its antero-posterior diameter. The unexperienced clinician may increase the fluid resuscitation which would further decrease the diameter. Furthermore, direct pressure on the IVC as in late pregnancy and acute gastric dilatation[10] can affect the measurement. The IVC diameter should be combined with focused

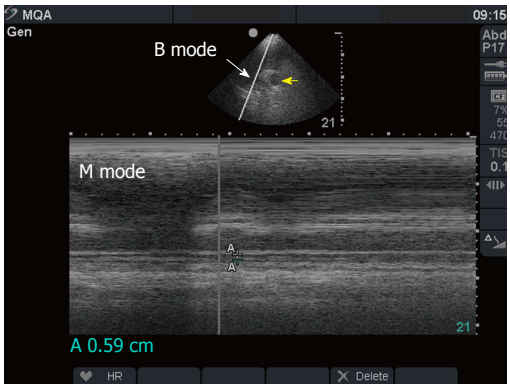

Figure 4 Inferior vena cava measurements in a 39-year-old man who was in septic shock and complete renal failure. The upper image is a transverse cross sectional B mode showing the aorta (yellow arrow) and the IVC (white arrow). The lower image is an M mode showing the IVC measurement (A-A) which is 59 mm indicating that the patient was hypovolemic. IVC: Inferior vena cava.

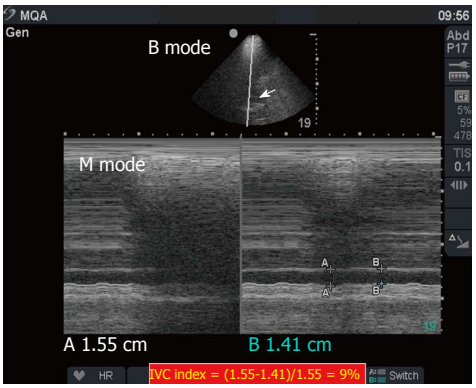

Figure 5 Two point five liters of crystalloids were given to the previous patient over 35 min and repeated measurements of the inferior vena cava diameter were performed. The upper image is a transverse cross sectional B mode showing the IVC (white arrow). The lower image is an M mode showing that the IVC increased to a maximum 1.55 cm with an IVC index of 9% [(1.55-1.41)/1.55]. A-A in the M mode represents the maximum IVC diameter while B-B represents the minimum IVC diameter. IVC: Inferior vena cava.

echocardiography and correlated with the clinical picture as a whole to be useful.

VALUE OF MEASURING IVC DIAMETER IN SHOCKED PATIENTS

IVC measurement can be used as part of defined protocols in diagnosing shocked patients to optimize its value. These protocols evaluate the heart, IVC, chest, and the abdomen to try defining the cause of the shock. Our group follows the RUSH protocol which examines the pump (heart), tubes (great vessels) and reservoir (free intra-peritoneal or intra-thoracic fluid)[2]. Vegas *et al*[7] use the same principles but in a different approach, whereby they classify the shocked patients into those with (1) reduced mean systemic venous pressure; (2) increased right atrial pressure; and (3) increased resistance to the venous return. They study the size of IVC, respiratory variation of the IVC, and the hepatic venous flow to define the type of shock[7].

In a study of 47 patients having septic shock, Coen *et al*[11] used the variability of IVC diameter to decide the volume of fluid resuscitation. They gave boluses of 500 mL of crystalloids as needed to reach an IVC index of 30%-50% which was defined as [(maximum IVC diameter - minimum IVC diameter)/maximum IVC diameter] × 100. IVC measurement was feasible in 92% of the cases and central venous catheter was avoided in more than one third of the patients. The IVC index was significantly higher in shocked patients compared with non shocked patients[12].

The IVC diameter was negatively correlated with the lactate level and positively correlated with the base excess level during hemorrhagic shock resuscitation indicating its good clinical value[8]. Furthermore, Yanagawa *et al*[13] prospectively studied 30 trauma patients and found that the relative change of IVC diameter is effective in differentiating stable resuscitation responders from transient responders who develop recurrent shock. These findings were supported by Feissel *et al*[14] who found the same results in ventilated septic patients. Furthermore, Schefold *et al*[15] found that IVC diameter was highly correlated with the central venous pressure and extravascular lung water index in septic ventilated intensive care unit (ICU) patients. This may be helpful in avoiding unnecessary volume expansion in these sick patients. In contrast, Corl *et al*[5] found that measuring the IVC index was not a good marker for proper fluid responsiveness in the emergency department and questioned its value.

Weekes *et al*[4] prospectively evaluated the gross appearance of IVC and correlated it with the actual measured size in 24 hypotensive patients. They developed a three point scale of visual appearance of IVC as follows: (1) decreased IVC index of $\leqslant$ 0.3; (2) normal range (0.31-0.69); and (3) increased index $\geqslant$ 0.7. Serial gross evaluation of IVC agreed with the actual measured IVC during fluid resuscitation. This study supports the opinion that relative changes are more important than absolute numbers. Gross collapsibility is a more useful marker for hypovolemia than IVC collapsibility index[3]. We advise using the longitudinal view (B mode) to evaluate the gross collapsibility, and the M mode to measure the diameter of IVC. Combining the collapsibility and diameter will increase the value of IVC measurement. This approach has been very useful in our hands (Figures 4-6).

EVIDENCED-BASED APPROACH

There is no doubt that this area needs more evidence based approach. Dipti *et al*[6] in a meta-analysis that was published in 2012, studied the value of IVC diameter in estimating volume status in adults. They searched 5 major databases and combined 5 prospective studies on this topic. The meta-analysis included 86 hypovolemic

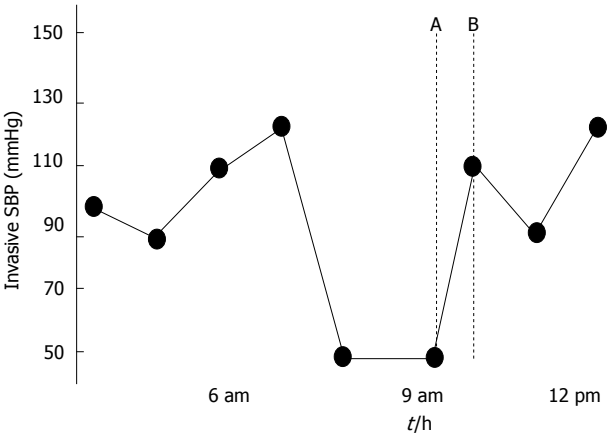

Figure 6 The patient's blood pressure quickly improved without evidence of pulmonary oedema. Point A is when images in Figure 4 were taken while point B is when images in Figure 5 were taken.

patients and 189 controls. IVC diameter was significantly less in hypovolemic patients compared with controls. These studies stemmed from 4 countries having good external validity and a spectrum of different disease severity. Nevertheless, the analysis had a very high heterogeneity (I^2 = 99%), no randomized controlled study was included, and the sample size was small.

A recent prospective randomized controlled trial in injured patients having hypotension or tachycardia treated in a level I trauma center in United States has just been published[16]. It compared transthoracic limited echocardiography including measuring IVC (106 patients) with usual care (134 patients). The outcome variables were fluid requirement, time to surgery, percentage of ICU admission, and mortality. This study shows that limited echocardiography significantly reduced the IV fluid requirements (average of 1.5 L compared with 2.5 L) and significantly reduced the time to the operating theatre (by 50%). It also alerted the physicians to the seriousness of some cases and increased the likelihood of ICU admission of such cases (from 67% to 80%).

It may be argued that the statements expressed in this editorial are biased. I have been interested in and passionate about point of care ultrasound for a quarter of a century, since time when it was not yet commonly used by surgeons or intensivists. I have observed the dramatic improvement in this field over time including the huge progress in point-of-care ultrasound and the development of acute care surgery as a special entity. I have been measuring the IVC diameter in critically-ill and trauma shocked patients as an acute care surgeon over the last 8 years and using it in making very critical decisions in a busy acute care hospital. From personal experience, I am confident that bedside measurement of IVC is to stay. It is useful in evaluating and resuscitating shocked patients. To achieve that, the operator should be well-trained, use standardized techniques, understand ultrasound limitations, and finally correlate the findings with the clinical picture as a whole.

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FRONTIER

Advanced trauma life support training: How useful it is?

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Author contributions: Abu-Zidan FM had the idea, critically read the literature, drew the images, wrote the paper, and approved its final version.

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Abstract

We have tried in a recently published systematic review (*World J of Surg* 2014; 38: 322-329) to study the educational value of advanced trauma life support (ATLS) courses and whether they improve survival of multiple trauma patients. This Frontier article summarizes what we have learned and reflects on future perspectives in this important area. Our recently published systematic review has shown that ATLS training is very useful from an educational point view. It significantly increased knowledge, and improved practical skills and the critical decision making process in managing multiple trauma patients. These positive changes were evident in a wide range of learners including undergraduate medical students and postgraduate residents from different subspecialties. In contrast, clear evidence that ATLS training reduces trauma death is lacking. It is obvious that it is almost impossible to perform randomized controlled trials to study the effect of ATLS courses on trauma mortality. Studying factors predicting trauma mortality is a very complex issue. Accordingly, trauma mortality does not depend solely on ATLS training but on other important factors, like presence of well-developed trauma systems including advanced pre-hospital care. We think that the way to answer whether ATLS training improves survival is to perform large prospective cohort studies of high quality data and use advanced statistical modelling.

Key words: Advanced trauma life support; Education; Course; Training; Death

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Core tip: We recommend teaching advanced trauma life support (ATLS) courses for doctors who may treat multiple trauma patients in their setting. Large prospective cohort studies of high quality data are needed to evaluate the impact of ATLS training on trauma death rates and disability.

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BIOGRAPHY

Professor Fikri M Abu-Zidan (Figure 1) is a Consultant Trauma and Acute Care Surgeon who gained his MD from Aleppo University, Syria, in 1981. He was awarded the Fellowship of Royal College of Surgeons of Glasgow, Scotland in 1987. He achieved his PhD in Trauma and Disaster Medicine from Linkoping University, Sweden in 1995 and then obtained his Postgraduate Diploma of Applied Statistics from Massey University, New Zealand, in 1999. He worked as a surgeon at Mubarak Al-Kabeer Teaching Hospital in Kuwait from 1983-1993, as a Trauma Research Fellow at Linkoping University, Sweden, from 1993-1995, as a Senior Research Fellow at Auckland University, New Zealand from 1996-2001; and as a Trauma Fellow at Royal Perth Hospital, Perth, Australia, during 2001. He is at present a Professor of Surgery at the Department of Surgery, College of Medicine and Health Sciences, United Arab Emirates (UAE) University, United Arab Emirates. He has contributed to more than 270 publications in refereed international journals. Professor Abu-Zidan is a well-respected international Judge, invited speaker, and visiting Professor at numerous international meetings with more than 350 presentations and invited lectures. At present, Professor Abu-Zidan is serving as the Statistical Consultant for *World Society of Emergency Surgery*, Statistical Consultant for *World Journal of Emergency Surgery*, Statistics Editor of *Hamdan Medical Journal*, and as an Invited Editor, member of Editorial board, and reviewer for several international journals. His clinical experience includes treating war injured patients during the Second Gulf War (1990). He has been promoting the use of Point-of-Care Ultrasound for more than twenty five years and he is considered a World Leader in this area. Furthermore, he is an international expert on trauma experimental methodology with particular expertise in developing novel clinically relevant animal models. He played an important role in establishing experimental surgical research in Auckland University, New Zealand which subsequently developed into a strong successful PhD Program. Professor Abu-Zidan has received numerous national and international awards for clinical, research and educational activities.

INTRODUCTION

Trauma is a leading cause of death and disability all over the world. Trauma management can be improved by implementing a trauma system that includes injury prevention, education, pre-hospital care, transportation, hospital care, and rehabilitation[1]. If properly implemented, trauma systems can reduce mortality of severe trauma patients by at least 15%[2]. Training physicians to manage multiple trauma patients is an essential part of developing proper trauma systems. The primary end point of any clinical educational activity is its impact on improving health care. Our trauma group has been extensively involved in teaching advanced trauma life support (ATLS) and focused assessment sonography courses for the last 15 years[3-6]. These courses are time consuming and need extensive resources and manpower. ATLS is one of the most common courses taught worldwide. In an evidenced-based era, it is legitimate to question the educational and clinical value of these courses. We tried in a recently published systematic review to study the educational value of ATLS courses and whether they improved survival of multiple trauma patients[7]. This article summarizes what we have learned and reflects on future perspectives in this area.

Figure 1 Fikri M Abu-Zidan, MD, FACS, FRCS, PhD, Dip Applied Statistics; Professor, Acute Care Surgeon, Point-of-Care Sonographer, and Statistical Consultant; Department of Surgery, College of Medicine and Health Sciences, UAE University, Al-Ain, United Arab Emirates.

ATLS COURSE

The ATLS course was established in 1976 by Dr James Styner in United States after a tragic private family plane crash. Dr Styner was not happy with the level of health care given to his family members. He developed ATLS so as to improve the management of multiple trauma patients in rural areas. This course was adopted by the American College of Surgeons and quickly spread worldwide[8,9]. To date it has been taught to more than one million doctors in more than 60 countries[10]. It is accepted as a standard protocol for the initial care of trauma patients in many trauma centers worldwide[11,12].

ATLS is a very demanding two/three full days course that uses different adult learning approaches[13] including interactive didactic teaching, simulated clinical cases (Figures 2 and 3), practical skill stations (Figure 4), and group discussions[14]. Following ATLS training, non-surgical physicians should be able to successfully manage severe trauma patients[15]. The interactive approach for teaching ATLS improves clinical assessment of trauma patients. It is more enjoyable and rewarding compared with classical teaching[16,17]. It actively involves students in discussions, encourages them to ask more questions, and gives direct feedback. ATLS simulations place candidates under stress in clinical scenarios so that they can later make critical decisions in a real world environment. ATLS aims high to reach the top layer of Miller's educational pyramid

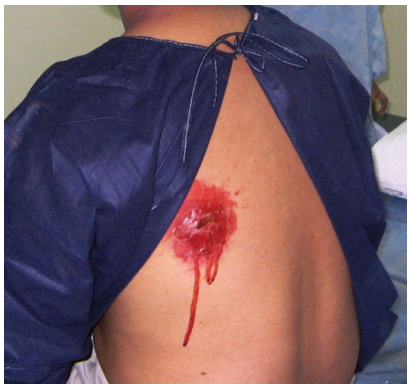

Figure 2 A moulaged simulated patient having a stab wound to the left chest wall with tension pneumothorax.

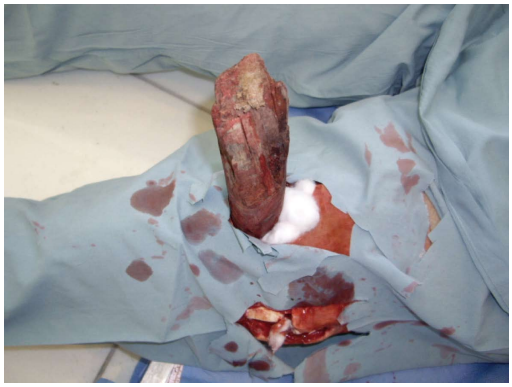

Figure 3 A moulaged simulated trauma patient with a penetrating impalement injury to the left thigh with left femur fracture and superficial femoral artery injury caused by a piece of wood.

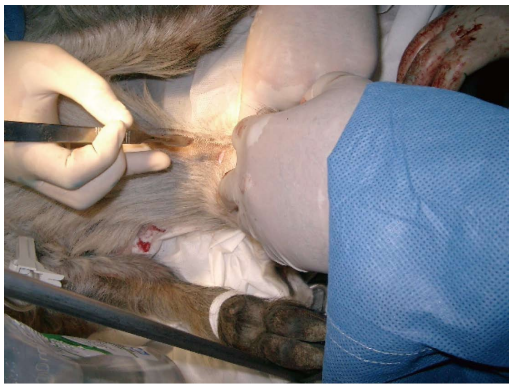

Figure 4 Practical training on performing diagnostic peritoneal lavage on anaesthetized goats using the open technique and a transverse sub-umbilical incision.

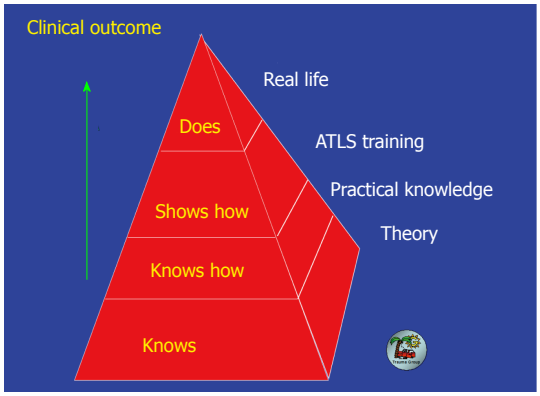

Figure 5 Miller's pyramid for gaining clinical skills in Advanced Trauma Life Support courses. ATLS: Advanced Trauma Life Support.

("does") (Figure 5)[18,19]. Physicians are observed performing certain procedures and applying them in simulated clinical scenario. It is important to stress that the real value of any educational medical activity is measured by its clinical benefit for patients in real life.

We started teaching ATLS in UAE in 2004. More than 2000 doctors have taken this course in UAE[20]. The majority of participants in UAE were residents (44.8%), and specialists (43.7%). Critical care physicians and anaesthetists constituted 11% of all participants of ATLS courses in UAE. Interestingly, critical care physicians showed similar theoretical (P = 0.89) and practical knowledge (P = 0.99) when compared with surgeons during ATLS courses in UAE[4].

METHODS USED

We searched MEDLINE, PubMed, and the Cochrane databases for articles studying the educational outcomes of ATLS courses and their impact on trauma death. Articles published during the period 1966-2012 were studied. Out of 384 papers, 23 met our selection criteria. Ten original papers investigated the effects of ATLS courses on knowledge and practical skills, six original papers studied the time needed to lose practical skills gained by ATLS courses, and seven original papers studied the impact of ATLS courses on trauma death. I critically appraised these papers regarding their research methodology and statistical analysis in this systematic review[7]. We used The Scottish Intercollegiate Guidelines Network handbook to grade the level of evidence of the papers[21]. Furthermore, we used the United States preventive Services Task Force grading system to grade overall quality of evidence[22].

WHAT IS THE EDUCATIONAL IMPACT OF ATLS?

ATLS significantly increases knowledge of trauma management, improves practical skills, organization of trauma management, and identification of management priorities (level Ⅰ evidence: Evidence obtained from at least one properly randomized controlled trial). The gained knowledge and skills start to decline gradually 6 mo after the course (level Ⅱ-1 evidence: Evidence obtained from well-designed controlled trials without randomization) and reach maximum decline after 2 years. Participants keep the gained organizational skills and identification of management priorities up to 8

years after taking the course. Teaching ATLS courses using the interactive approach significantly improved the practical skills compared with the old classical teaching (Level I evidence)[7].

Knowledge and practical skills gained by ATLS participants decline over time if these skills are not utilized. This supports the need for re-certification. We are of the opinion that ATLS re-certification should be under taken every four years so as to update candidates with recent advances in trauma management. Trauma management continuously changes depending on new scientific evidence that leads to modification of recommendations and guidelines.

DOES ATLS TRAINING IMPROVE SURVIVAL OF TRAUMA PATIENTS?

Medical literature does not show accumulative evidence that ATLS training reduces trauma death. All seven studies addressing the effects of ATLS training on trauma death were retrospective except one which was a prospective cohort study. Five of these studies did not show any effect of ATLS training on trauma death, one study showed significant improvement, while another showed a worse outcome of trauma patients who were managed by ATLS certified doctors[7].

LIMITATIONS OF OUR REVIEW

It is recommended that at least two independent researchers should do the literature search in systematic reviews and at least two methodologists should critically appraise the selected papers. This would reduce both search bias and evaluator bias. What worked for us during the search stage is that ATLS or "Advanced Trauma Life Support" is a very specific term. Furthermore, MEDLINE and PubMed have the ability to automatically search for alternative terms. This would have reduced the search bias. One of the major limitations in performing systematic reviews in developing countries is lack of research methodologists. The systematic review discussed[7] was critically appraised by only one evaluator which is definitely a limitation.

What assured us that our evaluation was proper is that a very recent Cochrane database systematic review that was published a few months after our paper had the same research question. This systematic review produced exactly the same results and conclusions as ours[23].

SUMMARY OF THE SYSTEMATIC REVIEW

Our recently published systematic review has shown that ATLS training is very useful from an educational point view. It significantly increased knowledge, and improved both practical skills and the critical decision making process in managing multiple trauma patients. These positive changes were evident in a wide range of learners including undergraduate medical students and postgraduate residents from different subspecialties. In contrast, clear evidence that ATLS training reduces trauma death is lacking. We recommend teaching ATLS courses for those doctors who may treat multiple trauma patients in their setting. Large prospective cohort studies of high quality data are needed to evaluate the impact of ATLS training on trauma death rates and disability.

PERSPECTIVE

It is obvious that it is almost impossible to perform randomized controlled trials to study the effect of ATLS courses on trauma mortality simply because all conditions cannot be standardized. Studying factors predicting trauma mortality is a very complex issue. There are multiple confounders and logistics that prevent such experimental design. Accordingly, trauma mortality does not depend solely on ATLS training but on other important factors, like presence of well-developed trauma systems with advanced pre-hospital care. In a population based study from different counties in United States, Rutledge *et al*[24] found that the effects of ATLS training differed between different county clusters. This indicates that factors affecting mortality are more complex and pertain not only to ATLS training[24]. We think that the way to answer whether ATLS training improves survival is to perform large prospective cohort studies of high quality data and use advanced statistical modelling for that.

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REVIEW

Antithrombin in the treatment of burn trauma

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Author contributions: Kowal-Vern A designed the review, acquired the literature and drafted the article; Kowal-Vern A and Orkin BA analysed and interpreted the data and literature, made critical revisions related to important intellectual content of the manuscript, and approved the final version of the article to be published.

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Abstract

Antithrombin (AT) is a natural anticoagulant with anti-inflammatory properties that has demonstrated value in sepsis, disseminated intravascular coagulation and in burn and inhalation injury. With high doses, AT may decrease blood loss during eschar excision, reducing blood transfusion requirements. There are no human randomized, placebo-controlled studies, which have tested the true benefit of this agent in these conditions. Two main forms of AT are either plasma-derived AT (phAT) and recombinant AT (rhAT). Major ovine studies in burn and smoke inhalation injury have utilized rhAT. There have been no studies which have either translated the basic rhAT research in burn trauma, or determined the tolerance and pharmacokinetics of rhAT concentrate infusions in burn patients. Advantages of rhAT infusions are no risk of blood borne diseases and lower cost. However, the majority of human burn patient studies have been conducted utilizing phAT. Recent Japanese clinical trials have started using phAT in abdominal sepsis successfully. This review examines the properties of both phAT and rhAT, and analyzes studies in which they have been utilized. We believe that it is time to embark on a randomized placebo-controlled multi-center trial to establish the role of AT in both civilian and military patients with burn trauma.

Key words: Antithrombin; Burn trauma; Burn injury; Inhalation injury; Recombinant antithrombin

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Core tip: Based on ovine and rat research, and civilian population studies, antithrombin (AT) therapy with either human plasma-derived AT or recombinant AT (rhAT) may be a valuable adjunct treatment in patients with ⩾ 25% total body surface area burn. AT has anticoagulant and anti-inflammatory properties, a positive effect on cardiopulmonary function, and wound healing, with concomitant decreases in pneumonia and mortality. Studies in human volunteers with endotoxemia have shown that rhAT doses as high as 200% and 500% are tolerated safely. With adequate high doses, AT may decrease blood loss during eschar excision, and reduce blood transfusion requirements.

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BACKGROUND

World-wide, there are an estimated 265000 deaths per year attributed to burns and inhalation injury, mainly in countries with lower incomes, especially in the World Health Organization South-East Asia area[1]. In the United States alone, the American Burn Association 2015 Fact Sheet compiled data estimates that there have been 3240 deaths from fire and smoke inhalation, 486000 burn injuries requiring medical treatment, and 40000 requiring hospitalization with a survival rate of 96.7%[2]. In spite of major improvements in burn care during the past 30 years, inhalation injury has not been adequately addressed, and is often the main reason patients die even when they have recovered from their burns. Currently, there are no definitive clinical trials for agents that would reverse or improve the inflammatory response, cytokine release, capillary leakage, pulmonary edema, and cellular influx into the lung parenchyma in these patients. It has been well documented in the literature that burn and inhalation injury patients have varying degrees of disseminated intravascular coagulation (DIC), hypercoagulability with thromboembolism, and systemic inflammatory response syndrome (SIRS). Current beneficial relevance of antithrombin (AT) to burn trauma has not been proven[3-6]. Human and ovine studies have shown that AT can have an impact on the morbidity and mortality associated with burn trauma[7,8]. In this review we will examine the utility of AT as a natural anticoagulant and anti-inflammatory agent in the treatment of ≥ 25% total body surface area (TBSA) burns and inhalation injury. The review will describe the status quo of overall research in the field and problems that have been resolved.

Human plasma-derived AT

Paul Morawitz[9] was the first to coin the word "anti-thrombin" (as an inhibitor of thrombin) in his review in 1904. AT was then identified in 1939 as a co-factor of heparin in preventing thrombin formation and inactivating thrombin by forming the thrombin-AT complex[10].

Plasma-derived AT (phAT) is a 58200 kDa serine protease inhibitor of the serpin family which, as a natural anticoagulant: Neutralizes activated serine proteases like factors Ⅹ, Ⅸ, Ⅺ, Ⅻ; complexes with and deactivates thrombin (factor Ⅱ); and increases the rate of dissociation of factor Ⅶa-tissue factor complex to reduce factor Ⅶa activity[11,12]. Since the anticoagulant activity of phAT is potentiated by interactions with endothelial heparin sulfates, this effect is localized to the blood vessels where it competes with heparin for the glycosaminoglycans through thrombomodulin to activate the release of prostacyclin[11,12]. phAT also has anti-inflammatory properties: It complexes with thrombin, removes it from circulation, and decreases production of tumor necrosis factor (TNF)-α which plays a major role in the SIRS syndrome initiated cytokine proliferation[13,14]. phAT may improve wound healing in a hypercoagulable system by reducing thrombosis and maintaining a more vascularized subcutaneous tissue[15,16]. If there is a decrease of thrombosis and microthrombi under the burned skin due to AT-treatment, there would be increased intensity of heat shock protein (hsp) expression in the underlying tissue of the burned area, leading to more viable cells expressing the *hsp* genes[16]. phAT-treated burned skin had a significantly increased intensity of expression of hps70 ($P < 0.02$) and of grp78 ($P < 0.01$) compared to controls[16].

AT plasma levels in healthy blood donors are age-related; between the ages of 25-30 years, women have lower phAT levels compared to men; between the ages of 35 and 50 years, the levels are the same; and over 50 years of age, women have higher phAT levels and increased levels of factor Ⅶ and fibrinogen[17,18]. phAT was used successfully in patients with hereditary AT deficiency[19].

In the past 20 years, published human studies and case reports have documented benefit from the use of phAT in patients with DIC and sepsis[20-23]. The Kybersept study of 2314 septic patients (multi-national, randomized, placebo controlled) was undertaken to determine if there was decreased mortality in patients with phAT treatment (30000 units over 4 d); there was no significant benefit of AT in 28 d mortality rates[24]. In addition, the subset of patients who received heparin with phAT had increased risk of bleeding episodes[24]. However, in this study, there was no adjustment of the AT dose for weight, and burn trauma patients were not included. In a subset of the Kybersept septic patients who had clinical DIC, Kienast *et al*[25] found that patients treated only with phAT did not have increased bleeding compared to controls. These results had a negative and cautionary impact on further investigations of phAT in critically ill patients with DIC and sepsis[25].

Recombinant AT

Recombinant AT (rhAT) as a sterile lyophilized powder became available in the 1990s. As a recombinant product, it eliminates the morbidity of blood borne pathogens and is less expensive than phAT[26]. It is currently FDA approved for hereditary AT deficient patients[26]. A detailed biochemical analysis found that rhAT transgenically produced from goat milk is comparable to clinical grade human plasma-derived AT with respect to specific activity, purity, amount of aggregates, primary sequence, secondary and tertiary structure[26]. Recombinant AT has a shorter half- life than phAT (10.16 ± 1.28 h *vs* 2.8-3.8 d)[26,27]. rhAT also has a greater affinity for heparin than phAT, which may be due to differences in glycosylation[26]. Because rhAT is cleared faster from the circulation compared to phAT, it is usually

Table 1 Literature review of plasma-derived antithrombin studies in human burn patients

Ref.	# phAT patients	# controls	Age (yr) mean	%TBSA	# doses	Admit AT % levels	phAT dose units	AT % level desired	AT % level achieved	AT Level predict mortality	Other
[1]Danielsson *et al*[31], 1997	6	8	37 (20-56)	49 (26-75)	9 d	< 50	333-3800	> 70	50-75	None	Heparin also
[3]Kowal-Vern *et al*[7,15], 2000-2001	9	9	45-30	40-45	9 q 8 h	45 (35-55)	97 U/kg per dose	175	120 (95-145)	None	Pneumonia↓ in AT-treated
[3]Kowal-Vern *et al*[40], 2003	2	0	1.8	70	9 q 8 h	25-66	1000 U/ dose	200	173 (114-224)	None	None
Del Principe[32], 2003	50	0	< 16	> 30	9 q 8 h	--	--	100	105 (85-125)	$P = 0.0005$	None
[2]Niedermayr *et al*[33], 2007	108	93	53 (30-76)	36 (12-60)	--	85 (63-107)	--	70-120	70-120	$P = 0.003$	Heparin also (APTT-50 s)
[4]Lavrentieva *et al*[34], 2008	15	16	22-66	44 (22-66)	3 d	44 (28-81)	65 U/kg per day	> 150	124 (106-148)	None	AT-treated ↑ survival $P = 0.004$

In age, %TBSA. [1]AT-treated group received continuous unfractionated heparin from day 3. One thousand six hundred and sixty-seven U/patient daily as did the controls; [2]The controls had less inhalation injury (14% *vs* 50%) and the %TBSA was much lower (17 ± 17 *vs* 36 ± 24); [3]Calculations for the loading dose were 97 U/kg per loading dose and the next 9 doses were at 2/3 of the loading dose; [4]Unknown if AT given q 8 h or as a continuous infusion. AT: Antithrombin; phAT: Plasma-derived antithrombin; TBSA: Total body surface area; U: Units.

administered as a continuous intravenous infusion. It has been studied in an ovine model of burn and inhalation injury. Other rhAT formulations are produced from the Chinese hamster ovary cells, baby hamster kidney cells and a methylotropic yeast, Pichia pastoris[28]. The primary available rhAT product is Atryn™ (GTC BioTherapeutics, Framingham, MA, United States). It is approved for use in patients with congenital AT deficiency, and is well tolerated and effective[29]. Leitner *et al*[30] studied the effects of rhAT in 30 healthy volunteers. rhAT was infused to increase AT plasma levels to 200% and 500% of normal in a randomized, double-blind, placebo-controlled fashion[30]. Then endotoxin (LPS), 2 ng/kg was administered. Infusion of rhAT dose-dependently decreased coagulation activation ($P < 0.01$), and interleukin-6 (IL-6) levels ($P < 0.01$)[30]. rhAT also decreased peak IL-6 levels by 40% in both study groups, 222 pg/mL and 216 pg/mL *vs* 357 pg/mL in the placebo group, ($P < 0.001$)[30]. In summary, rhAT dose-dependently inhibited tissue factor-triggered coagulation[30]. While rhAT has been used in normal volunteers and in patients with hereditary AT deficiency, there have been no human studies in patients with burn and inhalation injuries.

phAT studies in burn trauma

Table 1 is a compendium of six studies using phAT in human subjects. Of these, 5 reported patient benefits in terms of either pulmonary function, wound healing or mortality. All the studies used different treatment methods and could not be compared to each other. The results in the Danielsson *et al*'s[31] study were compromised by the use of very low doses of phAT, which were continued for 3-4 d. The study had a total of only 6 patients, with small and large burns in one cohort, each of whom were administered a different dose of phAT, without achieving levels above the "normal"[31]. In addition, the authors started heparin on day 3 in both the phAT-treated and non-treated patients, further complicating the clinical picture and data analysis[31]. Therefore, the study conclusion that phAT was not of benefit in burn trauma was based on inadequate numbers, low AT levels, and overall inconclusive evidence[31].

In contrast, Del Principe[32] reported a significant decrease in mortality with the use of infused phAT to > 100% of normal in an Italian pediatric population.

In the Niedermayr *et al*[33] study, burn and inhalation patients were followed by daily AT plasma levels and received AT concentrates to correct any deficiencies to physiologic levels of 70%-120%. Controls had less inhalation injury (14% *vs* 50%) and the %TBSA was much lower (17 ± 17 *vs* 36 ± 24); one might, therefore, expect the control arm with less injury severity to have a significantly lower mortality (7% *vs* 36%)[33]. In this study, all patients received heparin to maintain an APTT of 50 s[33]. Pharmacokinetics of bolus *vs* continual infusion of phAT revealed that continual infusion consumed less drug over time and sustained fewer unintentional decreases in plasma once the steady state was reached; this also provided a cost benefit for the patient[33].

Lavrientieva *et al*[34] published a prospective, randomized study of 31 severely burned patients comparing phAT-treated patients with controls. AT administration was started from the 1st post-burn day and continued for the next 3 d[34]. The AT dose was titrated to the target value of plasma AT activity > 150%[34]. The baseline AT in controls was 54.7% ± 26% on admission and increased to 70.4% ± 19% on day 4; the baseline AT in the phAT-treated patients was 44.3% ± 16% and increased to 121.2% ± 18%[34]. On the basis of specific coagulation markers for DIC such as thrombin-AT complex (TAT) and D-dimer, 19 (61.3%) of patients had non-overt DIC on admission and 9 (29%) had overt DIC on admission[34]. The study did not provide subset analyses of their patients, separating the less injured %TBSA from the more severely injured ones[34].

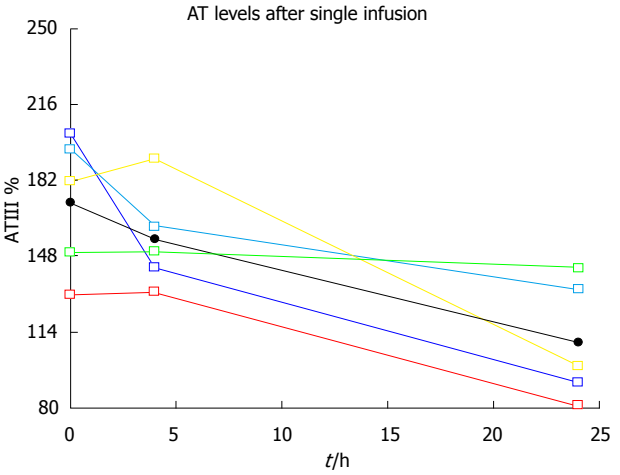


Figure 1 AT levels after calculations for bolus single infusions to attain > 175% plasma antithrombin levels (personal file AKV). AT: Antithrombin.

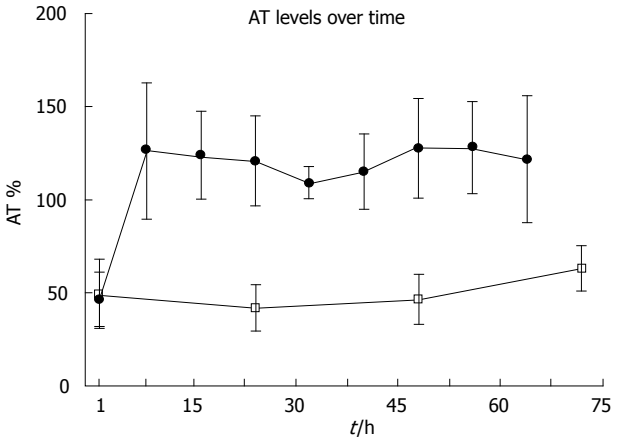


Figure 2 A 72 h depiction of q 8 h dosage coefficient of variations for the antithrombin-treated burn patients (black dots) compared to control plasma antithrombin levels (white squares) (personal file AKV). AT: Antithrombin.

Kowal-Vern *et al*[15] prospectively studied 18 patients with ⩾ 20% TBSA burns ± inhalation injury to assess phAT concentrate infusions for safety and efficacy, and impact on pulmonary function. Since phAT had not been previously utilized in burn trauma, patients were consented on the basis of their decision to either receive the concentrate or to enter as a control patient, not randomized. Nine patients received q 8 h phAT concentrate infusions to raise the plasma level in the first 72 h of hospitalization[15]. The empiric choice, to maintain a high level at > 175% plasma levels was not adequate in treating these patients, to prevent thrombosis of blood vessels, DIC, and stymie the SIRS response that was initiated by release of the thrombin into the circulation (Figure 1)[15].

The loading dose and q 8 h dosing strategy showed variable levels of phAT in patients over the course of 3 d, (Figure 2)[15].

Changes in coagulation activation, fibrinolysis, and anti-inflammatory effects did not extend past the last phAT concentrate dose[15]. More than likely, the half-life of phAT was decreased due to the consumption and loss during the acute resuscitative period. By day 5, control patient AT levels were returning to normal in the less severe cases; liver production of AT was, therefore, intact in most cases unless liver failure developed during treatment[15,35]. Aspartate aminotransferase levels are markedly elevated in burn patients compared to other liver enzymes most likely as a reaction to the inflammation that is occurring rather than liver disease or failure on admission[35].

Several investigators recommended that phAT concentrates be given to achieve > 200% plasma level for adequate anticoagulation and anti-inflammatory activity[36-39]. One patient with 80% TBSA and inhalation injury received the higher recommended doses of phAT concentrate and the four extremity eschar was easily separated from the viable subcutaneous tissues with no blood loss and no excision[40]. Figure 3 shows the severity of the burn with a well-defined escharotomy scar on the lower extremity. Figure 4 shows how easily the eschar is peeled back off the viable subcutaneous tissue below. Histopathology showed viable sebaceous glands and a vascular bed at the separation edge beneath the burnt non-viable skin[40].

Human and ovine studies of AT concentrates for pulmonary injury in burn trauma

Utilizing AT concentrates as replacement therapy for burn trauma, there has been one human study assessing pulmonary function and a number of ovine model studies evaluating burn trauma and specifically lung pathophysiology. Although a small study, the Loyola group compared nine phAT-treated burn patients to 23 control patients[7]. Forty-three percent of controls and 23% of phAT-treated patients developed pneumonia, $P < 0.01$[7]. With potential decreased airway resistance and increased oxygenation, phAT-treated patients had significantly fewer episodes of pneumonia compared to controls[7]. AT concentrate infusions were judged safe and a good option to shorten hospital stay, promote graft viability and survival, and improve pulmonary function in burn injury[7,15].

In a later comparison study of 11 Inhalation injury patients to 11 inhalation + burn injury patients, the inhalation group had a significantly lower 5% ± 4% TBSA compared to 37% ± 24% TBSA in the inhalation+burn group, $P < 0.001$[41]. phAT plasma levels were significantly decreased in inhalation ± burn injury patients (41% + 16% of normal) compared to those with inhalation injury (81% ± 26%), $P < 0.003$[41]. The bronchoalveolar lavage (BAL) did not show any AT levels in the inhalation only patients, but the inhalation + burn injury patients had 1% ± 3% phAT in the lavage[41]. TNF-α levels were significantly increased in BAL compared to plasma on admission and days 3-6 in both groups, $P < 0.001$[41]. BAL IL-6 levels increased in severity through days 3-6, in contrast to plasma levels which decreased in intensity

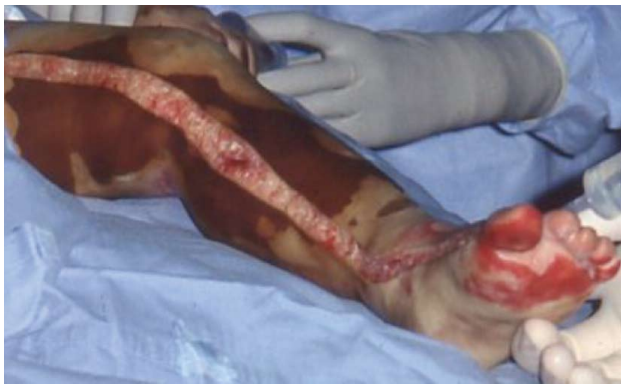


Figure 3 The severity of injury requiring an escharotomy in a burn patient with 80% total body surface area (personal file AKV).

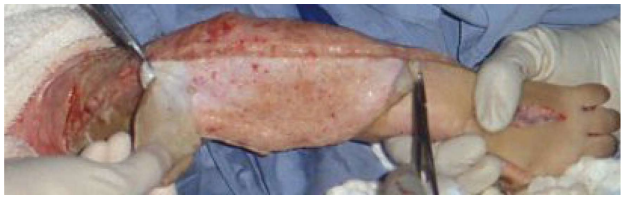


Figure 4 The "peeling off" of the eschar, not requiring knife excision with exposed viable subcutaneous tissue and minimal bleeding (personal file AKV).

by days 3-6[41]. This increase and persistence of BAL TNF-α and IL-6 may have contributed to the pulmonary perturbations of these patients.

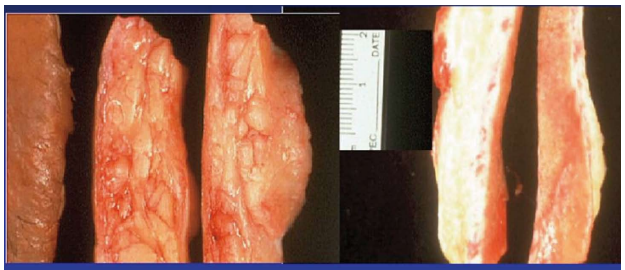
The major work on lung pathophysiology in burn trauma and smoke inhalation injury has been performed at the University of Texas Medical Branch in Houston, Texas[8,42-44]. They have shown therapeutic benefits of rhAT on burn injury and pulmonary function in their well-established ovine burn and smoke inhalation-induced model of acute lung injury/acute respiratory distress syndrome (ARDS)[8,42-44]. The ovine model is a 48 h protocol of burn and smoke inhalation injury in sheep with different medication regimens[8,42-44]. Murakami *et al*[8] investigated the treatment impact of rhAT on sepsis after smoke inhalation in sheep and found that rhAT attenuated the septic shock and the acute lung injury and maintained platelet counts at baseline. Enkhbaatar *et al*[42] were able to prevent the formation of airway fibrin clots causing airway obstruction and Acute Lung Injury and ARDS, with aerosolized anticoagulants (rhAT and heparin) and attenuated all the expected pulmonary pathophysiology.

In contrast to the Kybersept trial where the combination of phAT and heparin increased bleeding episodes, there was no increased bleeding noted by the combination of intravenous rhAT and aerosolized heparin[42]. This may possibly be a result of the increased affinity of rhAT to heparin, and less competition for attachment to the endothelial surfaces of blood vessels. The other explanation may be that the mode of agent delivery by separate intravenous and aerosolized routes results in different modes of interaction with the coagulation cascade and fibrinolysis. Rehberg *et al*[43] put together a useful compendium of their research with the ovine model and pulmonary pathophysiology in burn trauma. Two centers have described the phenomenon of leukocyte activation contributing to pulmonary vascular permeability and pulmonary edema in conjunction with inflammatory agents such as thrombin which promotes systemic capillary leakage and systemic interstitial edema[44,45].

DIC

DIC is defined by the International Society on Thrombosis and Hemostasis as an "acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes"[46]. It is a clinicopathologic diagnosis and requires the following laboratory diagnostic tests in an acute care setting: Platelets $\leqslant$ 100000/mm^3, increased fibrin related markers as D-dimer or fibrin degradation products, a prolonged prothrombin time (PT), a prolonged activated partial thromboplastin time (aPTT), and a fibrinogen (Fbg) < 1 g per liter[46]. Depending on the score, it can be diagnostic of either overt or non-overt DIC[46]. These required parameters for diagnosing DIC have not always been utilized by studies on burn in the literature. The clearest indication for use of AT replacement in trauma may be in the treatment of severe thermal burns. Hemostatic interactions are composed of the coagulation system, the fibrinolytic system, cellular elements (platelets, endothelium), and vasculature balanced in an intricate interrelationship to maintain homeostasis. Most of the global markers of hemostasis as PT, aPTT, and Fbg are not sensitive enough to detect a hypercoagulable state, changes in fibrinolysis, or non-overt DIC. Thus, PT, aPTT, and Fbg levels provide only a superficial impression of hemostasis and become abnormal only when severe coagulation-related disorders are established. Acute thermal injury initiates an activation of coagulation and fibrinolysis resulting in either an overt or non-overt DIC, which increases in severity with the severity of the injury (%TBSA/inhalation injury)[35,47,48]. These hemostatic abnormalities are a result of increased consumption of coagulation and fibrinolytic factors, dilution by the resuscitative fluids, and loss of plasma and fluids through the injured integument. AT concentrates have been used successfully in patients with DIC[20-23].

Significant coagulation abnormalities in burned patients have been demonstrated in the literature for the past 30 years. A detailed discussion of these would deserve a separate review. Prior to providing phAT concentrates to burn trauma patients, both Kowal-Vern *et al*[35] and Lavrentieva *et al*[47] investigated the coagulation and fibrinolytic markers in these burn patient populations to determine the extent of the coagulopathy present. Most pronounced was the decrease in AT, which was significantly suppressed on the first day of burn injury and correlated with the degree of burn injury; it was also the earliest to recover by day 5 to within normal



Comparison of AT(H)-treated skin on the left to the control burnt skin on the right of the ruler. There are more microthrombi in the control burnt skin beneath the surface. The under-surface of the burn is more vascular in the AT(H)-treated skin

Figure 5 A representation of the pathology in third degree burnt skin from a patient treated with plasma-derived antithrombin and in patient without plasma-derived antithrombin treatment. Whereas the skin beneath the control eschar is dead and non-viable with clotted and coagulated blood vessels, the skin and subcutaneous tissue beneath the phAT-treated skin is more viable in comparison with fewer thrombi (personal file AKV). phAT: Plasma-derived antithrombin.

levels[35]. These abnormalities caused an increased state of fibrinolysis and thrombogenicity in the patients, which was confirmed by specific markers of activation such as D-dimer, TAT complex, plasminogen activator inhibitor-1, and tissue plasminogen activator[35,47].

The DIC pathophysiology initiates coagulation and fibrinolysis through endothelial cells or tissue injury, with release of cytokines and other acute phase reactants. Once activated, the proteolytic enzymes, thrombin and plasmin, circulate systemically; their respective concentration determines either a bleeding or thrombotic tendency. AT protects the body against excess clotting by neutralizing thrombin; it is the most important physiological inhibitor of thrombin and factor Xa. In all instances of significant trauma, AT is consumed and plasma AT levels may rapidly decrease to levels at which the process of coagulation will proceed unchecked, quickly leading to deficits in oxygenation, organ failure and shock. There is a significant body of literature that correlates low levels of plasma AT following severe injury and trauma, with an increase of organ failure and death. AT replacement may affect the outcome of all of these conditions.

SIRS

The human body maintains homeostasis with all systems such as coagulation, inflammation, and innate immunity on a daily basis; any insult such as burn, inhalation, infection, sepsis induces a SIRS reaction to control and heal the injury imposed on the body[49]. The cytokine cascade initiates pulmonary inflammation even in the absence of smoke inhalation. AT is a key protagonist affecting not only the coagulation cascade, but also modulating the cytokine release and a major anti-inflammatory agent in plasma, counteracting the boundless SIRS release on the homeostasis of an acutely injured burn patient. AT promotes the release of prostacyclin on the endothelial surface which, as an anti-inflammatory agent, counteracts the production of monocytes and inhibits the release of cytokines such as TNF-α[13,14]. Hur *et al*[50] evaluated 67 burn patients with 27 cytokines and found that IL-1RA, IL-6, and MCP-1 may be used to predict mortality[50]. It appears that the presence and intensity of cytokines, chemokines and growth factors in the pulmonary bronchi and alveoli corresponds to the severity of the inhalation injury[51]. Neonatal rats receiving 100% oxygen for 9 d developed pulmonary edema and hypercellularity on days 1-3 which resolved by days 6-9; this condition was accompanied by the production of TNF-α and IL-6 in the bronchoalveolar lavage which were not present in the control rats[52]. Intra-alveolar TNF-α and IL-6 were also significantly increased in a rat model subjected to burn and inhalation injury[53].

Thrombosis and thromboembolism

There is an interrelationship between the degree of burn and the extent of thrombosis in burned tissue[54]. A second-degree burn has thrombi in the venules only, and a third-degree burn has thrombi in the venules and arterioles[55]. Cotran *et al*[56] have elegantly demonstrated by electron microscopy, in a rat model, that after a mild thermal injury and at the periphery of more severe burns, there is an increase in vascular permeability produced by gaps in the endothelium with no demonstration of endothelial damage[56]. As the severity of thermal injury increases, arterioles, small vessels, and capillaries undergo endothelial necrosis or stasis; larger vessels may continue to leak[56]. When stasis occurs, an amorphous material, chylomicra or thrombi of platelets, and necrotic debris clog the vascular lumen[56]. Animal studies have shown that the presence of infection and sepsis induces a significant increase in thrombosis and distant pyogenic abscesses[56-58]. Autopsy cases have shown pulmonary microthrombi and partially dissolved fibrin in vessels of burn patients contributing to sludging of cells in vessels[59]. However, there have been no prior published histopathological representations of "normal" and phAT-treated human third degree burnt skin, Figure 5 (unpublished data). Subcutaneous tissue vascular thrombi and debris are depicted in Figure 6 (unpublished data).

Cardiac function

Burn patients are known to have myocardial dysfunction which increases in severity with the severity of the injury and is worse if there are any cardiac co-morbidities present. In their ovine burn and smoke inhalation model, Rehberg *et al*[60] have noted that post injury infusion of 6 U/kg per hour of rhAT for 48 h improved myocardial contractility and decreased myocardial oxygen consumption. In addition, TNF-α and IL-6 were not released and the sheep did not accumulate as much systemic fluid[60].

Bacterial translocation

Many of the infections seen in burn patients appear to come from the bacteria transferred from the gut into the systemic circulation to provide the nidus for the infectious complications of burn patients[61]. The ovine model of

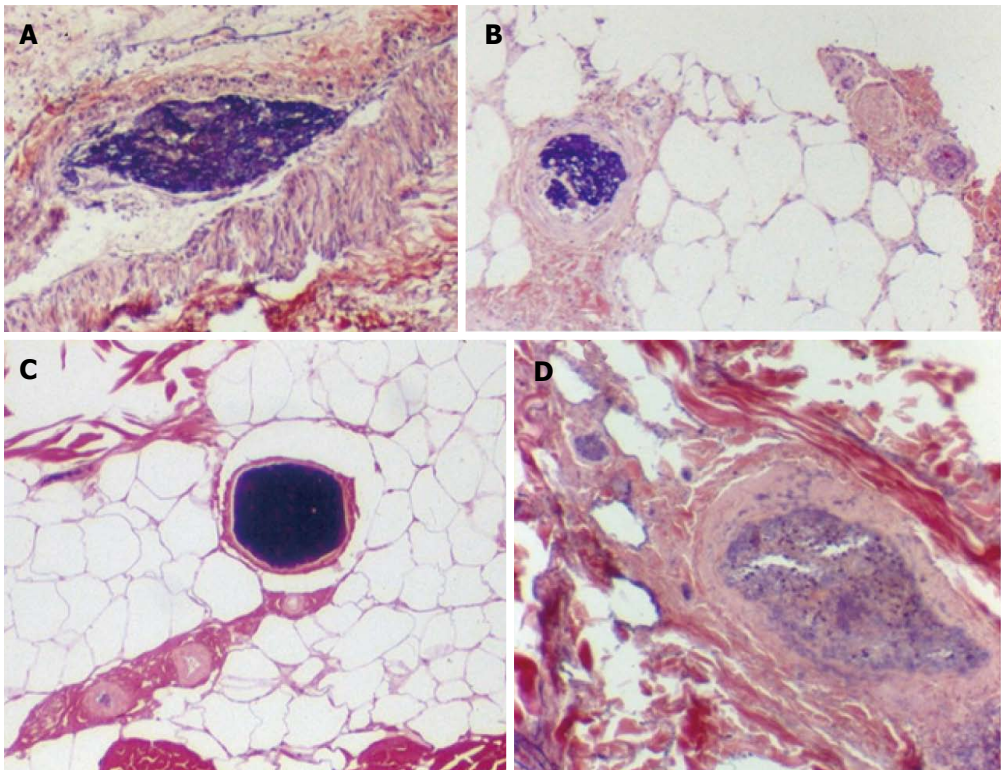


Figure 6 The thrombi, sludge and necrotic debris in burnt skin subcutaneous tissue blood vessels. A: Illustrates a blood vessel with sludge and fibrin debris; B: Depicts a small vessel with fibrin debris; C: Shows a clotted vessel; D: A larger vessel occluded with amorphous material. Magnification 40-100 ×, PTAH staining (personal file AKV).

burn and smoke inhalation injury documented that when the lung is injured, gut bacteria are transported systemically during acute injury because blood is shunted from the intestinal tract into the cardiopulmonary system, and through the systemic capillary leakage[43]. Using an Albino rat model, Herek infused the animals with phAT with 250 U/kg phAT prior to infecting them and creating a burned surface; phAT-treated rats had reduced intestinal villi degeneration and decreased bacterial translocation to mesenteric lymph nodes, spleen and liver compared to sham and control rat ($P < 0.02$)[62]. This study followed the work of Ozden *et al*[63] who showed that an infusion of phAT prevented an ischemic reperfusion injury in the rat.

DISCUSSION

There are two forms of AT used in these studies-rhAT and phAT. rhAT has been primarily used in basic/animal research studies, while phAT has been used in clinical studies. This may lead to questions about the relevance of the basic science studies to human care. The safety of the commercially produced phAT and rhAT concentrates in treating acquired and congenital AT (H) deficiencies has been well documented. High dose AT replacement has been supported in polytrauma and patients with septic shock and DIC[20,23,25].

AT use in disseminated intravascular coagulopathy and sepsis has been evaluated but has not yet been proven useful conclusively[3-6]. It is still worthwhile to pursue AT as a potential treatment in burn and inhalation injury[64]. AT would be of extreme value to the (3%-9% of burn patients with ⩾ 25% BSA) as well as to inhalation injury patients. With the research recommendations for high AT dosing (> 200%), the lack of bleeding during burn eschar removal may eliminate the need for blood transfusions, an intervention known to increase infectious complications and mortality in burn patients[65]. There are no new products in development with both anticoagulant and anti-inflammatory potential such as those possessed by phAT and rhAT to treat severe thermal burns. Not only do rhAT and phAT have the potential to inhibit thrombin and thrombin generation, they can also reduce the systemic inflammatory response that contributes to pulmonary and organ failure, and shock. The vast majority of products in active clinical development for the treatment of burns and inhalation injury does not address systemic injury and falls into the following categories: topical wound healing formulations, artificial skin products and temporary wound coverings, products for the control of bacterial colonization at wound sites, cultured skin and cells for dermal tissue repair, and proteolytic enzymes.

Future research to maximize the practical impact on the field

AT research requires a multicenter randomized placebo-controlled clinical trial. Accrual may be challenging because of smaller numbers (3%-9% of the burn population) than those of patients with sepsis or DIC, but 100-200

patients with reproducible and creditable results would likely determine the utility of AT therapy. This is certainly attainable.

Going forward, primary research objectives should be to determine whether rhAT can safely replace phAT and can maintain AT plasma levels between 200%-250% (normal AT plasma level = 80%-120%) in the first three days post-burn. Secondary objectives are to determine whether patients who receive rhAT or phAT realize significant reductions in pneumonia rates, extent of grafting needed, acute care stays, mechanical ventilation, the number of days of supplemental oxygen, positive end-expiratory pressure, and mortality. Decreases in the frequency of organ failure may also be found. It would also be quite worthwhile to assess the effect of high-dose AT on burn eschar "peeling off" to decrease the need for operative excision.

The lower cost of rhAT may also allow for dissemination of this treatment approach in lower income international communities, where burn injuries are prevalent, highly morbid and often fatal.

CONCLUSION

AT therapy for patients with major burn and inhalation injuries may be a very valuable adjunct to standard treatment. The current literature has shown, albeit in small studies in the civilian population and animal research, that AT therapy has a positive effect on pulmonary function, wound healing, with a decrease in pneumonia and mortality. rhAT may be a very viable option because the literature has shown that it is safe in humans and animals. AT infusions have shown a positive effect on capillary leakage, pulmonary function, wound healing, DIC, inflammation, cardiac function and decreasing bacterial translocation systemically, pneumonia and mortality. Human study volunteers, given endotoxin and rhAT concentrates in doses as high as 200% and 500% of normal AT levels, tolerated them safely. It is time for a multicenter, randomized, placebo-controlled. Standardization of burn trauma patients should include the DIC scoring system guidelines recommended by the International Society of Thrombosis and Hemostasis[46]. AT levels should be targeted to more than therapeutic levels (200%-250%) over a four day period after injury for the most beneficial clinical response in burn patients with $\geqslant$ 25% TBSA. rhAT pharmacokinetics should be initiated in burn and inhalation patients to determine the appropriate dosage for treatment response. Each of the proposal elements represents a significant technological challenge and medical advance. The development of this treatment modality has universal benefits for severe burn trauma patients, both on the battlefield or in the civilian sector. In addition, the broad benefits of AT treatment may be widely applicable in a variety of traumatic injuries and acute care settings.

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REVIEW

Alcoholism and critical illness: A review

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Abstract

Alcohol is the most commonly used and abused drug in the world, and alcohol use disorders pose a tremendous burden to healthcare systems around the world. The lifetime prevalence of alcohol abuse in the United States is estimated to be around 18%, and the economic consequences of these disorders are staggering. Studies on hospitalized patients demonstrate that about one in four patients admitted to critical care units will have alcohol-related issues, and unhealthy alcohol consumption is responsible for numerous clinical problems encountered in intensive care unit (ICU) settings. Patients with alcohol use disorders are not only predisposed to developing withdrawal syndromes and other conditions that often require intensive care, they also experience a considerably higher rate of complications, longer ICU and hospital length of stay, greater resource utilization, and significantly increased mortality compared to similar critically ill patients who do not abuse alcohol. Specific disorders seen in the critical care setting that are impacted by alcohol abuse include delirium, pneumonia, acute respiratory distress syndrome, sepsis, gastrointestinal hemorrhage, trauma, and burn injuries. Despite the substantial burden of alcohol-induced disease in these settings, critical care providers often fail to identify individuals with alcohol use disorders, which can have significant implications for this vulnerable population and delay important clinical interventions.

Key words: Alcoholism; Alcohol withdrawal delirium; Alcohol-related disorders critical illness; Intensive care; Pneumonia; Sepsis; Acute respiratory distress syndrome; Delirium; Trauma

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Core tip: Alcohol abuse is a major problem among hospitalized patients, and alcoholics are predisposed to developing critical illness while also facing increased rates of complications and mortality compared to non-alcoholics. The objective of this review is to examine the literature and summarize specific disorders encountered in intensive care unit settings that are impacted by alcoholism. Since alcohol use disorders are poorly recognized in hospitalized patients, this effort aims to raise awareness for critical care practitioners who frequently manage these susceptible

patients.

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INTRODUCTION

Social, pathological, and medicinal uses of alcohol have been a component of human tradition for thousands of years. While there are obvious therapeutic properties of alcohol, its excessive consumption poses a significant burden to healthcare systems in the United States and globally. Indeed, alcohol has become the most widely used and abused drug in the world[1]. A national survey illustrated that more than 50% of individuals above the age of 12 drink alcohol regularly on at least a social level, almost a quarter participate in binge drinking, and 7% described habitual heavy consumption, which translates into over 17 million Americans[2]. Epidemiological data report the lifetime prevalence of alcohol use disorders in the United States to be an astounding 18%[3]. The economic consequences of alcohol abuse have been estimated to be upwards of $200 billion annually, of which 11% is directly attributable to healthcare costs[4]. These figures are also likely underestimated as they fail to incorporate data from patients whose alcohol use disorders went unrecognized by their clinicians, a situation that occurs commonly in inpatient settings.

Driven by the widespread systemic effects of alcohol, multiple comorbidities, and poor nutrition, individuals with alcohol use disorders frequently require hospital admission for ailments both related and unrelated to alcoholism. Studies on hospitalized patients have suggested that between 20% to 40% of inpatients have alcohol-related conditions[5-7]. The effect is particularly felt in medical and surgical intensive care units (ICUs), which have been overwhelmingly impacted by the burden of unhealthy alcohol use. Alcoholics are not only at an increased risk for suffering critical illness, but they also experience a greater likelihood of complications, poorer outcomes, and increased healthcare utilization compared to those patients who do not have alcohol use disorders. Despite these observations, recognition of alcohol use disorders in hospitalized patients and particularly among individuals in the ICU is inadequate. This review will focus on specific conditions encountered in the critical care setting that are impacted by the considerable burden of pathologic alcohol consumption.

RECOGNITION OF ALCOHOL USE DISORDERS

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) recognizes the potential benefits of moderate alcohol consumption. According to dietary guidelines, "moderate" is considered to be an average of no more than two standard drinks per day for men and one standard drink per day in women[8]. Research from the NIAAA shows that staying within these weekly limits as well as not exceeding more than 3 drinks in any given day for women and 4 drinks for men poses a very low risk for developing an alcohol use disorder (AUD). An AUD is an unhealthy pattern of alcohol use that causes significant clinical impairment and has been explicitly defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) to meet at least two of 11 specified criteria[9]. The total number of criteria that are satisfied determines the severity, with two the three symptoms denoting a mild AUD, four to five signifying a moderate disorder, and six or more representing a severe problem. The DSM-V has abandoned the categorizations of "alcohol abuse" and "alcohol dependence" that were previously defined in the earlier edition, DSM-IV[10]. While alcohol abuse and dependence represent different physiological effects of alcohol, for classification purposes these terms have been replaced with the single characterization of an alcohol use disorder.

Given that AUDs are common in critical illness and contribute significantly to morbidity and mortality, it is surprising that we are so poorly equipped to recognize the presence of these disorders in this population. Excessive alcohol use impacts one out of every four to five admissions to the ICU[11]. One review of the literature reported this frequency to be as high as 33%[12], and the rate of AUDs are even higher among patients admitted after traumatic injury[13]. In parallel, studies among hospitalized patients with alcohol use disorders revealed that clinicians correctly identified the diagnosis in only 25% of cases[14], and in critical care settings almost three quarters of surveyed ICUs used no tool to assess for alcohol use disorders and alcohol withdrawal syndromes[15]. Several explanations may support these findings. First, individuals with alcohol use disorders may not always be forthcoming about the extent of their drinking, and worse, may not recognize that they themselves have a problem. Second, during acute illness-and especially in the ICU setting-patients may be unable to provide history or suffer from alteration in mentation that either precludes the gathering of this information or renders it significantly more challenging. Finally, practitioners may fail to elicit this history for a variety of reasons, such as a perceived lack of relevance of this information to the acute presentation. Regardless of the rationale, failure to recognize the impact of alcohol-related disease during critical illness can have significant implications for this vulnerable patient population. Precisely, it is important for critical care providers to understand that the potential for complications from acute interventions is heightened, and possible therapeutic opportunities may be delayed if alcohol use disorders are not appropriately identified.

ALCOHOL, DELIRIUM AND WITHDRAWAL SYNDROMES

Delirium is an acute state of confusion that is characterized primarily by inattentiveness. While many risk factors have been identified, medical illness commonly precipitates as well as exacerbates delirium. Thus, it occurs with high prevalence among hospitalized patients. Experts reveal that delirium occurs in about 30% of older patients at some point in time during their hospitalization, and individuals who develop delirium during their hospital stay have greater morbidity and mortality than those who do not[16,17]. In the ICU, delirium may perhaps be the most commonly encountered diagnosis with its reported prevalence reaching as high as 70%-90% depending on the patient population and method of assessment[18,19].

In a recent study, Mehta *et al*[20] assessed different risk factors for the development of delirium among critically ill, mechanically ventilated patients and found that delirium was significantly more common among those with a history of alcohol use compared to those without this history. Importantly, in this same study, those individuals that developed delirium had a longer duration of mechanical ventilation, a greater likelihood of requiring tracheostomy, and an overall longer hospital stay compared to those who did not develop delirium. Alcohol abuse as a risk factor for the development of delirium was also confirmed in a recent meta-analysis[21]. In the multivariate analysis, alcohol use had the highest odds ratio for the development of delirium after advanced age and mechanical ventilation. This key finding suggests that an assessment for alcohol use is absolutely necessary in critical care settings to identify those individuals who have a greater propensity towards experiencing delirium and ultimately poor outcomes. While many risk factors cannot be modified, it would be valuable to identify those patients with the greatest threat of developing delirium so that clinicians acknowledge and readily act upon those factors that are modifiable.

Recognition and identification of alcohol use disorders in critically ill patients is essential for a variety of other reasons as well. Specifically, chronic alcohol consumption significantly increases possibility of developing alcohol withdrawal syndromes, which include withdrawal seizures, alcoholic hallucinosis, and delirium tremens. Withdrawal syndromes, and especially delirium tremens, can be life threatening and occur in about 20% of alcoholics who stop drinking acutely[22]. Given the prevalence of alcohol use disorders in ICUs, this represents a significant burden among critically ill patients. Further, treatment of alcohol withdrawal syndromes has been linked to greater morbidity and resource utilization particularly in the ICU[23]. Delirium tremens carries a mortality rate between 5% and 15%[24], and treatment guidelines underscore the importance of early identification to ensure better effectiveness of therapy in these individuals. Despite its life-threatening nature, there continues to be a relative lack of data on how best to identify, screen, and prevent patients with a history of alcohol abuse from developing withdrawal syndromes, but the awareness of alcohol use disorders during critical illness is paramount.

ALCOHOL, PNEUMONIA, AND ASPIRATION

The connection between alcohol use and respiratory infections can be traced back over a century. William Osler in his book Principles and Practice of Medicine noted that a tendency towards alcohol abuse was extremely important in predisposing individuals to developing pneumonia[25]. In the United States, pneumonia is the eighth most common cause of death overall and the leading cause of death from an infection. Given the high morbidity and mortality associated with pneumonia, it is a commonly encountered diagnosis in the ICU. Further, pneumonia not only often necessitates ICU admission, it can also occur as a complication critical illness after traumatic injury, post-operative status, and mechanical ventilation.

More recent studies have continued to uphold the finding that alcoholism is an important risk factor for the development of both "typical" pneumonias as well as more severe respiratory infections caused by more virulent and atypical organisms. In a study among patients with community-acquired pneumonia, de Roux *et al*[26] showed that *Streptococcus pneumoniae* was seen more frequently and occurred with higher severity scores in alcoholics compared to non-alcoholics. In another prospective study among patients admitted with community acquired pneumonia, Chalmers *et al*[27] performed multivariate regression analysis and found that a history of alcohol use was an independent risk factor for the development of complicated parapneumonic effusion and empyema, further illustrating that alcoholic subjects have a more complex disease course even with so-called typical infections[27]. Prior to these investigations, Marik[28] undertook a study to identify clinical, microbiological, and prognostic features of patients with septic shock from community-acquired pneumonia. He showed that patients who presented with infections secondary to *Pseudomonas* and *Acinetobacter* had a particularly high mortality greater than 80%. In his study, the only variable that identified patients who developed infections from these virulent organisms was a history of alcohol abuse. In parallel, a prospective study by Bochicchio *et al*[29] implicated alcohol abuse in both the severity and frequency of ventilator-associated pneumonias in trauma patients admitted to the ICU.

There are several mechanisms that predispose individuals with alcohol use disorders to the development of these more severe pneumonias. First, chronic alcohol consumption alters the oropharyngeal flora such that is colonized by more gram-negative organisms[30]. Second, states of inebriation blunt upper airway reflexes and render these individuals more susceptible to aspiration of these more virulent bacteria[31]. Third, experimental

models have demonstrated that chronic alcohol exposure impairs normal host defense mechanisms of the airway such as mucociliary clearance[32]. Finally, pathologic alcohol consumption impairs function of the primary innate immune cell of the lower airways-the alveolar macrophage-in both experimental models and human subjects[33-37]. Taken together, these data highlight the significant alterations in host immunity that predispose alcoholics to the development of lower respiratory tract infections.

ALCOHOL AND SEPSIS

Sepsis is a systemic inflammatory syndrome that occurs as a result of a severe infection. It is a leading cause of death in the hospital and, as a result, is a frequently encountered diagnosis in the ICU. Studies have indicated the incidence is rising and amounts to more than a million cases annually[38]. Importantly, the mortality from sepsis is substantial and increases across the spectrum from SIRS to septic shock, which has a mortality rate close to 50%[39]. The role of alcoholism in increasing the risk and severity of sepsis has been shown in both experimental models and human studies. In 2013, Yoseph *et al*[40] demonstrated that mice that were alcohol-fed for 12 wk have almost double the mortality as water-fed mice when they were subjected to the same septic insult. The authors concluded that alcohol altered intestinal integrity and host immune response, which explained the significant difference in mortality. The prior year, Barros *et al*[41] showed similar findings in rats that were alcohol-fed for 4 wk. Interestingly, when the alcohol-fed rats were separated into two groups based on amount of alcohol consumed, they found that mortality was six fold higher on animals that received higher doses of alcohol compared to those receiving lower amounts of alcohol. In fact, those animals that consumed less alcohol had mortality rates similar to those that did not receive any alcohol at all. These findings are consistent with the idea that in moderation alcohol is not harmful, but excessive consumption is detrimental to health. These authors also demonstrated that cytokine profiles were significantly different in alcohol-fed compared to control-fed rats, indicating that chronic alcohol consumption led to a greater severity of infection. Several other experimental sepsis studies are consistent with the idea that sepsis has worse outcomes in the setting of alcohol abuse[42-44].

Human studies have largely been consistent with the well-established findings in experimental models that chronic alcohol use both predisposes to and worsens outcomes of sepsis. Specifically, when O' Brien *et al*[45] examined over 11000 patients admitted to the ICU of two urban hospitals over a six-year time frame, they found that alcohol dependence was independently associated with sepsis, septic shock, and mortality. Previously, Moss *et al*[46] showed in a prospective epidemiological study of 220 critically ill patients with septic shock that alcohol abuse was a significant risk factor for developing both pulmonary and non-pulmonary organ dysfunction. Taken together, these findings-along with an abundance of supporting experimental studies-highlight that the presence of alcohol use disorders, independent of other patient and illness characteristics, leave individuals vulnerable to infection, which occur with greater severity and more complications, compared to those who do not abuse alcohol.

ALCOHOL AND ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a form of inflammatory lung injury and hypoxemic respiratory failure with specific clinical and pathological features. It affects about 200000 individuals in the United States annually and carries a mortality risk that ranges anywhere from 20% to 50%[47]. It is a common diagnosis in the ICU and occurs in about 15% to 20% of all patients that require mechanical ventilation. Important risk factors for the development of ARDS include sepsis, traumatic injury, pneumonia, and aspiration. As discussed earlier in this review, each of these risks is significantly increased in the alcoholic patient.

A landmark study in 1996 identified alcohol abuse as an independent risk factor the development of ARDS[48]. In this prospective study, 351 individuals from medical and surgical intensive care were enrolled if they had a previously identified risk factor for ARDS. The incidence of ARDS for the entire population was 29%, but those with a history of alcohol use had almost twice the incidence compared to non-alcoholics (43% *vs* 22%). The risk was even higher among those specific patients with sepsis as their risk factor. In this group, 36% developed ARDS, but alcoholics had an incidence of 52% compared to 20% among non-alcoholics, more than doubling the risk. More importantly, mortality was also significantly higher among alcoholics who developed ARDS. In the aforementioned follow-up study by Moss *et al*[46] performed in patients with septic shock, the risk for developing ARDS was an astounding 70% for those who had a history of alcohol abuse compared with 31% for those who did not have this history.

These initial observations in ARDS patients inspired a great deal of investigation on the mechanisms by which alcohol abuse increases susceptibility to lung injury and ARDS. Animal models have focused on the alveolar epithelium, as leakiness of this barrier system and consequent pulmonary edema is the characteristic finding in ARDS. It is worth mentioning that alcohol abuse plays a complex and compounding role in lung injury, as pneumonia, sepsis, aspiration, and traumatic injury are leading risk factors for the development of ARDS, but alcohol abuse by itself does not cause injury unless it is coupled with an additional insult. However, experimental studies have demonstrated that alcohol abuse primes

the alveolar epithelium for injury by promoting oxidative stress[49], increasing epithelial permeability and protein leak[50], and impairing fluid clearance through alterations in tight junction proteins within the epithelial barrier[51]. These findings at least partially explain why alcoholics, independent of their risk for developing pneumonia and sepsis, are more likely to develop acute lung injury. While we still do not have any approved therapies aimed explicitly at reversing alcohol-induced pulmonary dysfunction, experimental investigations and early human studies show promise that specific nutritional supplements and antioxidants may one day have a role in the treatment of this phenotype[33,52-54].

ALCOHOL AND GASTROINTESTINAL ILLNESS

Chronic alcohol consumption has deleterious effects throughout the entire gastrointestinal system, including the liver, pancreas, esophagus, gastric mucosa, and malabsorption syndromes involving the small intestine. Cirrhosis of the liver is the characteristic organ dysfunction induced by longstanding unhealthy use of alcohol. According the American Liver Foundation, in the United States alcoholism is the number one cause of cirrhosis and chronic liver disease, which combine to represent the twelfth most common cause of death in the country[55]. In addition to morbidity and mortality associated with cirrhosis itself, it is an important comorbidity that portends a worse prognosis in critical illness as well. For instance, Watari *et al*[56] evaluated mortality and prognostic factors in individuals admitted for community-acquired pneumonia and found that liver cirrhosis was one of three factors that was associated with 30 d mortality. Importantly, cirrhosis was the only factor that was a pre-existing condition as the other two predictors-hypotension and hypoxemia-were directly related to the severity of actual infection.

In addition to liver disease, other gastrointestinal illnesses are also affected by alcoholism. For instance, acute pancreatitis is the most common gastrointestinal cause of hospitalization in the United States, with alcohol-induced disease accounting for 30% of cases[57,58]. This finding represents a significant disease burden and many of these cases-and especially severe forms-require ICU admission. Gastrointestinal hemorrhage is also a frequent cause of ICU admission and has a significant disease burden with an annual incidence of about 100 cases per 100000 in the United States[59]. In this study, peptic ulcer disease, mucosal erosions, and esophageal varices made up over 80% of cases, all of which are impacted by alcohol abuse. Alcoholism has been implicated in peptic ulcer disease[60,61], and alcohol-induced gastropathy and gastro-esophageal varices are known complications of alcoholic cirrhosis. While an alcohol abuse history is more predictive of a variceal source of gastrointestinal hemorrhage[62], studies have clearly shown that alcoholics are significantly more likely to have complications such as rebleeding from non-variceal sources of blood loss as well[63,64]. Taken together, these observations illustrate the profound impact that alcohol use disorders have in gastrointestinal disease and critical illness.

ALCOHOL AND TRAUMA

Trauma is one of the leading causes of mortality worldwide, and in the United States is the leading cause of death in those under the age of 35[65]. The Centers for Disease Control and Prevention reports that approximately 50 million individuals receive medical care for trauma annually, and traumatic injury comprises upwards of 30% of all ICU admissions[66]. The role of alcohol use has long been recognized as a contributor to traumatic injury for both unintentional (*i.e.,* fire, fall, motor vehicle accident, drowning) and intentional (*i.e.,* suicide, homicide, assault) injuries and death. It is estimated that 50% of all alcohol-related deaths are due to injury, and alcohol is the third leading cause of preventable death in the United States[67].

Studies examining the effects of alcohol intoxication at the time injury have produced conflicting results. Blondell *et al*[68] evaluated over 1300 patients hospitalized after traumatic injury and found that almost a quarter of them had positive blood alcohol levels, while a similar study by Cornwell *et al*[69] found that more than 50% screened positive for blood alcohol levels. Interestingly, Blondell *et al*[68] found that those that were acutely intoxicated had shorter lengths of stay and lower mortality rates. Other studies have shown worse outcome for acute intoxication[70,71], while some have shown no difference when compared to patients that are not intoxicated[69,72]. There may be several reasons for this conflicting data. First, these studies only examine the effect of acute intoxication on patients with trauma, which may not represent those that have chronic alcohol use disorders. Second, blood alcohol concentrations at the time of presentation may not tell an accurate story of the true alcohol exposure depending on the time that elapsed between exposure and presentation. Third, studies may use different cutoffs for blood alcohol concentration in order to be categorized as "intoxicated". Similarly, in this instance the blood alcohol concentration may not be representative of actual intoxication at the time of injury, and continues to fail in identifying the extent of chronic exposure. One study by Jurkovich *et al*[73] aimed to reconcile these differences by comparing the effect of acute intoxication against those that had an actual history of chronic alcohol abuse. Similar to Blondell's study, they found that acutely intoxicated patients had shorter lengths of stay and better outcomes, but those with behavioral and biochemical evidence of chronic alcohol abuse had a two-fold increase in complication rate. The complications seen in this study were consistent with known risk factors for alcoholics, including pneumonia and other infections. Later studies evaluating trauma and surgical patients are also consistent with findings that individuals with a chronic alcohol abuse experience worse outcomes[74-76].

While the effect of acute intoxication on trauma

outcomes in general may show conflicting results, the effect on burn injury is much more convincing. Specifically, the results of large review on the topic by Howland and Hingson[77] demonstrated that 50% of all people who died in a fire were legally intoxicated. A later study by McGill *et al*[78] compared alcohol users, drug users, and control subjects. They found that both alcohol users and drug users suffered significantly more severe burn injuries compared to control subjects. Mortality among alcohol users was twice that of drug users and six times that of control subjects. This study was interesting in that alcohol users, despite a similar injury pattern, had worse outcomes when compared to other substance abusers. In this study, it may not be completely unbiased to compare outcomes between the alcohol group and the control group since the extent of injury was more severe among the alcoholics. However, a more recent case-control study by Silver *et al*[79] matched burn-injured patients with a positive blood alcohol concentration to those without alcohol exposure. Due to the matching design, these researchers were able to match the control group by age, gender, and extent of injury (*i.e.,* total body surface area involved, inhalation injury, *etc.*). Despite a similar injuries and mechanism, those burn victims with positive blood alcohol concentration had significantly worse short-term and long-term outcomes with higher severity of illness scores, greater fluid requirements, worse acidemia, more than three-fold longer duration of mechanical ventilation, and more than double the ICU length of stay compared to matched controls. Taken together, these studies demonstrate the significant detrimental effects of alcohol exposure on burn injury outcomes.

OTHER CONSIDERATIONS

A history of alcohol abuse also has implications for critically ill patients undergoing surgery[75,80-83]. The accumulated data from these studies suggest that patients with alcohol use disorders who undergo surgery have greater risks for complications, including delayed wound healing, pneumonia, and infection. They also have longer ICU lengths of stay and increased mortality. These observations are analogous to the conclusions derived from studies on non-surgical alcoholic patients and suggest that surgeons may need to be judicious about considering major elective surgery in these susceptible patients.

While the focus of this review has been on known complications of alcoholism during critical illness, there is a potential for alcohol use disorders to play a role in previously unstudied associations. For instance, critical illness polyneuropathy (CIP) and myopathy (CIM) are significant complications of critical illness. Sepsis, systemic inflammatory response syndrome, multiple organ failure, and prolonged critical illness are crucial risks for developing CIP and CIM[84,85], and intriguingly these same factors are known threats that alcoholics face. Further, alcoholics are clinically prone to both myopathies and neuropathies[86,87]. While the risk for CIP and CIM with alcohol abuse has not been formally established, this may have specific implications for management. Experimental studies show that oxidative stress plays a role in alcoholic myopathy, and reversing this oxidant stress is able to attenuate the myopathy[88-90].

CONCLUSION

Alcohol use and abuse are commonplace in society and present a major burden for our healthcare system. Alcohol use disorders not only predispose individuals to develop critical illness, but also leave these vulnerable patients with longer ICU stays, more complications, and ultimately greater mortality. Despite the pervasiveness of alcohol use disorders in hospitalized patients, and especially among those admitted to the ICU, recognition of these disorders remains poor and no guidelines exist on the best way to screen for alcohol dependence and risk for withdrawal syndromes. While there may be several explanations for why alcohol use disorders are not consistently identified in the ICU setting, critical care providers should employ any and all methods to better evaluate their patients for these conditions and their potential implications. While there are currently limited therapeutic options aimed directly at combating the alcohol-induced organ dysfunction experienced by critically ill patients, earlier identification will allow for more timely intervention and an opportunity to assist these individuals to confront their addiction. Hopefully, this approach will lead to improved outcomes as we await newer treatments to benefit this susceptible patient population.

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REVIEW

Neuroprotective measures in children with traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is a major cause of death and disability in children. Severe TBI is a leading cause of death and often leads to life changing disabilities in survivors. The modern management of severe TBI in children on intensive care unit focuses on preventing secondary brain injury to improve outcome. Standard neuroprotective measures are based on management of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) to optimize the cerebral blood flow and oxygenation, with the intention to avoid and minimise secondary brain injury. In this article, we review the current trends in management of severe TBI in children, detailing the general and specific measures followed to achieve the desired ICP and CPP goals. We discuss the often limited evidence for these therapeutic interventions in children, extrapolation of data from adults, and current recommendation from paediatric guidelines. We also review the recent advances in understanding the intracranial physiology and neuroprotective therapies, the current research focus on advanced and multi-modal neuromonitoring, and potential new therapeutic and prognostic targets.

Key words: Paediatrics; Intracranial pressure; Traumatic brain injury; Neuroprotection; Paediatric critical care; Advanced neuromonitoring

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Core tip: Paediatric traumatic brain injury (TBI) causes significant morbidity and mortality. The modern management of severe TBI in children focuses on preventing secondary brain injury to improve outcome. In this article, we review the current management of severe TBI in children. We also review the recent advances in understanding intracranial physiology and neuroprotective therapies, advanced and multi-modal neuromonitoring, and potential new therapeutic and prognostic targets.

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INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability in children and young adults worldwide. It is considered a "silent epidemic" because the general public is mostly unaware of the scale of the problem[1]. In the United States, it is estimated that around 1.7 million people sustain TBI each year, and in Europe 235 per 100000 people are admitted to hospital following a TBI[2,3]. Data from many parts of the world consistently show peak incidence rates in children, young adults and elderly people.

TBI occurs when head suffers the influence of an external mechanical force. This force can displace brain inside the skull and induce injury against the meningeal membrane or the cranium. Acceleration and deceleration forces can also disrupt nervous tissue and blood vessels of the brain. All grades of injury can occur, ranging from mild to severe TBI with cerebral oedema or large collections of blood. Severe TBI, defined as a post resuscitation Glasgow coma scale (GCS) of less than 9[4], is associated with highest rates of mortality and significant morbidity in survivors often causing life changing disability and cognitive function loss[5].

The mechanism of injury in TBI comprises of primary and secondary injuries. The primary injury is the direct consequence of the initial physical insult. It comprises irreversible cell damage that is the main determinant of clinical outcome. In the secondary injury, inflammatory and neurotoxic responses triggered by the primary injury induce oedema, hypoperfusion, hypoxia and ischaemia[6-8]. These changes often lead to raised intracranial pressure (ICP), temperature dysregulation, loss of autoregulation and seizures[9]. Much of these secondary injuries may be amenable to intervention, and left untreated can significantly increase morbidity and mortality associated with TBI[6].

Raised ICP plays a key role in secondary brain injury[9]. Skull is a rigid fixed volume compartment; the three elements within it namely, the brain parenchyma, blood and cerebro-spinal fluid (CSF) are relatively incompressible and changes in the volume of one leads to compression of the other[10]. Beyond the limits of compensation, the pressure rises sharply, this can severely impact the cerebral blood flow (CBF). The secondary insults can also arise from systemic factors, hypoxia and hypotension post head injury being the key determinants for outcome[7,11].

Early stabilisation post TBI includes rapid assessment for life threatening injuries followed by secondary survey according to ATLS/APLS guidelines[12,13]. After the initial resuscitation to ensure adequate airway, ventilation and haemodynamic stability, early neuro-imaging is required to look for intra-cranial pathologies requiring surgical intervention and neuroprotection[14]. There is evidence to support multi-disciplinary input and protocolized management for improved outcomes from head injury[15]. All children with moderate to severe traumatic brain injury should ideally be managed in centres with expertise and experience in managing such patients. The contemporary post-injury resuscitation and management focuses on prevention and mitigation of secondary insults[7,14]. This review will focus on the neuroprotective measures to decrease the damage caused by secondary brain injury in children with TBI requiring intensive care treatment.

GENERAL INTENSIVE CARE MEASURES

Airway control and ventilation

All children with severe TBI and those with deteriorating GCS need definitive airway management with endotracheal intubation. As paediatric definitive airway needs specialist skills and experience, pre-hospital intubation at the scene for children with TBI is controversial[16]. However, early airway control is recommended to avoid hypoxemia, hypercarbia and aspiration[17]. The adequacy of oxygenation and ventilation should be measured continuously with pulse oximetry and end-tidal carbon dioxide (CO_2) monitoring respectively and serial blood gas measurements. In children with TBI requiring ventilation, arterial PaO_2 should be maintained above 11 kPa (saturations > 90%) and $PaCO_2$ between 4.5-5 kPa. Although there are no randomised controlled trials (RCT) to determine the exact values for PaO_2 in TBI, the damaging effects of hypoxia[17,18] and to a lesser extent hyperoxia[19] are well known. Similarly, the effect of CO_2 on cerebrovascular reactivity has been widely studied[19-21]. Hypercapnea causes vasodilatation leading to cerebral hyperaemia and hypocapnea causes ischemia by cerebral vasoconstriction[9,21,22].

Circulatory support

Hypotension (defined as systolic blood pressure below the fifth percentile for age) or shock any time after injury can have major implications for clinical outcome and should be actively prevented and aggressively treated with fluid boluses and vasoactive agents[16]. Isotonic saline is recommended for fluid resuscitation and maintenance. In the presence of hypotension, patient also needs careful evaluation for extracranial injuries as the potential source of blood loss[23,24]. It is important to consider adrenocorticotropic hormone (ACTH) deficiency in patients with refractory hypotension; TBI induced pituitary dysfunction has been reported in nearly one quarter of children with TBI in the acute phase[25,26]. As the primary injury often impairs cerebral autoregulation, the cerebral perfusion may become directly dependent on the mean arterial pressure. Management of blood pressure in the intensive care is one of the cornerstones of the management of severe TBI[14]. While hypotension can potentially cause brain ischemia, hypertension can exacerbate vasogenic oedema in the cerebral parenchyma[27] and requires careful titration of blood pressure based on various parameters studied (discussed in details under specific interventions).

Sedation, analgesia and neuromuscular blockade

Although there are no RCTs studying the effect of sedation on outcome, it's well known that any noxious stimulus

increases ICP[28] and cerebral metabolic demand for oxygen[29]. Appropriate sedation and analgesia reduces anxiety and pain, facilitates ventilation and general intensive care management, and helps reduce the cerebral oxygen demand, thereby reducing the risk of secondary brain injury[30]. In children, a combination of benzodiazepines and opioids is most often used. This combination can cause hypotension, so careful titration to the desired effect with continuous monitoring and management of blood pressure is essential to minimize risks of cerebral ischemia. Propofol, often used in adults, has restricted licence status in children, therefore, is only used in exceptional circumstances.

Neuromuscular paralysis can help reduce airway and intrathoracic pressure which improves the cerebral venous return. It can prevent shivering and posturing, and the lack of skeletal muscle movement also helps to reduce cerebral metabolic demand[30]. The main disadvantage of neuromuscular blockade is masking of clinical seizures which should then ideally be monitored by continuous electroencephalograph (EEG). Its continuous use can also induce myopathy, increase length of ventilation, and cause nosocomial pneumonia and cardiovascular side effects[31]. However, judicious neuromuscular blockage use in children with severe TBI can minimize complications[32]. Therefore, neuromuscular blockade is recommended as part of the first tier management of children with severe TBI[14].

Fluids and nutrition

There is no single best fluid for children with traumatic brain injury, but isotonic crystalloids are widely used and have good scientific basis. Normal saline or lactated ringer's solution should be the standard resuscitation fluid until further studies show a clear benefit from other therapies. Use of colloids is not routinely recommended and evidence suggests that use of albumin may have deleterious effects[33]. Fluid restriction is no longer recommended.

Nutritional support is required for tissue repair, wound healing and optimal organ function. Due to lack of evidence, there is no specific recommendation for the nutrition regimen. Adult data supports early introduction of feeds after haemodynamic stability aiming for full feeds, either enteral or parenteral, by the end of first week[34,35]. Hyperglycaemia frequently occurs associated with the stress response to injury; therefore glucose is not routinely added to maintenance fluids in early phase of recovery regardless of the child's age. Hyperglycaemia has been linked to poor neurological outcome in TBI[36-38] but the optimal glucose target has not been defined. Use of insulin to achieve tight glycaemic control may result in a net reduction in CSF microdialysis glucose and an increase in microdialysis glutamate and lactate pyruvate ratio (LPR) without conveying a functional outcome advantage[39]. Tight glycaemic control has also been associated with reduced cerebral extracellular glucose availability and increased prevalence of brain energy crisis, which in turn correlates with increased mortality[40]. Currently we recommend prevention of severe hyperglycaemia, keeping blood glucose levels below 180 mg/dL (10 mmol/L).

General care

Children should be nursed in neutral head position and head-end elevation by 15°-30° to improve cerebral venous drainage[41,42]. Good nursing care, with regular turning, eye care and physiotherapy are important. Stress ulcer prophylaxis and laxatives are used as per the child's requirements. Although evidence shows higher incidence of deep vein thrombosis (DVT) with increasing severity of trauma and increasing age in children[43], there are no universal recommendations for regular thromboprophylaxis in this age group. One study supports thromboprophylaxis to prevent DVT in paediatric trauma patients[44]. In our setting, compression stockings are routinely used in fully sedated and paralysed children with severe TBI, but the chemical prophylaxis is restricted to older children and is discussed on case by case basis.

SPECIFIC INTERVENTIONS

Intracranial pressure monitoring

The ICP can rise after TBI from either mass effect (haematoma) or cerebral oedema secondary to the injury. There is a direct association between raised ICP and poor clinical outcomes, and sustained raised ICP is an independent predictor of poor outcome following TBI[45-47]. While majority of evidence supports aggressive management of raised ICP[47-49], recent adult RCT failed to identify any benefit associated with ICP monitoring[50]. The results of this study[50] however need to be interpreted in the context of population studied and may not be generalizable to all TBI victims[51]. The lack of controlled trials for ICP monitoring has limited the recommendation (level Ⅲ) in the most up-to-date guidelines[14,52] although ICP monitoring remains the integral part in the management of patients with severe TBI in most centres.

There are various different methods for ICP monitoring using either fluid filled catheters or pressure microtransducers. Interventricular catheters are considered to be the gold standard for measuring ICP and also allow CSF drainage if ICP is high. However, there are practical limitations to their use including infection and technical difficulty in insertion in children with small ventricles[53,54]. Pressure microtransducers can reliably measure pressure from brain parenchyma (intraparenchymal) as well as epidural or subarachnoid spaces. Intraparenchymal probes are often preferred because they are easy to insert and have very low infection risk. However, they may not reflect the true ICP if there are pressure gradients within the cranium, and although the zero drift is minimal, they cannot be recalibrated once inserted[53].

The threshold for treating ICP in children has been extrapolated from adult guidelines[52]. There is some suggestion that the treatment thresholds for younger children and infants need to be different as the normal

values of mean ABP and hence Cerebral perfusion pressure (CPP) are lower in children[55]. Keeping the ICP < 20 mmHg is the standard part of management of severe TBI on PICU[14].

Our current local protocol uses an age related threshold for ICP in children (Figure 1). If the ICP stays above the target, we first optimise sedation and the ventilation targets. If it still stays up, we use hyperosmolar therapy and consider repeat neuroimaging. If the scan doesn't show any surgically correctible lesion (haematoma evacuation, ventricular drain), we move to tier 2 treatment (hypothermia, anticonvulsants). Decompressive craniectomy and thiopentone coma are used only in exceptional circumstances after multi-disciplinary input.

CPP

CPP is defined as the difference between mean arterial pressure (MAP) and ICP, and is considered the driving pressure for cerebral blood flow and perfusion. In the normal brain, cerebral autoregulation maintains CPP within a specific range to couple oxygen delivery with cerebral metabolic rate. However, TBI impairs the cerebral autoregulatory capacity making brain vulnerable to both systemic hypotension and raised ICP. In adults, keeping CPP above a recommended threshold (60 or 70 mmHg) is associated with improved clinical outcomes[52,55]; some paediatric evidence also supports targeting higher CPP in children[56,57]. However, there are age related differences in MAP, CBF, and cerebral metabolic rate and there are no studies to demonstrate active management of CPP above a target threshold reducing mortality or morbidity[14]. Therefore, defining an ideal CPP for children is challenging and the current guidelines support maintaining a minimum CPP of 40 mmHg and a threshold of 40-50 mmHg[14]. Targeting very high CPP with use of vasopressors and fluids is associated with serious systemic toxicity and does not give better outcomes[52]. Also, in the absence of autoregulation, very high CPP can increase cerebral blood volume leading to an increasing ICP and also increase vasogenic oedema by increasing the hydrostatic pressure across the capillary bed[27].

Our management targets are described in Figure 1, we achieve target CPP by maintaining systemic blood pressure towards the upper limit of normal blood pressure for age with the use of fluids to achieve normovolemia and inotropic support (most commonly noradrenaline infusion). However, if the ICP is very high, we do not increase MBP beyond the age related MBP limits and instead, focus on improving CPP by reduction in ICP.

Hyperosmolar therapy

Hyperosmolar therapy has been the hallmark of ICP management for decades. Hyperosmolar agents create osmotic gradient across the cerebral vascular bed, thereby decreasing oedema. They work best for acute rises in ICP. Various osmotic agents have been studied in the treatment of TBI, but mannitol and hypertonic saline are the most widely used.

Mannitol has been used to reduce raised ICP for close to a century. It reduces ICP by reducing blood viscosity (rapid response) and by an osmotic effect (delayed response)[58]. These effects are more pronounced when the blood brain barrier is intact and autoregulation is preserved. In TBI, these mechanisms may be disrupted, so the response can be variable[59]. Mannitol can also reduce intravascular volume by causing osmotic diuresis (which could have a negative impact on CPP) and has the potential to induce reverse osmotic gradient by accumulating in the brain parenchyma (which could cause an increase in ICP) especially with prolonged use[60].

Hypertonic saline has been studied extensively in the last few decades as treatment for raised ICP. It shares the same rheologic and osmolar properties with mannitol that lower the ICP. It can also act as a volume expander, enhance cardiac output, improve CBF and inhibit inflammation[61-63]. Current guidelines support the use of hypertonic saline, but make no specific recommendation on the concentration[14]. Different studies and institutions use various concentrations from 1.7% to 29.2%[64,65]; in our institute, we use 5% saline (Figure 1). Delivery through a central access is recommended (but not essential) due to high osmolality. We use 2-4 mL/kg boluses of 5% saline (Figure 1).

Serum osmolarity plays an important role in determining fluid shifts in injured brain. Low serum osmolarity can increase vasogenic brain oedema, so hyperosmolar agents are used to normalise or increase serum osmolarity. Different upper limits of osmolarity are recommended for treatment with mannitol (320 mOsm) and hypertonic saline (360 mOsm), respectively. If using hypertonic saline, serum sodium levels need to be monitored as well and kept < 160 mmol/L. Due to lack of evidence for mannitol use in children with TBI, hypertonic saline has been recommended as the preferred osmotic agent in management of paediatric TBI[65,66].

Children with TBI are also susceptible to develop disorders of salt and water, like central diabetes insipidus, cerebral salt wasting and syndrome of inappropriate anti-diuretic hormone. A detailed description of these is beyond the scope of this article, but a careful understanding and monitoring of serum and urine electrolytes and osmolarity is required[67].

Temperature control

Hyperthermia can cause significant secondary brain injury by increasing cerebral metabolic demand, promoting inflammation and decreasing the seizure threshold, so needs to be avoided aggressively to protect brain[68]. Temperature control to avoid hyperthermia has become an integral part of neuroprotection in children with TBI[14]. Inducing hypothermia to reduce cerebral metabolic demand, inflammation and seizures, is more contentious.

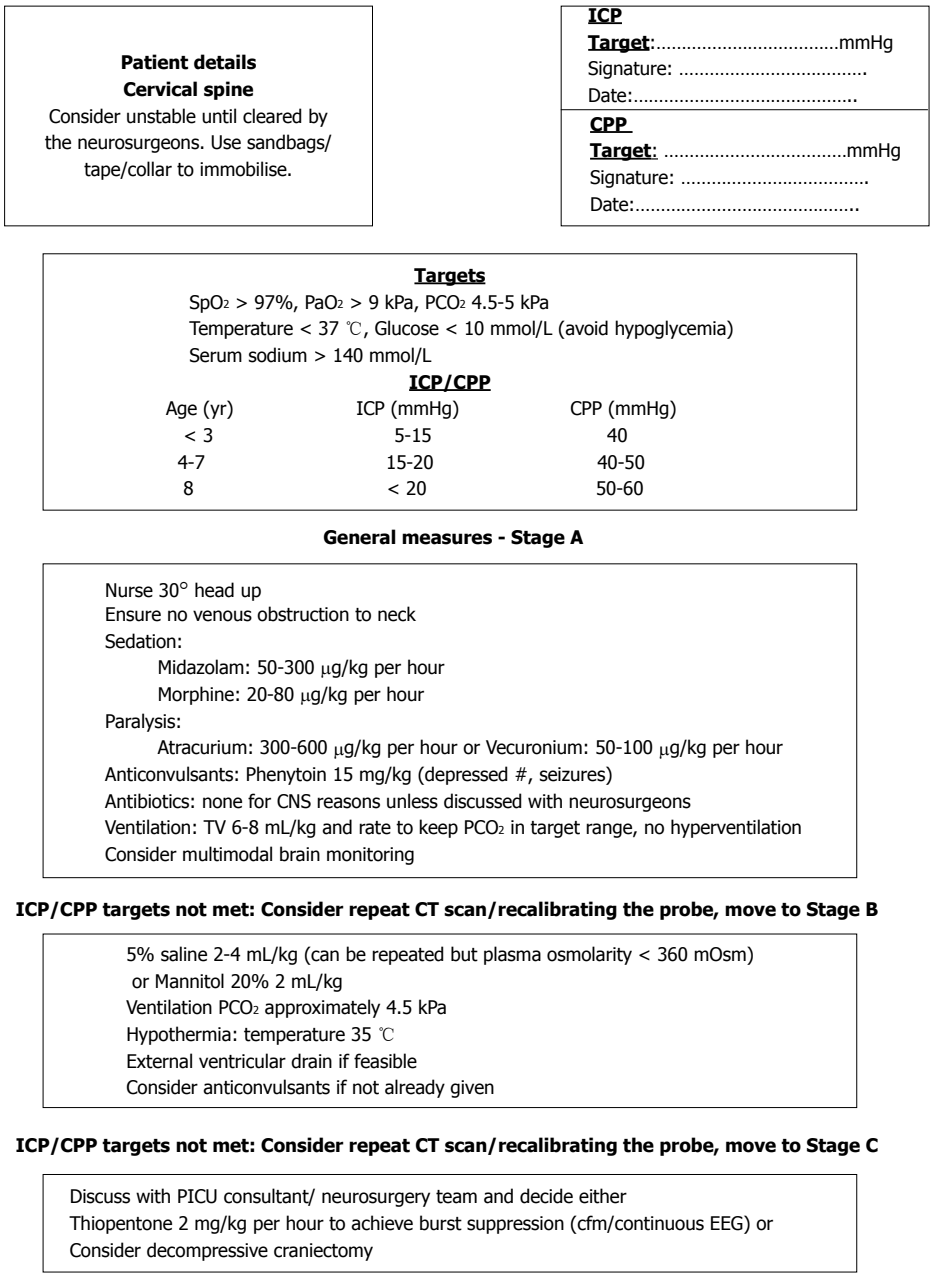

Figure 1 Protocol for managing severe traumatic brain injury in children. ICP: Intracranial pressure; CPP: Cerebral perfusion; CT: Computed tomography; PICU: Pediatric intensive care unit; EEG: Electroencephalograph.

The theoretical benefits of induced hypothermia have not been confirmed in multi-centric trials despite a consistent decrease in ICP in the hypothermic patients. Rebound rise in ICP during rewarming and the delay to achieve target temperature have been suggested as the limiting factors that lead to no difference in neurological outcome of children receiving hypothermia[69,70]. Despite the lack of evidence, induced moderate hypothermia (32 ℃-33 ℃) is used as a second tier strategy to control ICP if the first tier strategies (sedation, analgesia, paralysis, osmolar therapy) have failed. The specific recommendation is to induce hypothermia early (within 8 h) for 48 h followed by very gradual rewarming (≤ 0.5 ℃/h)[14].

We use cooling blankets to keep patients normothermic (36 ℃-37 ℃) and only use hypothermia (35 ℃) for uncontrolled ICP after optimising other therapies and ruling out surgically correctible pathologies (Figure 1).

Hyperventilation

CO_2 is a potent determinant of cerebral vessel diameter. Lowering CO_2 reduces ICP by causing vasoconstriction, but it also causes cerebral ischemia with a reduction in cerebral blood flow[21,22,71]. For this reason, hyperventilation cannot be recommended for treatment of ICP unless the patient has advanced neuromonitoring in place[14]. Despite the lack of evidence to support this strategy, evidence suggests it remains the most commonly used strategy to lower ICP[22,72]. We do not hyperventilate children with severe TBI and actively manage $PaCO_2$ levels between 4.5-5 kPa (Figure 1).

Barbiturate coma

Barbiturates lower ICP through suppression of cerebral metabolic demand and alteration of vascular tone[73,74]. It improves coupling of regional blood flow to metabolic demands resulting in improved brain oxygenation at lower cerebral blood flow and decreased ICP. Although barbiturates are effective in lowering ICP, some studies suggest it does not improve clinical outcome in adults[75] and the literature in children is very scarce. Barbiturates have very significant systemic side effects, most notably severe haemodynamic compromise and increased intrapulmonary shunt. These side effects significantly limit the use of barbiturates in PICU and may be responsible for a number of complications observed in patients receiving this therapy. Also, the agent half-life is very long, making neurological assessment difficult. Barbiturates currently cannot be recommended for routine use in care of patients with raised ICP[76], but may be used as a rescue therapy in raised ICP unresponsive to first line treatment. Continuous EEG monitoring is recommended in children with TBI using barbiturates, and the agent should be titrated to achieve burst suppression[14].

Anti-seizures medication

Seizures are common post head injury and are often missed as patients are sedated and paralysed, but not always receive continuous EEG monitoring[77]. Although there is limited evidence to support the use of prophylactic anti-convulsants in severe TBI patients, the current guidelines still make a level Ⅲ recommendation for their use to reduce early post traumatic seizures[14].

Surgical treatment

Surgical management is a crucial part of management in TBI. If there is space-occupying haematoma post head-injury, its evacuation is the most effective mechanism of reducing ICP and avoiding secondary brain insult. Neuro-imaging is the cornerstone for diagnosing these and should be repeated for any persistent ICP rise. Space occupying lesions are often time-sensitive injuries and surgical evacuation should be performed as soon as possible, without delays.

Other surgical options for controlling ICP are CSF diversion (ventricular/lumbar drain) and decompressive craniectomy. CSF diversion can reduce CSF volume and ICP, and is recommended for eligible patients[14]. External ventricular drain (EVD) is a common method for CSF diversion and can also be used for monitoring ICP. Insertion of an EVD can be technically challenging in injured brain and may not offer any benefit if there is significant cerebral oedema causing collapsed ventricles[78]. Lumbar drain is only advised in conjunction with the EVD when there is no mass effect and cisterns are open[79].

Decompressive craniectomy can reduce ICP by allowing oedematous brain to expand by raising a bone flap and opening the dura. Although the technique lowers ICP, its benefits for outcome are not proven[80]. The current guidelines only make a level Ⅲ recommendation for its use in refractory intracranial hypertension which is resistant to other treatment strategies[14]. A recent randomized controlled trial in adults suggested that decompressive craniectomy increase the number of unfavourable outcomes despite lowering ICP and shortening length of ICU stay[80].

ADVANCED NEUROMONITORING

The pathophysiology of secondary brain injury is complex. It involves interactions between cerebral metabolic demand and supply with a complex relationship of cerebral blood flow, oxygenation, autoregulatory mechanisms and physiological derangements within an injured brain. Monitoring and maintaining ICP and CPP may be too simplistic to prevent secondary insults and there is growing evidence to support that factors other than ICP and CPP independently relate to the outcome. Some of these factors can be monitored with additional therapeutic targets with a potential to improve patient outcome. Although limited in paediatric TBI, some of these modalities are being increasingly studied and hold promise. The most common targets are CBF, cerebral autoregulation, cerebral oxygenation and metabolism. Also continuous monitoring of various physiological parameters in modern intensive care environment, such as oxygen saturations, respiratory rate, heart rate, ECG, CO_2, temperature, blood pressure and intracranial pressure allow for the development of multi-modal monitoring in neurocritical care. Multi-modal monitoring can interpret the relationship of these different parameters with each other and give unique information over and above the individual numbers that could be used to optimise clinical management[81].

CBF and autoregulation

CBF is the single most important parameter in defining the outcome after TBI. The normal brain is able to maintain near constant CBF over a range of systemic blood pressure fluctuations from about 50 to 150 mmHg by cerebrovascular pressure reactivity and autoregulation mechanisms[82]. Impaired cerebral autoregulation is common post TBI and influences the patient outcome[83-86].

Pressure reactivity index

Pressure reactivity index (PRx), which is a correlation coefficient between ABP and ICP, relating the ABP changes with slow fluctuations in ICP, has been studied extensively[87,88]. In intact autoregulation state, fluctuations in ABP are compensated by reactive changes in vasomotor tone. For example, a drop in ABP induces vasodilatation which increases cerebral blood volume and ICP, giving a negative correlation between ABP and ICP, and a negative PRx. Impaired autoregulation on the other hand, would lead to passive transmission of ABP fluctuations to ICP and hence a positive PRx[87]. By continuously studying cerebrovascular reactivity through PRx and plotting it against CPP, the CPP at which the vasculature is most

reactive can be calculated and the optimum CPP (CPPopt) can be estimated[89,90]. This is particularly important in young children in whom CPP data is scarce and CPPopt gives an ideal therapeutic target. It is important to remember that autoregulation is dynamic and changes both between individuals and at different times within an individual patient depending on type of injury and time since injury[91,92]. Therefore, PRx and CPPopt also provide dynamic values in real time that can be used to individualise therapeutic targets for a given patient and changing targets over time depending on the state of cerebral autoregulation[93,94]. The time CPP stays above or below CPPopt has been shown to be associated with outcome[89]; whether an active management of PRx and CPPopt would affect the outcome remains to be proven in randomised controlled trial.

Transcranial Doppler ultrasonography

Transcranial Doppler ultrasonography (TCD) is a non-invasive method that measures the flow velocity in middle cerebral artery[95]. It gives non quantitative estimate of CBF and state of cerebral autoregulation based on the assumption that the diameter of the vessels insonated is relatively constantly maintained despite changes in BP and $PaCO_2$, so the changes in flow velocity would estimate the changes in CBF. It is easy to use and can be repeated bedside, however, it is difficult to get a continuous assessment and it is liable to inter-observer variability. Various indices have been developed to interpret state of CBF and autoregulation, CPP and ICP and CO_2 reactivity by using TCD. One such index called pulsatility index (PI) is based on analysing the waveform of diastolic and systolic flows in the middle cerebral artery. PI has been used to assess brain compliance and CPP, and has been shown to have an association with ICP[96,97]. Cerebrovascular resistance is estimated by a ratio of MAP to changes in flow velocity measured by TCD which is then used to calculate autoregulation index which reflects the state of autoregulation[86,98]. Alternatively, manipulation of systemic blood pressure can also be used to study the effect of ABP changes in the TCD parameters to assess autoregulation[85,86]. TCD is being increasingly used in children[85,86]; further studies are required to validate the preliminary results.

Brain tissue oxygenation

Adequate oxygen delivery to brain tissue is important to prevent secondary brain injury. The relationship between oxygen demand (cerebral metabolic rate, $CMRO_2$) and supply (CBF) is complex post head injury due to unknown changes in metabolic demands at the cellular level, hence optimal management of ICP and CPP (surrogates for CBF) does not always prevent brain hypoxia[99].

Direct brain tissue oxygenation monitoring

Direct brain tissue oxygenation monitoring ($PbtO_2$) has been used for over two decades and there is significant evidence to support its use in paediatric TBI[56,100]. The latest guidelines make a level Ⅲ recommendation to keep $PbtO_2$ above 10 mmHg in paediatric TBI[14]. The commonest method used to monitor $PbtO_2$ is by insertion of a polarographic electrode in the brain parenchyma with the ICP bolt and the value measured is the oxygen accumulated in the brain parenchyma at the tip of the transducer, which is influenced by oxygen supply, demand and utilization. The probe placement is crucial. In focal injury, it should be placed in the pericontusional area while in diffuse injuries; it is usually placed in the non-dominant hemisphere. Although the normal values of $PbtO_2$ are not clearly understood, animal studies suggest 20-30 mmHg as the normal values for normal uninjured brain[101]. A threshold of 10 mmHg has been accepted as the ischemic threshold and $PbtO_2$ levels below 10 mmHg have been associated with poor outcome. $PbtO_2$ values can be improved by increasing inspired oxygen/ventilation, haemoglobin levels and MBP[57,102].

Continuous jugular venous saturation monitoring

Continuous jugular venous saturation monitoring ($SjvO_2$) is another method used to understand the relationship between CBF and brain metabolism and gives the difference between cerebral oxygen supply and demand. A retrograde catheter inserted in the jugular venous bulb measures continuous $SjvO_2$. There is no consensus for normal levels of $SjvO_2$ in children but in adults 50%-75% is considered normal. Values outside this range are considered abnormal and have been shown to be associated with poor outcome[52,103]. Due to technical difficulties, paediatric experience with the use of $SjvO_2$ is limited. It is also not a good indicator of regional changes in the injured brain.

Thermal diffusion probes

Regional cerebral blood flow can be measured directly by thermal diffusion probes (TDP) inserted in brain parenchyma. The technique has been validated with good agreement between TDP and xenon-CT for regional CBF measurements. In combination with PbtO2, TDP can be potentially useful in optimizing management of CPP[104].

Brain metabolism and chemistry

It is possible to study the concentration of chemicals found in the brain parenchyma by using microdialysis and is now frequently used in monitoring and managing adult TBI. It is possible to measure markers of brain metabolism (glucose, lactate and pyruvate), neurotransmitters (glutamate) and tissue damage (glycerol) at select intervals on small amounts of interstitial fluid collected by the microdialysis catheter inserted into the brain parenchyma alongside the ICP monitor and $PbtO_2$ probe and there are established normal values for adults for some of these chemicals[105]. LPR is of particular interest as it signifies the balance between aerobic and anaerobic metabolism; LPR can also be elevated in states of hyperglycolysis or mitochondrial

dysfunction[105,106]. Sustained elevations of LPR have been identified in pericontusional tissue[107] and have been shown to be associated with poor outcome[108]. Similarly, brain glucose levels can be used to guide optimal threshold for blood glucose levels[40]. At present, microdialysis is predominantly used for research purposes, but holds promise for future. Similar to $PbtO_2$ probe, the position of the catheter is crucial and influences the results.

CONCLUSION

Paediatric TBI is a complex disease and requires multi-disciplinary input. Advancements in the field of paediatric neurocritical care and improved understanding of TBI pathophysiology are being translated to bedside therapies but clinical benefit from most of these therapies is yet to be proved in clinical trials. Despite this, implementations of guideline-based management protocols have impacted significantly on the outcome of TBI in recent years. New monitoring techniques have improved our ability to recognise adverse events and mechanisms of secondary brain injury. The role of these new techniques of individualized management need to be further evaluated.

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REVIEW

Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock

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Abstract

The mixed venous-to-arterial carbon dioxide (CO_2) tension difference [P (v-a) CO_2] is the difference between carbon dioxide tension (PCO_2) in mixed venous blood (sampled from a pulmonary artery catheter) and the PCO_2 in arterial blood. P (v-a) CO_2 depends on the cardiac output and the global CO_2 production, and on the complex relationship between PCO_2 and CO_2 content. Experimental and clinical studies support the evidence that P (v-a) CO_2 cannot serve as an indicator of tissue hypoxia, and should be regarded as an indicator of the adequacy of venous blood to wash out the total CO_2 generated by the peripheral tissues. P (v-a) CO_2 can be replaced by the central venous-to-arterial CO_2 difference (ΔPCO_2), which is calculated from simultaneous sampling of central venous blood from a central vein catheter and arterial blood and, therefore, more easy to obtain at the bedside. Determining the ΔPCO_2 during the resuscitation of septic shock patients might be useful when deciding when to continue resuscitation despite a central venous oxygen saturation ($ScvO_2$) > 70% associated with elevated blood lactate levels. Because high blood lactate levels is not a discriminatory factor in determining the source of that stress, an increased ΔPCO_2 (> 6 mmHg) could be used to identify patients who still remain inadequately resuscitated. Monitoring the ΔPCO_2 from the beginning of the reanimation of septic shock patients might be a valuable means to evaluate the adequacy of cardiac output in tissue perfusion and, thus, guiding the therapy. In this respect, it can aid to titrate inotropes to adjust oxygen delivery to CO_2 production, or to choose between hemoglobin correction or fluid/inotrope infusion in patients with a too low $ScvO_2$ related to metabolic demand. The combination of P (v-a) CO_2 or ΔPCO_2 with oxygen-derived parameters through the calculation of the P (v-a) CO_2 or ΔPCO_2/arteriovenous oxygen content difference ratio can detect the presence of global anaerobic metabolism.

Key words: Venous-to-arterial carbon dioxide tension difference; Carbon dioxide production; Oxygen supply dependency; Cardiac output; tissue hypoxia; Anaerobic metabolism; Oxygen consumption; Resuscitation; Septic shock

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Core tip: Early recognition and correction of tissue hypoperfusion are cornerstones in the management of septic shock patients. The venous-to-arterial carbon dioxide tension difference, which is a marker of the adequacy of cardiac output to global metabolic demand, is a helpful additional means to detect patients who stay under-resuscitated after optimization of O_2-derived parameters. In this regard, its monitoring should help the clinicians for the decision of giving therapy targeting at increasing cardiac output.

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INTRODUCTION

A shock is a form of acute circulatory failure associated with an inequality between systemic oxygen delivery (DO_2) and oxygen consumption (VO_2), which result in tissue hypoxia[1]. Early recognition and adequate resuscitation of tissue hypoperfusion are of particular importance in the management of septic shock to avoid the development of tissue hypoxia and multi-organ failure. Assessment of mixed venous oxygen saturation (SvO_2) from a pulmonary artery catheter has been proposed as an indirect marker of global tissue oxygenation[2]. SvO_2 reflects the balance between oxygen demand and supply. A low SvO_2 represents a high oxygen extraction (O_2ER) in order to maintain aerobic metabolism and VO_2 constant in response to an acute decrease in DO_2. However, when DO_2 drops under a critical value, O_2ER is no longer capable of upholding VO_2, and global tissue hypoxia appears, as indicated by the occurrence of lactic acidosis[3-5].

Since the assessment of central venous oxygen saturation ($ScvO_2$) can be achieved more easily, and is less risky than from pulmonary artery catheter, it would be useful if $ScvO_2$ could function as an accurate reflection of SvO_2. In fact, SvO_2 is not similar to $ScvO_2$ because the latter primarily reflects the oxygenation of the upper side of the body. In normal patients, $ScvO_2$ is lower than SvO_2 by about 2% to 3%, largely because of the less rate of oxygen extraction by the kidneys[6]. In shock state, the absolute value of $ScvO_2$ was more often reported to be higher than $ScvO_2$, probably due to the oxygen extraction increases in splanchnic and renal tissues[7-11]. This suggests that the existence of a decreased $ScvO_2$ implies an even smaller SvO_2. Because of the lack of agreement regarding absolute values, some authors questioned the clinical utility of $ScvO_2$[12,13]. However, despite absolute values differ, trends in $ScvO_2$ closely mirror trends in SvO_2[8,9], suggesting that monitoring $ScvO_2$ makes sense in critically ill patients.

It has been shown that an early hemodynamic optimization using a resuscitation bundle aimed at increasing $ScvO_2$ > 70% was related to an important reduction in septic shock mortality[14]. Since that, monitoring $ScvO_2$ has become widely recommended[1,14,15]. Recently, three large multicenter studies[16-18] failed to demonstrate any benefits of the early goal-directed therapy approach. Nevertheless, the design of these trials was not to answer the question of whether targeting an $ScvO_2$ > 70% was effective. Also, in these studies, the mean baseline $ScvO_2$ values were already above 70%. Thus, these findings do not indicate that clinicians should stop monitoring $ScvO_2$ and adjust DO_2 by optimizing $ScvO_2$ levels, particularly in septic shock patients with low $ScvO_2$, who are at the highest risk of death[19].

On the other hand, normalization of $ScvO_2$ does not rule out persistent tissue hypoperfusion and does not preclude evolution to multi-organ dysfunction and death[20]. The obvious limitation of $ScvO_2$ is that normal/high values cannot distinguish if DO_2 is sufficient or in excess to demand. In septic conditions, normal/high $ScvO_2$ values might be due to the heterogeneity of the microcirculation that generates capillary shunting and/or mitochondrial damage responsible of disturbances in tissue oxygen extraction. Because $ScvO_2$ is measured downstream from tissues, when a given tissue receives inadequate DO_2, the resulting low local oxygen venous saturations may be "masked" by admixture with highly saturated venous blood from tissues with better perfusion and DO_2, resulting overall in normal or even high $ScvO_2$. Although $ScvO_2$ may thus not miss any global DO_2 dysfunction, it may stay "blind" to local perfusion disturbances, which exist in abundance in sepsis due to damaged microcirculation. Indeed, high $ScvO_2$ values have been associated with increased mortality in septic shock patients[21,22]. Thus, in some circumstances the use of $ScvO_2$ might erroneously drive a clinician to conclude that the physiologic state of the patient has ameliorated when, in fact, it may not have improved.

Lactate has also been proposed as a resuscitation endpoint[23,24]. However, no benefits have been observed for lactate decrease-guided therapy over resuscitation guided by $ScvO_2$ in septic shock patients[25]. Moreover, given the nonspecific nature of lactate level elevation, hyperlactatemia alone is not a discriminatory factor in establishing the source of the circulatory failure. Hence, additional circulatory parameters such as the venous-to-arterial carbon dioxide tension difference are needed to identify patients with septic shock who presently may still insufficiently reanimated, especially when $ScvO_2$ values are normal/high in the context of hyperlactatemia. The purpose of this review is to discuss the physiologic background and the potential clinical usefulness of the venous-to-arterial carbon dioxide tension difference in septic shock.

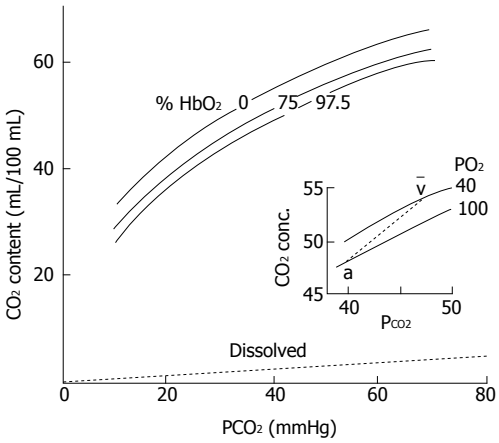

Figure 1 CO_2 dissociation curve. CO_2 content (mL/100 mL) *vs* CO_2 partial tension (PCO_2). Differences between the curves result in higher CO_2 content in the blood, and smaller PCO_2 differences between arterial and venous blood. Hemoglobin-O_2 saturation affects the position of the CO_2 dissociation curve (Haldane effect).

PHYSIOLOGICAL BACKGROUND

CO_2 transport in the blood

CO_2 is transported in the blood in three figures[26]: Dissolved, in combination with proteins as carbamino compounds, and as bicarbonate. Physically dissolved CO_2 is a function of CO_2 solubility in blood, which is about 20 times that of oxygen (O_2); therefore, considerably more CO_2 than O_2 is present in simple solution at equal partial pressures. However, dissolved CO_2 shares only around 5% of the whole CO_2 concentration in arterial blood.

Carbamino compounds comprise the second form of CO_2 in the blood. These compounds occur when CO_2 combines with terminal amine groups in blood proteins, especially with the globin of hemoglobin. However, this chemical combination between CO_2 and hemoglobin is much less important than haemoglobin-O_2 binding, so carbamino compounds comprise only 5% of the total CO_2 in the arterial blood.

The bicarbonate ion (HCO_3^-) is the most significant form of the CO_2 carriage in the blood. CO_2 combines with water (H_2O) to form carbonic acid (H_2CO_3), and this dissociates to HCO_3^- and hydrogen ion (H^+): $CO_2 + H_2O = H_2CO_3 = HCO_3^- + H^+$. Carbonic anhydrase is the enzyme that catalyzes the first reaction, making it almost instantaneous. Carbonic anhydrase occurs mainly in red blood cells (RBC), but it also occurs on pulmonary capillary endothelial cells, and it accelerates the reaction in plasma in the lungs. The uncatalyzed reaction will occur in plasma, but at a much slower rate. The second reaction happens immediately inside RBC and does not require any enzyme. The H_2CO_3 dissociates to H^+ and HCO_3^-, and the H^+ is buffered primarily by hemoglobin while the excess HCO_3^- is transported out the RBC into plasma by an electrically neutral bicarbonate-chloride exchanger. The fast conversion of CO_2 to HCO_3^- results in nearly 90% of the CO_2 in arterial blood being transported in that manner.

Hemoglobin-O_2 saturation is the major factor affecting the capacity of hemoglobin to fix CO_2 (Haldane effect). Consequently, CO_2 concentration increases when blood is deoxygenated, or CO_2 concentration diminishes when blood is oxygenated, at any assumed carbon dioxide tension (PCO_2)[26] (Figure 1). H^+ ions from CO_2 can be deemed as competing with O_2 for hemoglobin binding. Accordingly, rising oxygen reduces the affinity of hemoglobin for H^+ and blood CO_2 concentration (Haldane effect). The physiological assets of the Haldane effect are that it promotes removing of CO_2 in the lungs when blood is oxygenated and CO_2 filling in the blood when oxygen is delivered to tissues. Additionally, the Haldane effect leads to a sharper physiologic CO_2 blood equilibrium curve that has the physiologic interest of rising CO_2 concentration differences for a given PCO_2 difference.

CO_2 is rapidly excreted from the circulation by the lungs by passive diffusion from the capillaries to the alveoli, and its production approximately matches excretion.

The relationship between PCO_2 and the total blood CO_2 content (CCO_2) is curvilinear even though more linear than the oxygen dissociation curve[26]. Oxygen saturation, hematocrit, temperature, and the degree of metabolic acidosis influence the PCO_2/CCO_2 relationship[26]. Hence, for a given value of CCO_2, PCO_2 is higher in the case of metabolic acidosis than in the case of normal pH (Figure 2).

Determinant of venous-to-arterial CO_2 tension difference

The venous-to-arterial CO_2 tension difference [P (v-a) CO_2] is the gradient between PCO_2 in mixed venous blood ($PvCO_2$) and PCO_2 in arterial blood ($PaCO_2$): P (v-a) $CO_2 = PvCO_2 - PaCO_2$; $PvCO_2$ and $PaCO_2$ are partial pressures of the dissolved CO_2 in the mixed venous and arterial blood, respectively.

The application of Fick equation to CO_2 shows that the CO_2 elimination (identical to CO_2 generation in a stable condition) equals the product of the difference between mixed venous blood CO_2 content ($CvCO_2$) and arterial blood CO_2 content ($CaCO_2$) and cardiac output: Total CO_2 production (VCO_2) = cardiac output × ($CvCO_2$ - $CaCO_2$). In spite of a global curvilinear shape of the relation between PCO_2 and the total CCO_2, there is a rather linear association between CCO_2 and PCO_2 over the general physiological range of CO_2 content so that CCO_2 can be substituted by PCO_2 ($PCO_2 = k \times CCO_2$)[27-29]. Therefore, VCO_2 can be calculated from a modified Fick equation as: VCO_2 = cardiac output × k × P (v-a) CO_2 so that P (v-a) $CO_2 = k \times VCO_2$/cardiac output, where k is the pseudo-linear coefficient supposed to be constant in physiological states[27]. Therefore, P (v-a) CO_2 would be linearly linked to CO_2 generation and inversely associated to cardiac output. Under normal conditions, P (v-a) CO_2 values range between 2 and 6 mmHg[30].

Influence of CO_2 production on P (v-a) CO_2

Aerobic CO_2 production: Oxidative phosphorylation proceeds with the formation of energy-laden molecules, CO_2 and water. Total CO_2 production is directly related to VO_2: $VCO_2 = R \times VO_2$, where R is the respiratory

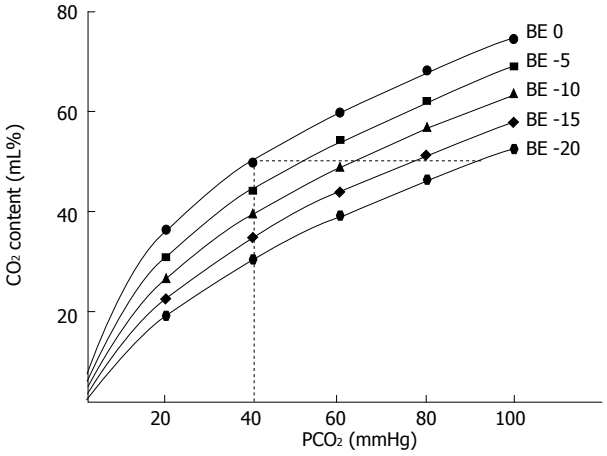

Figure 2 CO_2 dissociation curve. CO_2 content (mL/100 mL) *vs* CO_2 partial tension (PCO_2). Each curve is described at constant base excess (BE). As displayed, for the same CO_2 content, changing the BE results in a great change in PCO_2.

quotient varying among 0.7 and 1.0 according to the energy intake. Under circumstances of important carbohydrate consumption, R becomes close to 1.0. Thus, CO_2 generation should increase either with elevated oxidative metabolism or for a constant VO_2 when a balanced alimentation regime is substituted by a high carbohydrate consumption regime[31]. Under both situations of increased VCO_2, P (v-a) CO_2 should increase unless cardiac output can increase to the same extent.

Anaerobic CO_2 production: Under conditions of tissue hypoxia, there is an increased generation of H^+ ions from an excessive generation of lactic acid due to an acceleration of anaerobic glycolysis, and the hydrolysis of high-energy phosphates[32]. These H^+ ions will then be buffered by the bicarbonate existing in the cells so that CO_2 will be produced. Decarboxylation of metabolic intermediates such as α-ketoglutarate and oxaloacetate during hypoxia is, also, a possible but trivial cause of anaerobic CO_2 generation[32].

Anaerobic CO_2 generation in hypoxic tissues is not simple to identify. Indeed, the effluent venous blood flow can be sufficiently high to wash out the CO_2 generated under these conditions of a significant decline in aerobic CO_2 production[33]. Consequently, PCO_2 could be not increased in the efferent vein, and anaerobic CO_2 generation not recognized from the calculation of P (v-a) CO_2. Nevertheless, if afferent and efferent blood flows are artificially arrested, hypoxia will happen inside the organ and the sustained CO_2 production would then be disclosed by measuring an augmented PCO_2 in the sluggish efferent blood flow, in spite of the drop in CO_2 generation from the aerobic pathway[34,35].

Influence of cardiac output on P (v-a) CO_2

According to the modified Fick equation, P (v-a) CO_2 is related to VCO_2 and inversely linked to cardiac output. Under steady states of both VO_2 and VCO_2, P (v-a) CO_2 was observed to increase in parallel with the reduction in cardiac output[33,36,37]. In other words, when cardiac output is adapted to VO_2, P (v-a) CO_2 should not increase due to increased clearance of CO_2, whereas P (v-a) CO_2 should be high following cardiac output reduction because of a low flow-induced tissue CO_2 stagnation phenomenon. Due to the decreasing of transit time a higher than usual addition of CO_2 per unit of blood passing the efferent microvessels leads to produce hypercapnia in the venous blood. As long as alveolar respiration is sufficient, a gradient will occur between $PvCO_2$ and $PaCO_2$. However, under spontaneous breathing situations, hyperventilation, stimulated by the decreased blood flow, may reduce $PaCO_2$ and thus may prevent the CO_2 stagnation-induced rise in $PvCO_2$[38]. This finding underscores the utility of calculating P (v-a) CO_2 rather than simply assessing $PvCO_2$, particularly in the case of spontaneous breathing[39].

Can P (v-a) CO_2 be used as a marker of tissue hypoxia?

Marked increases in P (v-a) CO_2 were reported in patients during cardiopulmonary resuscitation[40]. Furthermore, higher P (v-a) CO_2 values were observed in patients with circulatory failure compared with those without circulatory failure[41]. These observations were attributed to the decrease of blood flow and the development of anaerobic metabolism with anaerobic CO_2 production. Thus, it has been suggested that P (v-a) CO_2can be used to detect the presence of tissue hypoxia in patients with acute circulatory failure[33,36]. In fact, under conditions of tissue hypoxia with a decreased VO_2, the relationship between changes in cardiac output and P (v-a) CO_2 are much more complex. Indeed, in these circumstances, the increase in CO_2 production related to the anaerobic pathway is counterbalanced by a reduced aerobic CO_2 production, so that VCO_2 and hence P (v-a) CO_2 could be at best unchanged or decreased[37]. Nevertheless, since the k factor should rise during tissue hypoxia[33] while VCO_2 must decrease, the resultant effect on P (v-a) CO_2 depends mainly on the flow state (cardiac output)[27].

Tissue hypoxia with low blood flow

Experimental studies in which blood flow was progressively reduced, an elevation in P (v-a) CO_2 following the reduction in DO_2 was reported, while a constant VO_2 was measured[33,36,37,42]. In this state of O_2 supply-independency and steady CO_2 generation, rising of P (v-a) CO_2 after flow decrease can be explained clearly by CO_2 stagnation.

In those studies, when DO_2 was more diminished under its critical value, a drop in VO_2 was noticed, insinuating O_2 supply-dependency and occurrence of anaerobic metabolism. The progressive widening of P (v-a) CO_2 seen before DO_2 had achieved the critical point, was amplified by an acute rise in $PvCO_2$ when DO_2 declined below that point. The authors[33,36,42] assumed that this brisk increase in P (v-a) CO_2 can be utilized as a good indicator of tissue dysoxia. However, since both VCO_2 (aerobic production) and venous efferent blood flow decrease, P (v-a) CO_2 should not be considerably

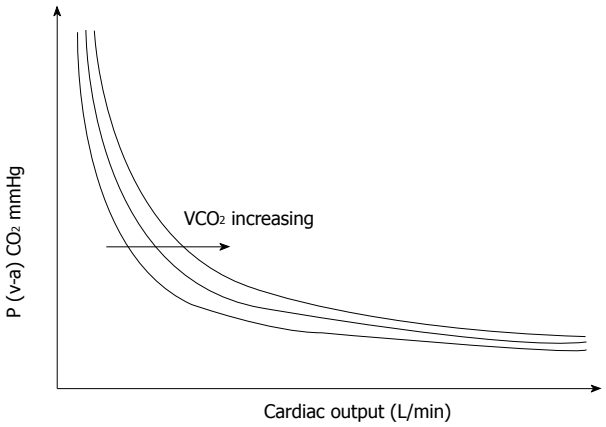

Figure 3 Relationship between the mixed venous-to-arterial PCO_2 difference P (v-a) CO_2 and cardiac output. For a constant total CO_2 production (VCO_2), changes in cardiac output result in large changes in P (v-a) CO_2 in the low values of cardiac output, whereas changes in cardiac output will not result in significant changes in P (v-a) CO_2 in the high values of cardiac output.

changed unless very low values of blood flow were achieved during the supply dependent period. Therefore, from the analysis of the data of these experimental studies[33,36,37,42], it can be reasonably supposed that an abrupt increase in P (v-a) CO_2 should not be easily attributed to the outset of hypoxia but rather to an additional decrease in cardiac output. This fact can be explained by the two following reasons.

Since the association between P (v-a) CO_2 and cardiac output is curvilinear (Fick equation), an enormous rise in P (v-a) CO_2 must be noticed for a reduction in cardiac output in its lowest scale. In fact, even if this mathematical phenomenon may be robust under conditions of maintained VCO_2, it should be moderated in hypoxic states because the decline in VCO_2 leftward shift the isopleth which describes the P (v-a) CO_2/cardiac output relationship (Figure 3).

The curvilinearity of the relationship between $CvCO_2$ and $PvCO_2$ may be another cause for this sharp increase in P (v-a) CO_2. Indeed, due to this particular relationship, $PvCO_2$ changes are greater than $CvCO_2$ changes at the highest range of CCO_2[29]. Furthermore, the disproportions between CCO_2 and PCO_2 at high values of CCO_2 are magnified in the presence of an elevated O_2 saturation and by the decrease in venous pH[29], which is frequently associated with the increase in $PvCO_2$ and may be of greater significance if metabolic acidosis coexists (Figure 2). Therefore, in the case of low flow states, P[v-a]CO_2 can substantially increase resulting from CO_2 stagnation in spite of the decrease in VCO_2 as reported in those experimental studies[33,36,37,42].

Tissue hypoxia with maintained or high blood flow

Under conditions of tissue hypoxia with maintained flow state, venous blood flow should be sufficiently elevated to assure adequate clearance of the CO_2 generated by the hypoxic cells, so that P (v-a) CO_2 should not increase even if the CO_2 production is not decreased. Conversely, low flow states can result in a widening of P (v-a) CO_2 due to the tissue CO_2 stagnation phenomenon[43] even if no additional CO_2 production occurs. This point was nicely demonstrated by Vallet *et al*[44] in a canine model of isolated limb in which a diminished DO_2 by reducing blood flow (ischemic hypoxia) was related to a rise in P (v-a) CO_2. On the other hand, when blood flow was preserved, but arterial PO_2 was decreased by lowering the input oxygen concentration (hypoxic hypoxia), P (v-a) CO_2 did not rise despite a significant decline in VO_2. This because the preserved blood flow was sufficient to clear the generated CO_2[40]. Accordingly, Nevière *et al*[45] demonstrated that for the same level of induced oxygen supply dependency, P (v-a) CO_2 was risen only in ischemic hypoxia but not in hypoxic hypoxia, indicating that augmented P (v-a) CO_2 was mostly linked to the reduction in cardiac output. These studies clearly show that the absence of elevated P (v-a) CO_2 does not preclude the presence of tissue hypoxia and hence underline the good value of P (v-a) CO_2 to detect inadequate tissue perfusion related to its metabolic production but also its poor sensitivity to detect tissue hypoxia. A mathematical model analysis also established that cardiac output plays the key role in the widening of P (v-a) CO_2[46].

Clinical studies

Results from clinical investigations in septic shock patients have also supported that the decreased cardiac output is the major determinant in the elevation of P (v-a) CO_2[37,38]. Mecher *et al*[47] observed that septic shock patients with P (v-a) CO_2 > 6 mmHg had a significantly lower mean cardiac output when compared to patients with P (v-a) CO_2 $\leqslant$ 6 mmHg. No differences in blood lactate levels were found between the two subgroups. Interestingly, the volume expansion engendered a reduction in P (v-a) CO_2 associated with an increase in cardiac output only in patients with elevated P (v-a) CO_2. Moreover, the changes in cardiac output induced by volume expansion were correlated with changes in P (v-a) CO_2 ($R = 0.46$, $P < 0.01$). The authors rightly concluded that in patients with septic shock, an elevated P (v-a) CO_2 is related to a decreased systemic blood flow. In septic shock patients, Bakker *et al*[48] similarly found a significant negative correlation between cardiac output and P (v-a) CO_2. Thus, a strong association between cardiac output and P (v-a) CO_2 is also well documented in septic shock. Furthermore, increased P (v-a) CO_2 was found merely in patients with lower cardiac output. In that study, the dissimilarities in P (v-a) CO_2 cannot be explained by the inequalities in CO_2 production, as implied by the identical VO_2 and lactate concentration found in the two groups of patients[48]. On the other hand, many patients in those studies[47,48] had normal P (v-a) CO_2 despite the presence of tissue hypoxia, presumably since their elevated cardiac output had simply washed out the CO_2 generated in the peripheral circulation.

Creteur *et al*[49] examined the association between impairment in microcirculatory perfusion and tissue PCO_2. They showed that the reperfusion of damaged

microcirculation (assessed using orthogonal polarized spectroscopy) was associated with normalized sublingual tissue PCO_2 levels. Thus, there is a clear relation between tissue CO_2 accumulation and blood flow leading to increasing venous-arterial CO_2 gradients.

In short, altogether, these results strengthen the conception that low flow situations act a crucial part in the enlargement of P (v-a) CO_2 in states of tissue hypoxia. Elevated P (v-a) CO_2 might imply that: (1) cardiac output is not enough under states of supposed tissue hypoxia; and (2) microcirculatory flow is not sufficiently high or adequately distributed to remove the additional CO_2 in spite of the existence of normal/high cardiac output.

The P (v-a) CO_2 should, therefore, be regarded as an indicator of the ability of an adequate venous blood flow return to clear the CO_2 excess rather than as a marker of tissue hypoxia.

Recently, Ospina-Tascon *et al*[50] have shown that the persistence of high P (v-a) CO_2 ($\geqslant$ 6 mmHg) during the first six hours of reanimation of septic shock patients was linked to more severe multiple organ failure and higher mortality rate (Relative Risk = 2.23, P = 0.01). However, further studies are required to test if P (v-a) CO_2 used as a resuscitation endpoint would be associated with improved outcomes.

Central venous-to-arterial PCO_2 difference as a target in resuscitation of septic shock

The measurement of P (v-a) CO_2 requires the presence of a pulmonary artery catheter, which is rarely practiced nowadays[51]. Since the central venous catheter is implanted in most septic shock patients, the usage of central venous-arterial carbon dioxide partial pressure difference (ΔPCO_2) is greatly easier and similarly helpful. Interestingly, a strong agreement between P (v-a) CO_2 and ΔPCO_2, calculated as the difference between central venous PCO_2 sampled from a central vein catheter and arterial PCO_2, was reported in critically ill patients[52] and severe sepsis and septic shock patients[53].

As emphasized above, high values of $ScvO_2$ do not preclude the presence of tissue hypoperfusion and hypoxia in cases of impaired O_2ER capabilities that can occur in septic shock[21,22]. Since the solubility of CO_2 is very high (around 20 times than O_2), its capability of spreading out of ischemic tissues into the efferent veins is phenomenal, making it an extremely sensitive indicator of hypoperfusion. Consequently, in conditions where there are O_2 diffusion difficulties (resulting from shunted and obstructed capillaries), "covering" reduced O_2ER and increased tissue O_2 debt, CO_2 still diffuses to the efferent veins, "uncovering" the hypoperfusion situation for the clinician when ΔPCO_2 is evaluated[54]. Accordingly, Vallée *et al*[55] tested the hypothesis that the ΔPCO_2 can be used as a global indicator of tissue hypoperfusion in reanimated septic shock patients in whom $ScvO_2$ was already greater than 70%. They showed that despite a normalized DO_2/VO_2 ratio, patients who had impaired tissue perfusion with blood lactate concentration > 2 mmol/L remained with an elevated ΔPCO_2 (> 6 mmHg). Also, patients with low ΔPCO_2 values had greater lactate decrease and cardiac index values and exhibited a significantly higher reduction in SOFA score than patients with high ΔPCO_2. In a prospective study that included 80 patients, we recently examined the usefulness of measuring ΔPCO_2 during the initial resuscitation period of septic shock[56]. We found that during the very early period of septic shock, patients who reached a normal ΔPCO_2 ($\leqslant$ 6 mmHg) after six hours of resuscitation had greater decreases in blood lactate and in SOFA score than those who failed to normalize ΔPCO_2 (> 6 mmHg). Interestingly, patients who achieved the goals of both $\Delta PCO_2 \leqslant$ 6 mmHg and $ScvO_2$ > 70% after the first six hours of resuscitation had the greatest blood lactate decrease, which was found to be an independent prognostic factor of ICU mortality[56]. In addition, Du *et al*[57], in a retrospective study, showed that the normalization of both $ScvO_2$ and ΔPCO_2 seems to be a better prognostic factor of outcome after reanimation from septic shock than $ScvO_2$ only. Patients who achieved both targets seemed to clear blood lactate more efficiently[57].

Taken all these studies together[55-57], we believe that monitoring the ΔPCO_2 from the beginning of the reanimation of patients with septic shock may be a valuable means to evaluate the adequacy of cardiac output in tissue perfusion and, thus, guiding the therapy (Figure 4). Indeed, in patients with decreased $ScvO_2$, an augmented ΔPCO_2 is suggestive of the involvement of low cardiac output, and assessing ΔPCO_2 could assist in expediting treatments intended at increasing cardiac output, rather than the arterial O_2 saturation and hemoglobin concentration. When $ScvO_2$ is normal/high ($\geqslant$ 70%), the presence of elevated ΔPCO_2 is indicative of the persisting impaired perfusion. ΔPCO_2 provides further assistance in making the relevant choices about inotropes and fluids. Randomized clinical trial, however, is required to validate this hypothesis.

How to interpret ΔPCO_2 in septic shock sates?

As developed extensively above, the ΔPCO_2 should be considered as a marker of tissue perfusion (*i.e.,* the adequacy of blood flow to wash out the CO_2 generated by the tissues) rather than a marker of tissue hypoxia.

The clinical inferences of this approach can be outlined as follows: (1) in a patient with an initially increased ΔPCO_2 ($\geqslant$ 6 mmHg), clinicians should be aware that blood flow might not be sufficient despite apparent normal macrocirculatory parameters, including $ScvO_2$. Thus, with respect to the metabolic states, an elevated ΔPCO_2 could encourage clinicians to rise cardiac output in order to improve tissue perfusion, especially under suspected hypoxic conditions (elevated blood lactate levels). Nevertheless, we should stress out that, in the absence of suspected conditions of tissue ischemia, increasing cardiac output to supranormal

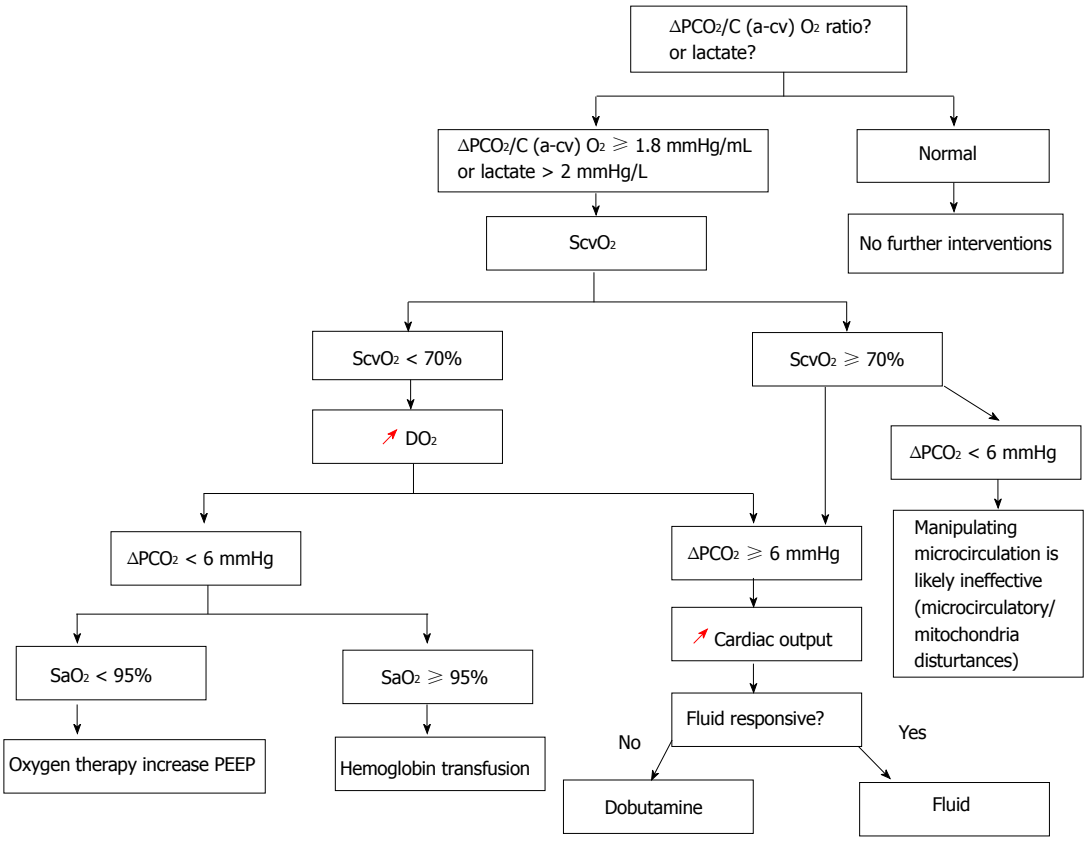

Figure 4 $ScvO_2$-ΔPCO_2 guided protocol. $ScvO_2$: Central venous oxygen saturation; ΔPCO_2: Central venous-to-arterial carbon dioxide tension difference; SaO_2: Arterial oxygen saturation; C (a-cv) O_2: Central arteriovenous oxygen content difference; DO_2: Oxygen delivery; PEEP: Positive end expiratory pressure; red arrows: Increasing.

values not only failed to demonstrate any benefit but could also be potentially harmful in septic shock patients[58,59]; and (2) A normal ΔPCO_2 (< 6 mmHg) would suggest that blood flow is sufficiently high to remove the global CO_2 production from the peripheral circulation, and increasing cardiac output could not be a first concern in the management approach even in the presence of tissue hypoxia. On the other hand, clinicians should keep in mind that a normal ΔPCO_2 with high cardiac output did not preclude the inadequacy of regional blood flow.

The change in ΔPCO_2 - as an index of VCO_2/cardiac output ratio - should be interpreted in line with changes in cardiac output and VCO_2. Under aerobic conditions, ΔPCO_2 along with $ScvO_2$ and O_2ER can serve to guide therapy with dobutamine better than cardiac output in septic shock patients[60]. Indeed, dobutamine in parallel to its effects on systemic hemodynamics may increase VO_2, and therefore VCO_2, through its potential thermogenic effects related to its β_1-adrenergic properties[61]. Recently, we showed that during the stepwise increase of dobutamine dose from 0-10 μg/kg per minute, ΔPCO_2 decreased in parallel with an increase in cardiac output. However, an unchanged ΔPCO_2 was observed when dobutamine was increased from 10-15 μg/kg per minute in spite of the further increase in cardiac output because of the thermogenic effects of the drug at that rate[60]. Thus, ΔPCO_2 can assist the clinician in distinguishing between the hemodynamic and the metabolic effects of dobutamine. Similar results were reported in stable chronic heart failure patients, but with P (v-a) CO_2[43].

Otherwise, the increase in systemic blood flow can affect VCO_2 production under situations of tissue hypoxia. Indeed, under conditions of O_2 supply dependency, an increase in cardiac output may lead to an increase in aerobic VCO_2 production through the supply-dependent increase in VO_2. In this situation, the changes in cardiac output may have no effect on the time-course of ΔPCO_2. Accordingly, almost unaffected ΔPCO_2 with treatment would not indicate that the treatment has been unsuccessful. In such situation, the therapeutic approach would be preferably kept until achieving a significant drop in ΔPCO_2 that would imply that the critical value of DO_2 has been overcome.

Moreover, the clinicians should be aware that because the relationship between ΔPCO_2 and cardiac output is curvilinear, large variations in cardiac output will not necessary engender important variations in ΔPCO_2 (Figure 3). In other words, the interpretation should be cautious in case of high flow states.

Limitations of ΔPCO_2

There are many pre-analytical sources of errors in PCO_2 measurement that should be avoided to interpret ΔPCO_2 correctly: inappropriate sample container, insufficient

sample volume compared to anticoagulant volume, and contaminated sample with resident fluid in the line or with air or venous blood, *etc*. Even after have taken all precautions to minimize the pre-analytical and analytical errors, we, recently, found, in a prospective study[62], that the measurement error for ΔPCO_2 was ± 1.4 mmHg and the smallest detectable difference, which is the least change that requires to be measured by a laboratory analyzer to identify a genuine change of measurement, was ± 2 mmHg. This means that the changes in ΔPCO_2 should be more than ± 2 mmHg to be considered as real changes and not due to natural variation[62].

Combined analysis of P (v-a) CO2 or ΔPCO_2 and O_2-derived parameters

Under situations of tissue hypoxia, a drop in VO_2 is associated with a decline in aerobic CO_2 generation while an anaerobic CO_2 generation can still arise[36,37]. Therefore, the VCO_2 being reduced less than the VO_2, a rise of the respiratory quotient (VCO_2/VO_2 ratio) can be observed[37,63]. Therefore, the rise in the respiratory quotient was suggested to identify global tissue hypoxia[63]. Because VO_2 is equal to the product of cardiac output by the difference between arterial and mixed venous O_2 content C (a-mv) O_2, and VCO_2 is proportional to the product of cardiac output and P (v-a) CO_2 the P (v-a) CO_2/C (a-mv) O_2 ratio could be utilized as indicator of the presence of global tissue hypoxia in critically ill patients. Accordingly, Mekontso-Dessap *et al*[64] tested this hypothesis in a retrospective study of critically ill patients with normalized cardiac output values and DO_2. The authors found a good correlation between P (v-a) CO_2/C (a-mv) O_2 ratio, presented as a substitute of the respiratory quotient, and arterial blood lactate level, while no correlation was found between blood lactate and P (v-a) CO_2 alone and between blood lactate and C (a-mv) O_2 alone. Moreover, for a threshold value > 1.4 the P (v-a) CO_2/C (a-mv) O_2 ratio was able to predict with reliability the presence of hyperlactatemia[64]. The authors concluded that this ratio could be utilized as a reliable indicator of the presence of global anaerobic metabolism in critically ill patients. In a more recent study, Monnet *et al*[65] found that this ratio, calculated from central venous blood [ΔPCO_2/C (a-cv) O_2], predicted an increase in VO_2 after a fluid-induced increase in DO_2 (VO_2/DO_2 dependency), and thus, can be able to detect the presence of global tissue hypoxia as accurately as the blood lactate level and far better than $ScvO_2$. In a series of 60 fluid-responder patients, we recently found that ΔPCO_2/C (a-cv) O_2 ratio at baseline predicted accurately the presence of VO_2/DO_2 dependency phenomenon and better than blood lactate (unpublished data).

In a population of 35 septic shock patients with normalized mean arterial pressure and $ScvO_2$, Mesquida *et al*[66] showed that the presence of elevated ΔPCO_2/C (a-cv) O_2 values at baseline was associated with the absence of lactate clearance within the following hours, and this condition was also associated with mortality. However, this was a retrospective study and it was not powered to explore the prognostic value of the ΔPCO_2/C (a-cv) O_2 ratio. In a recent prospective study that included 135 septic shock patients[67], Ospina-Tascon *et al*[50] found that the mixed venous-to-arterial CCO_2 difference/C (a-mv) O_2 ratio at baseline and six hours after resuscitation was an independent prognostic factor of 28 d mortality, but not P (v-a) CO_2/C (a-mv) O_2 ratio. The authors attributed this discrepancy to the fact that the PCO_2/CCO_2 relationship is curvilinear rather than linear and is influenced by many factors such as pH and oxygen saturation (Haldane effect), and under these conditions, the mixed venous-to-arterial CCO_2 difference/C (a-mv) O_2 ratio might not be equivalent to P (v-a) CO_2/C (a-mv) O_2 ratio.

From the results of those above studies[64-67], we believe that we can reasonably admit that the ΔPCO_2/C (a-cv) O_2 ratio can be used as an indicator of the presence of global tissue hypoxia in critically ill patients. Further clinical trials are needed to assess its prognostic value in patients with septic shock.

CONCLUSION

Early identification and improvement of tissue hypoperfusion are critical factors in the treatment of septic shock patients. The deficit in tissue perfusion with reduced blood flow should be considered as the primary determinant of an increase in ΔPCO_2. ΔPCO_2 should be seen as an indicator of the adequacy of venous blood flow (cardiac output) to clear the CO_2 generated by the peripheral tissues rather than as a marker of tissue hypoxia. Thus, monitoring ΔPCO_2 could be a useful complementary tool to guide the resuscitation in the early phase of septic shock (Figure 4). It can also be combined with the O_2-derived parameters in order to calculate the ΔPCO_2/C (a-cv) O_2, which can be used to detect the presence of global anaerobic metabolism. In such situation, the presence of low $ScvO_2$ (< 70%) should push the physician to increase DO_2, and if ΔPCO_2 is increased (⩾ 6 mmHg), that indicates that increasing cardiac output is the rational choice to achieve this target (Figure 4). In the presence of a normal/high $ScvO_2$ (⩾ 70%), an elevated ΔPCO_2 still suggests that rising cardiac output can be indicated with the purpose of reducing global tissue hypoxia (Figure 4). However, if both $ScvO_2$ and ΔPCO_2 are normal in a state of global anaerobic metabolism, manipulating the microcirculation will probably be ineffective to reduce oxygen deficit (Figure 4).

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REVIEW

Prevention of stress-related ulcer bleeding at the intensive care unit: Risks and benefits of stress ulcer prophylaxis

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Abstract

Stress-related mucosal disease is a typical complication of critically ill patients in the intensive care unit (ICU). It poses a risk of clinically relevant upper gastrointestinal (GI) bleeding. Therefore, stress ulcer prophylaxis (SUP) is recommended in high-risk patients, especially those mechanically ventilated > 48 h and those with a manifest coagulopathy. Proton pump inhibitors (PPI) and, less effectively, histamine 2 receptor antagonists (H2RA) prevent GI bleeding in critically ill patients in the ICU. However, the routine use of pharmacological SUP does not reduce overall mortality in ICU patients. Moreover, recent studies revealed that SUP in the ICU might be associated with potential harm such as an increased risk of infectious complications, especially nosocomial pneumonia and *Clostridium difficile*-associated diarrhea. Additionally, special populations such as patients with liver cirrhosis may even have an increased mortality rate if treated with PPI. Likewise, PPI can be toxic for both the liver and the bone marrow, and some PPI show clinically relevant interactions with important other drugs like clopidogrel. Therefore, the agent of choice, the specific balance of risks and benefits for individual patients as well as the possible dose of PPI has to be chosen carefully. Alternatives to PPI prophylaxis include H2RA and/or sucralfate. Instead of routine SUP, further trials should investigate risk-adjusted algorithms, balancing benefits and threats of SUP medication in the ICU.

Key words: Proton pump inhibitors; *Clostridium difficile*; Intensive care unit; Gastrointestinal hemorrhage; Stress; Histamine H2 antagonists; Risk assessment; Pneumonia; Physiological; Sucralfate

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Core tip: To prevent gastrointestinal (GI) bleeding due to stress-related mucosal disease, critically ill patients are often routinely treated with proton pump inhibitors (PPI) or histamine 2 receptor antagonists (H2RA) for stress ulcer prophylaxis (SUP) in the intensive care unit (ICU). While major GI bleeding is currently rare in the ICU, SUP has not improved the overall survival of ICU patients in large clinical trials. Moreover, PPI and H2RA pose significant risks including toxicity, drug-drug-interactions

and infectious complications (*e.g.*, nosocomial pneumonia or *Clostridium difficile*-associated diarrhea). Instead of routine SUP, risk-adjusted algorithms may better balance benefits and threats of SUP in the ICU.

Buendgens L, Koch A, Tacke F. Prevention of stress-related ulcer bleeding at the intensive care unit: Risks and benefits of stress ulcer prophylaxis. *World J Crit Care Med* 2016; 5(1): 57-64 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/57.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.57

INTRODUCTION

The gastric mucosa is sensitive to both hemodynamic changes and inflammatory signals in critical illness. The term stress-related mucosal disease (SRMD) has been introduced to describe the resulting mucosal damage ranging from single lesions to multiple gastric ulcers that may lead to major bleeding complications in critical ill patients[1].

With proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA) potent options for pharmacological prophylaxis of such lesions are available. Both are able to decrease the risk of a bleeding event effectively[2] and are usually well tolerated. However, pharmacological stress ulcer prophylaxis (SUP) in the intensive care unit (ICU) has not translated into a mortality benefit in prospective trials. Thus, recently, some intensivists have expressed concerns about the safety of SUP, especially with respect to infectious complications.

EPIDEMIOLOGY

SRMD, as defined by clinical, endoscopic or histological characteristics, is present in most critically ill patients[3]. However, only a few patients experience overt bleeding complications. The fraction of ICU patients with SMRD-related gastrointestinal (GI) bleeding has been reported to be as high as 17% in earlier trials and in patients without prophylaxis[4,5] but has remarkably decreased at present to rates as low as 1% or below[2,6,7].

PATHOPHYSIOLOGY

In most critically ill patients, the gastric mucosal blood flow is impaired. Reasons include systemic hemodynamic changes (hypotension and/or vasopressor therapy) and/or local alterations, *e.g.,* reduced splanchnic blood flow because of positive end-expiratory pressure in mechanical ventilated patients[8]. In addition to the ischemic tissue damage itself, hypoperfusion leads to a reduced production of several protective mechanisms that exist in a healthy stomach (Figure 1)[4]. The latter include various components such as mucus, phospholipids, bicarbonate, trefoil factor family peptides and heat-shock proteins[9]. For example, gastric ischemia/reperfusion in an experimental rat model led to an inhibition of both cyclooxygenase and lipoxygenase pathways, resulting in lower prostaglandin levels (especially PGE2), lower bicarbonate levels and decreased gastric mucosal defense[10,11]. Moreover, two important molecular regulators of vascular tension are dysregulated in critical illness. While the production of the vasodilator nitric oxide is reduced, the level of endothelin-1, a strong vasoconstrictor, is significantly increased[12,13]. This shift can further harm the mucosa.

While these mechanisms can cause mucosal damage, they are often insufficient by themselves to cause major ulcerations and gastric bleeding. A crucial component for overt damage is the presence of gastric acid. Without acid, mucosal damage is only minimal. In animal models of gastric ischemia, the addition of acid increased the damage by factor of ten[12]. This provides the rationale for the use of acid-suppressive drugs such as PPI or H2RA for pharmacological prophylaxis.

MORTALITY RISK OF STRESS ULCER-RELATED BLEEDING

An acute bleeding episode due to a stress ulcer is associated with an increased risk of death in the ICU. In a large prospective trial by Cook *et al*[14] the mortality of patients with stress ulcer bleeding was 49% compared to 9% in those without an episode of GI bleeding. This latter figure, however, appears unusually low for a general ICU population, raising the concern that related co-factors (*e.g.,* co-morbidities, medication) might have affected the mortality risk of ICU patients who experienced bleeding.

Moreover, the patients in this study mainly underwent cardiovascular surgery and only 1.6% presented with sepsis, provoking the question whether the numbers can be extrapolated to other settings of critical illness[14]. Nonetheless, a more recent study by the same authors using multivariate analysis for adjustment showed an increased relative risk (RR) of 1 to 4 (dependent on the model used) as well as an extension of the ICU stay by up to eight days in ICU patients with GI hemorrhage[15].

In contrast to these findings, in a more recent study including 1034 patients in 97 ICUs, GI bleeding was not associated with an increased mortality in multivariate analysis after adjusting for severity of comorbidity, other organ failure and age[7], in line with two meta-analyses reported in 2012 and 2013[2,16]. However, these recent studies all reported a very low incidence of stress ulcer-related bleeding due to effective pharmacological and non-pharmacological prophylactic measures, which may not allow proper assessment of true mortality risk.

RISK FACTORS FOR STRESS ULCER-RELATED BLEEDING

Multiple investigations have been conducted to identify patients at risk for stress ulcer-related bleeding. A

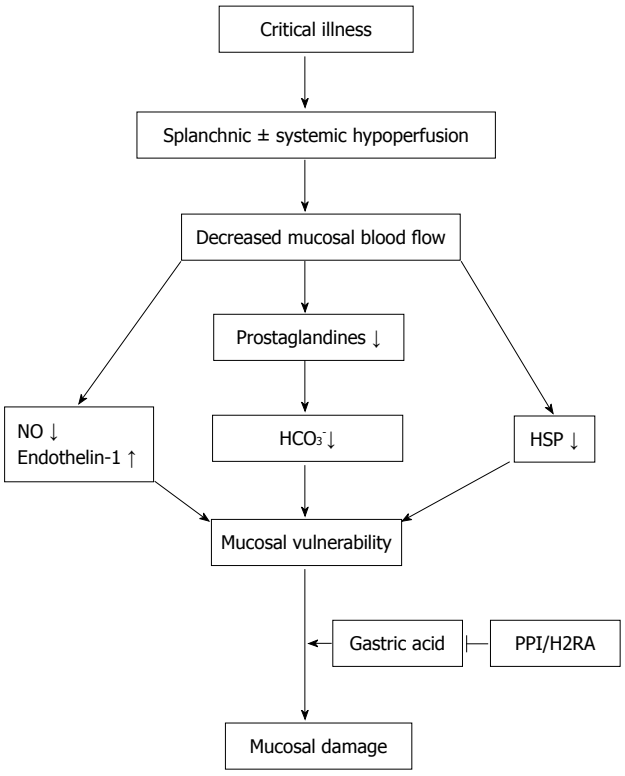

Figure 1 Pathophysiology of stress-related mucosal disease and rationale for the routine use of proton pump inhibitor/histamine 2 receptor antagonists at the intensive care unit. NO: Nitric oxide; PPI: Proton pump inhibitor(s); H2RA: Histamine 2 receptor antagonists; HSP: Heat-shock proteins; HCO_3^-: Bicarbonate.

large, prospective multicenter trial of 2252 ICU patients was able to identify at multiple regression two main risk factors: mechanical ventilation (OR = 15.6; $P < 0.001$) and coagulopathy (OR = 4.3; $P < 0.001$). In the absence of both risk factors the bleeding rate was as low as 0.1%[14]. A smaller, earlier trial came to the same conclusion[17]. A more recent inception cohort study ($n = 1034$) identified the presence of more than three or more comorbidities (OR = 8.9; 95%CI: 2.7-28.8), liver disease (OR = 7.6; 95%CI: 3.3-17.6); use of renal replacement therapy (OR = 6.9; 95%CI: 2.7-17.5); a coexisting (OR = 5.2; 95%CI: 2.3-11.8) or acute coagulopathy (OR = 4.2; 95%CI: 1.7-10.2) and higher SOFA-score (OR = 1.4; 95%CI: 1.2-1.6) as significant risk factors after multivariate analysis. Interestingly, mechanical ventilation was not associated with an increased risk of GI bleeding in this trial[7].

Other risk factors with a lower degree of evidence include patients with severe head trauma, those who have had extended surgeries with operation times exceeding 4 h as well as patients with acute kidney or hepatic failure, sepsis, hypotension, a history of gastrointestinal bleeding, high-dose corticosteroids, burn patients, advanced age and male sex[1,3,17,18]. This wide spectrum of suggested risk factors has prompted the rather unselected use of pharmacological SUP in the ICU setting, resulting in the routine use of PPI and/or H2RAs in > 80% of critically ill patients as reported in in many observational studies[6,7].

INDICATIONS FOR PHARMACOLOGICAL PROPHYLAXIS

While SRMD-related bleeding can have severe clinical impact, acid-suppressive medication effectively decreases bleeding rates as demonstrated by multiple meta-analyses on this topic[19-22]. Although the quality of the available data has been criticized[23], both national and international guidelines recommend stress ulcer prophylaxis (SUP) in critically ill patients with sepsis and other risk factors[24,25].

In our ICU, patients with at least one of the following risk factors are recommended to receive pharmacological ulcer prophylaxis based upon current evidence: Mechanical ventilation, coagulopathy, history of an upper gastrointestinal bleeding within the past 12 mo, severe sepsis or septic shock, or cardiogenic shock. Additionally, we consider ulcer prophylaxis for the following patients based on weaker evidence: burn patients, those with cranio-cerebral injury, acute renal failure, known peptic ulcer disease, those post kidney or liver transplantation and patients taking non-steroidal anti-inflammatory drugs (NSAID) or high-dose glucocorticoids. The algorithm that we propose for SUP in the ICU is presented as Figure 2.

However, it is mandatory to frequently re-evaluate the individual indication both during and after ICU stay. Buckley *et al*[26] could show that 14.4% of patients in an ICU received acid suppression without proper indication, which resulted in unnecessary risk of side effects (see below) and unnecessary costs (> 200000 dollar annually in the study hospital).

While prophylaxis effectively decreases the risk of stress ulcer-related bleeding, it is important to stress that no single trial and/or meta-analysis has been able to convincingly demonstrate a benefit regarding survival. Outside an ICU or even in outpatients, very little evidence supports the use of stress ulcer prophylaxis; for instance, patients with cardiovascular diseases who have concomitant newly prescribed with the oral anticoagulant dabigatran may be at lower risk for severe GI bleedings if PPI are administered[27]. Without a proper indication or a clear high-risk assessment, SUP should be discontinued, because it might cause unnecessary harm (see below) as well as costs[22].

PHARMACOLOGICAL PROPHYLAXIS

If a stress ulcer prophylaxis is necessary, different options are available: Options include the acid-suppressing drugs, PPI and H2RA, or the mucosa-protective agent sucralfate. Sucralfate is a reasonable option and reduces the risk of stress ulcer-related bleeding. However, a large trial revealed its inferiority to H2RA[28], so that an acid-suppressive medication is preferred for SUP.

There are several trials and meta-analyses comparing PPI to H2RA. Most of them favor PPI with respect to reduction of bleeding rates (Table 1). Regarding mortality, no analysis has been able to show a significant difference. Currently, PPI are the agents of choice in SUP.

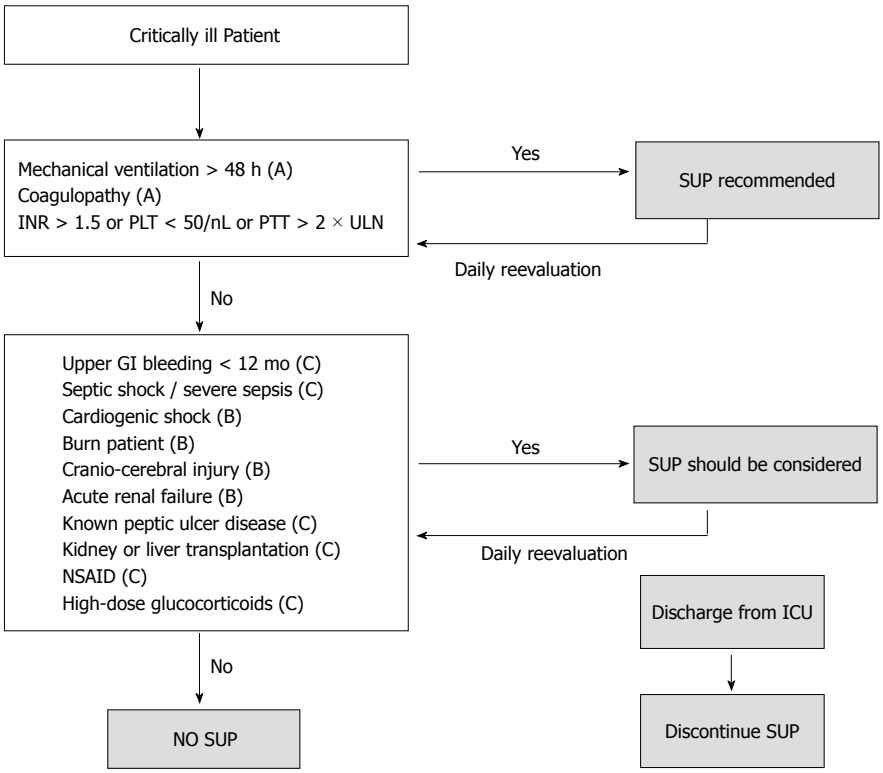

Figure 2 Proposed algorithm for stress ulcer prophylaxis. For the different indications for SUP, the level of evidence is provided [A: Multiple randomized trials or meta-analysis, B: Single randomized or large non-randomized trial(s), C: Expert opinion or retrospective studies]. GI: Gastrointestinal; ICU: Intensive care unit; INR: International normalized ratio; NO: Nitric oxide; NSAID: Nonsteroidal anti-inflammatory drugs; PLT: Platelets; PTT: Partial thromboplastin time; SUP: Stress ulcer prophylaxis.

Table 1 Efficacy of proton pump inhibitor compared to histamine 2 receptor antagonists at the intensive care unit

Meta-analysis	*n*	Risk reduction (bleeding)	Risk reduction (mortality)
Alhazzani *et al*[2]	1720	RR = 0.36 (95%CI: 0.19-0.67)	RR = 1.01 (95%CI: 0.83-1.24)
Pongprasobchai *et al*[59]	569	OR = 0.42 (95%CI: 0.20-0.91)	n/a
Barkun *et al*[60]	1587	OR = 0.30 (95%CI: 0.17-0.54)	OR = 1.19 (95%CI: 0.84-1.68)
Lin *et al*[61]	936	RD = 0.04 (95%CI: 0.09-0.01)	RD = 0.00 (95%CI: 0.04-0.05)

n/a: Not assessed; *n*: Patients included in the meta-analysis; RR: Relative risk; OR: Odds ratio; PPI: Proton pump inhibitor(s); RD: Risk difference.

ADVERSE EVENTS

Gastric acid is a natural physiological barrier against ingested pathogens. Pharmacological acid suppression alters this barrier significantly. Subsequently, it is associated with gastric and duodenal bacterial overgrowth[29]. This effect is stronger in patients receiving PPI than in those taking H2RA[30]. The loss of this natural barrier may lead to intestinal (*e.g., Clostridium difficile*-associated diarrhea), but also to extra-intestinal infections (*e.g.,* pneumonia, possibly *via* retrograde microaspiration). In addition, both PPI and H2RA potentially affect leucocyte function: Experimental studies have shown an effect of these drugs on both phagocytosis by neutrophils itself and the acidification of the phagolysosome in neutrophils necessary to kill its contents[31,32].

As the effects of acid-suppressing drugs may render patients susceptible for infections, two main complications have to be considered: *Clostridium difficile*-associated diarrhea (CDAD) and pneumonia. In outpatients and patients on standard care wards, it has been shown that PPI increase the risk of both significantly[6,33-44]. Additionally, experiments in mice suggest that acid suppression favors intestinal colonization with multi-resistant bacteria such as Vancomycin-resistant *Enterococcus faecium* (VRE) or multi-resistant *Klebsiella pneumonia*[45].

In the setting of SUP in the ICU, the data are controversial (Table 2). Two meta-analyses failed to show any effect on the rate of nosocomial and/or ventilator-associated pneumonia[2,16]. However, only seven of the original studies included reported on pneumonia. In contrast, a small (n = 137) but prospective and randomized trial showed a strong increase in ventilator-associated pneumonia within the PPI group compared to placebo (36.4% *vs* 14.1%, $P < 0.001$)[46].

A retrospective study from our group found a significant association of PPI with pneumonia only by univariate but not by multivariate analysis[6]. A prevalence study including over 10000 patients from 17 countries identified SUP as an independent risk factor for infections[47]. Thus, the role of acid suppression as a risk factor for pneumonia is unclear but remains likely. Larger randomized prospective

Table 2 Acid suppression as a risk factor for pneumonia at the intensive care unit

Acid suppression as a risk factor for		Pneumonia
Barkun *et al*[16]	Meta-analysis	OR = 1.05 (95%CI: 0.69-1.62)
Alhazzani *et al*[2]	Meta-analysis	RR = 1.06 (95%CI: 0.73-1.52)
Khorvash *et al*[6]	Randomized controlled trial	14.1% without *vs* 36.4% with PPI, $P < 0.001$
Buendgens *et al*[6]	Retrospective cohort study	OR = 1.28 (95%CI: 0.95-1.73)

OR: Odds ratio; RR: Relative risk; PPI: Proton pump inhibitor.

trials are warranted to resolve this issue.

The main infection route of *C. difficile* is *via* ingestion of its spores and its vegetative forms. While the spores are naturally resistant to acid, the vegetative form is normally killed by acid in the stomach. If the stomach pH is raised above 5, *Clostridia* species show drastically improved survival. Given that the stool of infected individuals contains tenfold more vegetative forms than spores, this might explain an association of PPI and H2RA with CDAD[48].

Although no prospective data is available on this matter for critically ill patients, studies suggest an association between pharmacological SUP and CDAD in the ICU (Table 3). A small case-control study showed a positive association between the duration of PPI therapy and the risk of CDAD[49]. A retrospective study with 3286 ICU patients demonstrated PPI as an independent risk factor for CDAD by multivariate analysis (OR = 3.11; 95%CI: 1.11-8.74), comparable to the risk for CDAD associated with the use of fluoroquinolones or third-generation cephalosporins. Moreover, in this trial an ICU-onset CDAD was associated with an increased mortality (OR = 1.59; 95%CI: 1.06-2.41)[6]. Another recent study from Canada revealed a significant association with CDAD recurrence rates and continuation of PPI therapy (OR = 1.5; 95%CI: 1.1-2.0), similar to antibiotic reexposure (OR = 1.3; 95%CI: 0.9-1.7)[50].

Patients with liver cirrhosis appear to pose a population particularly prone to adverse effects of SUP. A prospective study including 272 patients with cirrhosis found the use of PPI to be an independent risk factor for overall mortality by multivariate analysis in those patients (HR = 2.3; 95%CI: 1.3-4.3)[51]. Reasons for this might be an increased risk of spontaneous bacterial peritonitis in addition to higher rates of pneumonia and CDAD[52-54].

Drug-drug-interactions are another concern for using PPI, especially in ICU patients. An important possible interaction exists between the antiplatelet agent clopidogrel and various PPI. In 2009, a study reported increased cardiovascular events in patients taking both clopidogrel and PPI[55]. The antiplatelet agent clopidogrel is a prodrug, dependent on the enzyme CYP2C19. *In vitro* PPI inhibit CYP2C19 and potentially inhibit clopidogrel. It remains unclear if this experimental finding is of clinical

Table 3 Proton pump inhibitor as a risk factor for *Clostridium difficile*-associated diarrhea at the intensive care unit

PPI as a risk factor for		*Clostridium difficile*-associated diarrhea (OR, 95%CI)
Barletta *et al*[49]	Case control study	1.14 (1.02-1.27)
Buendgens *et al*[6]	Retrospective cohort study	3.11 (1.11-8.74)

OR: Odds ratio; PPI: Proton pump inhibitor.

importance, since the patients with concomitant use of PPI and clopidogrel might have had a higher intrinsic risk due to greater age and more cardiovascular risk factors. In order to overcome this potential interaction, independent ingestion times, the use of pantoprazole (a PPI with low interaction potential) and/or replacing clopidogrel with ticagrelor, which is not a prodrug, have been suggested.

Other side effects of PPI potentially relevant for critically ill patients include toxicity to liver or bone marrow and hypomagnesaemia. The latter has resulted in a recent warning from the Food and Drug Administration of the United States[56]. Osteopenia, another known association, seems less important acutely in ICU patients[57]. It is currently unknown if those adverse effects affect the prognosis of patients in an ICU.

ENTERAL NUTRITION

With regard to the potential adverse effects of SUP as described above, potential alternatives have been discussed. One should also keep in mind that both PPI and H2RA do not have a direct effect on the SRMD pathophysiology of reduced blood flow and altered balance between vasoconstrictors and dilatators (Figure 1). Enteral nutrition, in contrast, potentially has a positive impact on both[58]. Enteral nutrition could therefore be a viable alternative to pharmacological SUP. However, no prospective data is available on this subject. A meta-analysis of data available on 1836 patients disclosed that in presence of enteral nutrition a pharmacological SUP did not significantly change the risk of stress ulcer-related bleeding. Interestingly, in those patients that were enterally fed and treated with SUP the risk of pneumonia was increased (OR = 2.81; 95%CI: 1.2-6.6) compared to patients on parenteral nutrition. In this subgroup, even an increase in mortality was observed[21]. Therefore, the role of enteral nutrition in SUP should be further explored in randomized prospective trials.

CONCLUSION

Critically ill patients often develop gastrointestinal lesions due to altered perfusion of the gastric mucosa, reduced protective mucosal factors and increased gastric acid, rendering them at risk for GI bleeding due to SRMD or ulcers. Pharmacological SUP is performed in the majority of ICU patients at present, with PPI or H2RA effectively preventing GI bleeding. However, this common practice

is currently debated, due to the fact that SUP does not significantly improve mortality of ICU patients, while acid suppression poses relevant risks. Specifically, nosocomial pneumonia and *Clostridium difficile* associated diarrhea are potential serious complications of SUP. Thus, SUP should follow a clear algorithm balancing risks and benefits (Figure 2). Alternative strategies like enteral feeding or restricting SUP to the early phase of ICU treatment or to patients with an exceptional high-risk profile deserve evaluation in prospective randomized trials.

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REVIEW

Respiratory mechanics in brain injury: A review

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Abstract

Several clinical and experimental studies have shown that lung injury occurs shortly after brain damage. The responsible mechanisms involve neurogenic pulmonary edema, inflammation, the harmful action of neurotransmitters, or autonomic system dysfunction. Mechanical ventilation, an essential component of life support in brain-damaged patients (BD), may be an additional traumatic factor to the already injured or susceptible to injury lungs of these patients thus worsening lung injury, in case that non lung protective ventilator settings are applied. Measurement of respiratory mechanics in BD patients, as well as assessment of their evolution during mechanical ventilation, may lead to preclinical lung injury detection early enough, allowing thus the selection of the appropriate ventilator settings to avoid ventilator-induced lung injury. The aim of this review is to explore the mechanical properties of the respiratory system in BD patients along with the underlying mechanisms, and to translate the evidence of animal and clinical studies into therapeutic implications regarding the mechanical ventilation of these critically ill patients.

Key words: Brain damage; Respiratory mechanics; Positive end-expiratory pressure; Lung injury; Ventilator-induced lung injury

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Core tip: Clinical and experimental evidence supports that preclinical lung injury occurs shortly after brain damage. Brain-damaged patients exhibit altered respiratory system mechanics and hypoxemia, even in the absence of clinically evident lung injury. Measurement of respiratory mechanics in such patients may reveal brain damage related lung injury early enough, and facilitate selection of the appropriate ventilator settings to avoid ventilator induced lung injury. Lung protective ventilation, consisting of low tidal volume and moderate levels of positive end-expiratory pressure, may prevent a further deterioration of respiratory dysfunction, and could be possibly associated with improved outcome.

Koutsoukou A, Katsiari M, Orfanos SE, Kotanidou A, Daganou M, Kyriakopoulou M, Koulouris NG, Rovina N. Respiratory mechanics in brain injury: A review. *World J Crit Care Med* 2016; 5(1): 65-73 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/65.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.65

INTRODUCTION

Brain damage (BD), either due to spontaneous hemorrhage or trauma, represents one of the most important causes of death and disability in modern societies. Although morbidity and mortality of these patients are due principally to their primary disease, medical complications are frequent, with respiratory dysfunction being the most common[1-3]. Up to one third of BD patients develop acute respiratory distress syndrome (ARDS), a complication that has been associated with poor outcome[4,5].

Several clinical and experimental studies have confirmed that lung injury occurs shortly after brain damage. Rogers *et al*[6] found a significant increase of the lung weight along with edema, congestion and hemorrhage in 50% of patients who died within 96 h after isolated brain damage.

Ultrastructural changes in type Ⅱ pneumocytes along with an inflammatory response in the lung, similar to that induced by high tidal volume ventilation, have been observed in animals within the first hours of traumatic brain injury[7]. Similarly, alterations in lung architecture, such as alveolar hemorrhage, proteinaceous debris and neutrophilic infiltration were detected by Weber *et al*[8] in experimental traumatic brain damage. In addition, decreased pulmonary tolerance to subsequent mechanical stress due to mechanical ventilation[9], as well as aggravation of preexisting lung injury[10] have been reported after massive brain damage in animals.

Although experimental as well as clinical evidence support the existence of a close interaction between the brain and lungs[11], the mechanisms by which brain damage leads to alterations in pulmonary function are unclear. They may involve neurogenic pulmonary edema, inflammation, neurotransmitter-related engagement, or adverse effects of neuroprotective therapies[12,13].

Mechanical ventilation is an essential component of life support in brain damaged patients. It is well known that, despite being lifesaving, mechanical ventilation may nonetheless cause or perpetuate lung injury if alveolar overdistention and repeated alveolar collapse and re-expansion occurs with each breath [ventilator-induced lung injury (VILI)][14]. Non lung protective mechanical ventilation could thus constitute an additional traumatic factor to the already injured or susceptible to injury lungs of such patients[9,15]. Indeed, recent research has found that a lung protective strategy is an independent predictor of favorable outcome of BD patients[16]. Furthermore, it has been shown that lung protective strategy prevented the decline of pulmonary function consequent to brain death and increased the number of lungs available for transplantation[17], a finding particularly important in the context of lung transplantation because of the scarcity of lung donors. In relation to the latter, it should be noted that preclinical lung injury may be present in BD patients with "normal" chest X-rays; thus it is of paramount importance to have a marker that could detect such an injury.

Measurement of respiratory mechanics in brain damaged patients, as well as assessment of their evolution during mechanical ventilation, may help in the detection of lung injury early enough, but also in selecting the appropriate ventilator settings to avoid VILI.

The aim of this review is to explore the mechanical properties of the respiratory system in brain damaged patients along with the underlying mechanisms, and translate the evidence of animal and clinical studies into therapeutic implications regarding the mechanical ventilation of these critically ill patients.

RESEARCH

The information in this review is based on results of a Medline and OVID search. The key words used were related to brain damage (traumatic brain injury, hemorrhagic stroke, intracranial pressure, brain death), and to acute lung injury/ARDS and mechanical ventilation (pulmonary edema, acute respiratory distress syndrome, ventilator induced lug injury, inflammation, respiratory mechanics, mechanical ventilation, tidal volume, positive end-expiratory pressure, lung transplantation). We read relevant articles in full, searched their reference lists, and chose the most relevant on the basis of findings and clinical significance. Bibliographies of identified articles, guidelines and conference proceedings of professional societies were reviewed for additional references.

FROM THE BRAIN TO THE INJURY OF THE LUNGS

Several nonexclusive mechanisms have been implicated in the brain to lungs' injury process. Pulmonary dysfunction

after brain damage has long been attributed to an increased sympathetic activity. Massive catecholamine release may lead to neurogenic pulmonary edema[18], that is the extravasation of fluid from the blood into the alveolar and interstitial space of the lungs in patients who have suffered an acute neurological event. Several theories have been proposed considering the pathophysiology of this entity. The mostly recognized is the "blast injury" theory, suggesting that the sympathetic storm which follows a sudden increase in intra-cranial pressure induces a transient increase in intravascular pressure and the consequent disruption of the alveolo-capillary membrane[18]. The development of neurogenic pulmonary edema is attributed either to hydrostatic forces, as it is supported by a low pulmonary/plasma protein ratio[19], or to high permeability mechanisms supported by increased accumulation of pulmonary extravascular protein[20]. The association between massive sympathetic discharge and neurogenic pulmonary edema is further supported by a more recent experimental study showing that pretreatment of brain-damaged rats with alpha-adrenergic antagonists prevented the hypertensive response and attenuated the subsequent lung injury[21].

In addition to the "blast injury" theory, a systemic inflammatory response seems to play a critical role in the development of lung injury after brain damage. Clinical studies in acutely brain-damaged patients have suggested an increased intracranial production[22] and release[23] of pro-inflammatory mediators into the systemic circulation along with possible activation of inflammatory cascades. Intracranial production of inflammatory cytokines probably takes place in brain microglia and astrocytes[23], while through the altered blood-brain barrier these mediators can reach peripheral organs leading to multi-organ dysfunction[22,24,25]. Indeed, Fisher *et al*[26] detected an increased concentration of proinflammatory cytokines in the bronchoalveolar lavage fluid (BALF) of patients with fatal BD. The same group later reported that increased levels of BALF interleukin-8 (IL-8) in brain dead lung donors correlated with severe early graft dysfunction and recipient mortality, pointing out to the key role of such a preclinical inflammatory process[27].

Several experimental studies have confirmed the existence of a systemic inflammatory process in BD. In animals with acute brain injury, Kalsotra *et al*[28] detected a significant migration of macrophages and neutrophils into the lungs at 24 h post injury, associated with enhanced pulmonary leukotriene B4 production. Skrabal *et al*[29] investigated the very early organ-specific inflammation responses after brain death in pigs and found an up-regulation of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), IL-1β and IL-6 in the animal lungs. All these substances are mediators that may modulate the expression of adhesion molecules and consequent activity[30]. In fact, an up-regulation of the soluble intercellular adhesion molecule-1 (ICAM-1) was found in the lungs of BD animals[29]. Similarly, Cobelens *et al*[31] found that experimental subarachnoid hemorrhage was associated with neutrophil influx into the lungs as well as increased expression of pulmonary adhesion molecules and chemokines. Adhesion molecules through activation, firm adhesion, and the chemotactic migration of leukocytes[32] may contribute to lung injury. In this respect, a strong association between increased serum levels of ICAM-1 and poor neurological outcome has been found by McKeating *et al*[33] in a cohort of BD patients. Among other molecules that have been linked with the brain to lung injury process are S-100B, E-Selectin and caspase-1[10,34]. Moreover, altered activity of pulmonary capillary endothelial angiotensin converting enzyme is present in brain dead subjects denoting preclinical pulmonary endothelial dysfunction[35]. In a similar respect, the presence of preclinical pulmonary inflammation in mechanically ventilated BD patients was revealed by markers measured in exhaled breath condensate[36].

Very recently, Nicolls *et al*[37] demonstrated that acute lung injury that followed traumatic brain injury in animals was mediated by high-mobility group box-1 (HMGB1), a nuclear protein that serves as an early mediator of inflammation[8]. The authors additionally showed that HMGB1 activates inflammatory responses through binding to receptor for advanced glycation end products (RAGE). The fact that RAGE is highly expressed on lung epithelial cells could partially explain why the lung is so sensitive to damage after brain injury.

Severe brain damage may induce lung injury through modulation of neurokinins since such substances are released in patients with BD[38,39]. Substance P and neurokinin A have been implicated in bronchoconstriction, mucosal edema, increased vascular permeability, pulmonary edema and leukocyte adhesion activation[39]. Chavolla-Calderón *et al*[40] demonstrated that the derangement of the substance P receptor protects against pulmonary inflammation.

Finally, it has been suggested that excessive lung inflammation may be the result of BD-induced impairment of the parasympathetic nervous system leading to loss of the protective cholinergic anti- inflammatory pathway[41,42]. Kox *et al*[43] have suggested that BD-associated increased intracranial pressure (ICP) may alter the immunoregulatory function of the vagus nerve, which may operate as an additional means through which the brain exerts control over cytokine expression[41]. Indeed, it has been reported that vagus nerve stimulation was followed by inhibition of TNF-α, IL-1, IL-6, IL-8 and HMGB1 release[44]. dos Santos *et al*[45] supported the protective role of the cholinergic ant-inflammatory pathway, demonstrating that vagus nerve stimulation attenuated lung injury while in contrast vagotomy exacerbated VILI.

Regardless of the responsible mechanisms, an injurious ventilatory strategy in the presence of an established inflammatory process may act as an additional stimulus that can aggravate lung damage. A "double hit" model could explain the development of organ failure associated

with acute brain injury[15]. "First hit" corresponds to the adrenergic boost and systemic production and release of inflammatory mediators that make the lungs more vulnerable to a subsequent "second hit", such as the mechanical stress induced by mechanical ventilation or the ischemia/reperfusion that may be seen in lung transplants[15].

RESPIRATORY MECHANICS AND GAS EXCHANGE

Although, as already mentioned, pulmonary dysfunction is a well-recognized complication of brain damage, it is surprising that until now very few studies have assessed respiratory mechanics in this group of patients. Moreover, although these patients usually need prolonged mechanical ventilation due to coma, few studies have assessed the impact of ventilatory settings on respiratory mechanics.

Two decades ago, Tantucci *et al*[46] studied a group of BD patients and found increased respiratory system flow resistance (Rmin,rs). Increased respiratory system resistance was also detected by Gamberoni *et al*[47] in BD patients with and, importantly, without respiratory failure. It should be noted that increased Rmin,rs was also found on the first day of mechanical ventilation in BD patients without acute lung injury[48].

Increased Rmin,rs could be attributed to bronchoconstriction, as a result of hyperventilation and consequent hypocapnia that are usually therapeutically applied in these patients. In anesthetized and paralyzed normal subjects (*i.e.*, without apparent lung pathology), D'Angelo *et al*[49] have shown that decreased partial pressure of arterial carbon dioxide ($PaCO_2$) was associated with a significant increase in Rmin,rs. However, additional factors inducing bronchoconstriction and airway mucosal edema, such as neuropeptides, cannot be excluded as potential mechanisms, since such substances appear to be released and circulate in patients with BD[38,39]. Finally, an altered control of airway caliber has been proposed as a likely explanation for the increased respiratory system resistance[47].

Increased respiratory system elastance (Est,rs) has been found in experimental[8,50] as well as in clinical BD without acute lung injury[47,48,51]. Interestingly, only one study[46] reported non increased Est,rs, but this may reflect the high tidal volumes used for ventilation in the past (15 mL/kg).

Increased extravascular lung water, a manifestation of pulmonary edema resulting from the sympathetic hypereactivity elicited by the central nervous system injury, might partially explain the aforementioned increased Est,rs. In this regard, it should be noted that, despite relatively normal chest X-rays, increased lung densities have been detected in CT scans of patients with BD[47]. In a similar respect, increased extravascular lung water along with CT scan lung densities were detected in animals soon after the induction of intracranial hypertension[10].

Finally, atelectasis, associated with anesthesia and paralysis or with impaired production/function of pulmonary surfactant as a result of brain damage, as well as alterations in chest wall mechanics, may be additional potential explanations for the increased Est,rs in this setting[7,47,48,52,53].

Gas exchange

Although hypoxemia is present in a substantial percentage of BD patients[15,47,48,54] and has been recognized as a secondary insult associated with poor neurological outcome[55-57], data on gas exchange in such patients are scarce. A moderate to severe impairment of oxygenation has been noted in patients with isolated brain injury in the absence of abnormal chest X-rays[6,58,59]. Similarly, a ratio of partial pressure of arterial of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) below the normal limit was detected on the first day of mechanical ventilation in BD patients without acute lung injury[48], while oxygenation further deteriorated after 5 d on mechanical ventilation.

Weber *et al*[8] reported that in animals with BD the degree of inflammation, as expressed by serum levels of HMGB1 were correlated with PaO_2/FiO_2. Mascia *et al*[60] found that BD patients who subsequently developed ARDS had at baseline an abnormal PaO_2/FiO_2 ratio (< 300 mmHg), and that hypoxemia was the strongest independent predictor of ARDS development. Ventilation/perfusion (V/Q) mismatch and shunt, the main pathophysiological mechanisms of hypoxemia[61] ensuing from airway closure and atelectasis due to lung surfactant depletion[7,53] and/or increased extravascular lung water[10,47] might explain oxygenation impairment.

Given that brain damage patients are usually hyperventilated for neuroprotection, data on ventilation and $PaCO_2$ disturbances are missing.

VENTILATORY STRATEGIES

Ventilatory management of brain-damaged patients presents a major challenge for physicians since the fragile lung-brain balance must be preserved. The ventilatory strategy on one hand aims at maintaining adequate oxygenation and avoiding hypercapnia in order to protect the intracranial pressure and cerebral blood flow, and thus prevent secondary brain injury; on the other hand though it should avoid VILI. In addition, it should be noted that injurious mechanical ventilation per se may cause brain activation[62] or damage to selected brain areas[63] and thus, the selection of appropriate ventilatory settings becomes of paramount importance.

According to the guidelines for the management of severe traumatic brain injury intense hypocapnia should be avoided, because it may compromise cerebral blood flow and aggravate hypoperfusion[64]. However, traditional ventilatory management of BD patients involves high tidal volumes to maintain mild hypocapnia ($PaCO_2$-30-35 mmHg) for the treatment of intracranial

hypertension accompanied by low levels of positive end-expiratory pressure (PEEP) to optimize oxygenation without impeding cerebral venous drainage[64].

Furthermore, it is well established that this ventilatory strategy can exacerbate the pulmonary and systemic inflammatory response in patients with ARDS[65]. Even in patients without ARDS, ventilation with high tidal volumes proved to have deleterious effects and to induce VILI[66]. Moreover, according to the "double hit" theory, once the lungs are primed from a severe brain injury, they may become more susceptible to the injurious effects of mechanical ventilation[15] making VILI development more probable. In this respect, it was demonstrated that apparently healthy lungs of animals subjected to massive brain-injury developed more alveolar damage under injurious mechanical ventilation[9].

In clinical settings, high tidal volume and low PEEP have been implicated in deterioration of respiratory mechanics and unfavorable outcome in BD patients. A recent clinical study reported that in patients with severe brain injury, high tidal volumes, high respiratory rates, and hypoxemia were the stronger independent predictors of ARDS development[60]. Similarly, in mechanically ventilated patients with intracerebral hemorrhage, Elmer *et al*[16] showed that high tidal volumes were among the factors associated with ARDS development. High mechanical stretch with consequent alveolar distention, alveolar epithelial and vascular endothelial disruption and inflammation[14] may have contributed to the exacerbation of lung injury and ARDS in the already primed lungs of these patients[16].

Furthermore, in BD patients without acute lung injury, application of moderate levels of PEEP for 5 d prevented lung damage, as assessed by the increased Est,rs, present in the group of patients ventilated on zero end-expiratory pressure (ZEEP)[48]. In a later study, BD patients with no apparent lung pathology ventilated with ZEEP exhibited early and sustained increases of circulating inflammatory indices as compared to patients on 8 cmH_2O of PEEP[36]. Avoiding end-expiratory collapse and maintenance of recruited alveoli by applying PEEP, may protect against "low volume" injury, that is the lung damage attributable to airway closure or heterogeneous constriction[67-72]. Atelectasis in the dependent lung zones and peripheral airway closure usually develop during general anesthesia even in normal lungs[52]. In BD patients, abnormal surfactant production due to injury of pneumocytes Ⅱ[7] or release of inflammatory mediators could enhance peripheral airway closure and atelectasis formation. Under these disorders, opening and closing of peripheral airways during tidal breathing would be possible, leading to the development of shear stresses that can damage peripheral airways[67]. In the presence of airway closure there is heterogeneous lung filling and emptying, conditions which might contribute to lung injury[73-75].

Application of PEEP in mechanically ventilated brain-injured patients has been considered controversial. Although PEEP can optimize oxygen delivery to the brain[54,76], it may result in raised mean intrathoracic pressure and therefore might increase ICP through reducing venous drainage. Additionally, the increased intrathoracic pressure could lead to a decrease in arterial pressure, which in turn may decrease cerebral blood flow in patients with impaired cerebral autoregulation[77].

Clinical studies addressing the effect of PEEP in BD patients have mainly focused on the ICP and cerebral perfusion pressure (CPP) showing conflicting results[78-80]. The Starling resistor model serves the most suitable interpretation of the PEEP effect on the ICP[81]. Luce *et al*[81] documented in an animal study that the consequences of PEEP on ICP were more evident whenever the applied PEEP was higher than ICP. Later, McGuire *et al*[82], in a clinical study, provided evidence that PEEP levels up to 15 mH_2O were not transmitted to central nervous system if baseline ICP values were higher than the applied PEEP.

Unexpected findings have been reported by Huynch *et al*[83] who have shown that increases in PEEP up to 15 cmH_2O, in 5 cmH_2O increments, correlated with reduction in ICP and augmented CPP. Nevertheless, no physiologic explanations have been provided for these findings.

Decrease in mean arterial pressure as a consequence of increased intrathoracic pressure has been implicated as a responsible mechanism of PEEP-induced decrease in CPP. An observational study involving patients with subarachnoid hemorrhage demonstrated that restoration of mean arterial pressure returned CPP to baseline, supporting a PEEP-dependent decrease of the former as the underlying mechanism of CPP reduction post PEEP application, rather than an increase in ICP[84]. In this regard, Doblar *et al*[85] showed that euvolemia, achieved with hypertonic volume expanders, averted an undesired reduction in arterial and cerebral perfusion pressure after application of various levels of PEEP.

The elastic properties of the respiratory system and its components could have an impact on the PEEP effect on ICP. In cases of low chest wall compliance or normal lung compliance, PEEP may increase intrathoracic pressure. On the contrary, reduced lung compliance could exert a protective role by minimizing airway pressure transmission[86]. However, clinical studies investigating the influence of respiratory system mechanics on the transmission of PEEP to the intracranial compartment have reported conflicting results[78,87]. Caricato *et al*[51] found that PEEP application resulted in reduction of CPP only in patients with normal respiratory system compliance, but had no effect on ICP regardless of the latter. Recently, a clinical study in patients with hemorrhagic stroke and respiratory system compliance within normal range displayed that, although PEEP up to 14 cmH_2O significantly increased ICP, arterial and cerebral perfusion pressures were not affected and thus the observed increases in ICP were not clinically meaningful[88].

Application of PEEP may affect cerebral circulation through CO_2-mediated mechanisms[89]. An increase in

$PaCO_2$ directly causes vasodilation of cerebral arteries and a consequent increase in cerebral blood volume, which might result in a rise in ICP if intracranial compliance is reduced. In patients with severe brain injury and acute lung injury, Mascia *et al*[60] studied the cerebro-pulmonary interactions during the application of low PEEP levels. In brain-damaged patients with "relatively normal" ICP, these investigators found that when the application of PEEP induced hyperinflation with consequent increase in $PaCO_2$, the ICP increased; in contrast when PEEP resulted in alveolar recruitment there were no effects on ICP and cerebral perfusion.

Despite the aforementioned clinical and experimental studies, the ideal ventilation strategy for patients with massive brain damage has not been clarified. The "open lung" approach which integrates the use of low tidal volumes with high PEEP, despite its beneficial effect on morbidity and/or mortality in ARDS patients, has not been extensively studied in brain-injured patients. Wolf *et al*[93] found that an "open lung" approach, consisting of low tidal volumes and elevated PEEP levels after performing recruiting maneuvers, improved respiratory function in neurosurgical patients with severe respiratory failure without generating negative effects on cerebral physiology. A recent animal study demonstrated that an "open lung" approach, consisting of low tidal volumes and PEEP set according to the minimal Est,rs, attenuated lung injury in rats with massive brain damage[90]; however neurological parameters and therefore the potential impact of the open lung strategy on brain damage were not evaluated in this study.

At present, it seems that the use of low tidal volume to avoid overdistention, and of moderate levels of PEEP to improve oxygenation and to avoid "low volume" injury, may be appropriate in patients with brain damage; however mean arterial pressure should be preserved and close attention to ICP and CPP alterations should be given.

CONCLUSION

Several clinical and experimental studies have confirmed that lung injury occurs shortly after brain injury. Brain-damaged patients without acute lung injury exhibit alterations of respiratory system mechanics, mainly increased respiratory system elastance and airway resistance, and hypoxemia. Ventilatory management of such patients should aim at optimizing neurologic protection, but at the same time at preventing further deterioration of respiratory dysfunction. Modifiable ventilator parameters possibly associated with improved outcome include low tidal volumes and moderate levels of PEEP. Nevertheless, more studies are needed to elucidate the potential beneficial role of an "open lung"approach in brain-damaged patients with respiratory compromise.

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MINIREVIEWS

Preemptive mechanical ventilation can block progressive acute lung injury

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Abstract

Mortality from acute respiratory distress syndrome (ARDS) remains unacceptable, approaching 45% in certain high-risk patient populations. Treating fulminant ARDS is currently relegated to supportive care measures only. Thus, the best treatment for ARDS may lie with preventing this syndrome from ever occurring. Clinical studies were examined to determine why ARDS has remained resistant to treatment over the past several decades. In addition, both basic science and clinical studies were examined to determine the impact that early, protective mechanical ventilation may have on preventing the development of ARDS in at-risk patients. Fulminant ARDS is highly resistant to both pharmacologic treatment and methods of mechanical ventilation. However, ARDS is a progressive disease with an early treatment window that can be exploited. In particular, protective mechanical ventilation initiated before the onset of lung injury can prevent the progression to ARDS. Airway pressure release ventilation (APRV) is a novel mechanical ventilation strategy for delivering a protective breath that has been shown to block progressive acute lung injury (ALI) and prevent ALI from progressing to ARDS. ARDS mortality currently remains as high as 45% in some studies. As ARDS is a progressive disease, the key to treatment lies with preventing the disease from ever occurring while it remains subclinical. Early protective mechanical ventilation with APRV appears to offer substantial benefit in this regard and may be the prophylactic treatment of choice for preventing ARDS.

Key words: Mechanical ventilation; Acute lung injury;

Acute respiratory distress syndrome; Airway pressure release ventilation

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Core tip: Mortality from acute respiratory distress syndrome (ARDS) remains unacceptably high. Treating fulminant ARDS, however, is currently relegated to supportive care measures only. Thus, the best treatment for ARDS may lie with preventive measures. Indeed, since ARDS is a progressive disease, treating this disease in its subclinical phases may prevent the disease from ever occurring. In this regard, early protective mechanical ventilation with airway pressure release ventilation appears to offer substantial benefit and may be the prophylactic treatment of choice for preventing ARDS.

Sadowitz B, Jain S, Kollisch-Singule M, Satalin J, Andrews P, Habashi N, Gatto LA, Nieman G. Preemptive mechanical ventilation can block progressive acute lung injury. *World J Crit Care Med* 2016; 5(1): 74-82 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/74.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.74

ACUTE RESPIRATORY DISTRESS SYNDROME AND ITS SEQUELAE REMAIN A MAJOR AND COSTLY PUBLIC HEALTH CARE BURDEN

Acute respiratory distress syndrome (ARDS) and its sequelae remain a significant public health care burden in North America and worldwide[1-3]. The mean hospital costs for a patient with ARDS can easily cross the $100000 mark before discharge; this figure does not include the cost of subsequent hospital visits for complications from ARDS or any outpatient services including physical therapy, in-home nursing, or pharmaceuticals[1].

Compounding this significant cost is the broad spectrum of disability suffered by ARDS patients[2-6]. These disabilities are both physical and psychological, and they can last for at lease 5 years after the initial ARDS insult[1-6]. Most importantly, the sum total of these disabilities ultimately leads to a quality of life for ARDS patients that is significantly reduced compared to both the general population and other patients without ARDS who survived a critical illness[4,6].

It would appear that the most effective way to reduce the economic, physical, and psychological burden of ARDS would be *via* prevention of the disease process from ever occurring. Fulminant ARDS is resistant to all current treatment therapies, be they pharmacologic, mechanical, or a combination of the two[7-9]. We believe, however, that employment of a protective ventilation strategy early in the course of acute lung injury (ALI) or in patients at risk for ALI can block progression of this disease and prevent ARDS. Thus, our goal with this review is to detail the longstanding futility of treating established ARDS while examining the evidence that preemptive protective mechanical ventilation can reduce ARDS incidence. Furthermore, we will examine both the basic science and clinical studies demonstrating that airway pressure release ventilation (APRV) is the premier mode of ventilation for delivering an optimal protective breath with a specific mechanical breath profile (MBP) that prevents progression to ARDS for those patients at risk.

ONCE ESTABLISHED, THERE ARE NO EFFECTIVE TREATMENTS FOR ARDS

The landmark ARDSnet trial in 2000 marked the first time in decades that a significant, positive treatment effect was noted in patients with ALI and ARDS. In this trial, patients with ALI or ARDS were randomized to a "traditional", high-tidal volume (12 cc/kg) ventilation group or a low-tidal volume (6 cc/kg) ventilation group. The trial was terminated after enrollment of 861 patients, as mortality was significantly lower in the low-tidal volume ventilation group compared to the high-tidal volume ventilation group (31% *vs* 38.9%, P = 0.007)[10].

Although this certainly was a step forward in ARDS treatment, the optimism of this study should be tempered with the following considerations. First, the patient population studied in this trial underrepresents certain patient groups at high risk for ARDS. In particular, trauma patients only accounted for 13% of the patients in the low-tidal volume group and 9% of the patients in the high-tidal volume group[10]. Many trauma patients have well-known risk factors for ARDS development including: Injury severity scores > 16, thoracic injury or pulmonary contusions with abbreviated injury scale score of > 3, longbone and/or pelvic fractures, and transfusion of > 2 units of blood products within the first 24 h of injury[11]. Second, although the results of the study were statistically significant, in-hospital mortality from ARDS remained quite high at 31%. Lastly, and perhaps most importantly, the overall mortality of ARDS worldwide has not substantially changed since the original ARDSnet study was published and remains static at approximately 40%[12-14].

ARDS is a progressive disease, and there is a treatment window early in this progression that can be exploited

Why has ARDS remained a vexing clinical entity, highly resistant to all of our attempts at effective treatment? The answer to this question may lie in the way we view the disease process itself. For decades, ARDS has been viewed through the lens of a binary construct: the disease is either present or it is not. However, this

paradigm has started shifting in recent years, and this shift may hold the key to effectively combating ALI and ARDS. In particular, ARDS is now being viewed as a progressive disease with an early treatment window that can be targeted[15-25]. To that end, ARDS investigators are turning their attention toward identifying patients at-risk for developing ALI/ARDS and investigating preventive treatment strategies.

Unfortunately, identifying at-risk patients for ALI has proven difficult. The complexity of this process is highlighted by a recent prospective observational study in three Spanish teaching hospitals. In this study, 815 patients were identified with at least one clinical insult, the most common being sepsis, pneumonia, and pancreatitis[26]. However, the majority of patients in this study with risk factors for developing ALI/ARDS never developed lung injury at all[26]. What is clear across multiple studies, however, is the fact that ALI is rarely present on initial presentation and develops over hours to days while patients are in the hospital[27-30]. Thus, there is a window of opportunity early in the progression of developing lung injury that can be exploited with the following caveat: whatever intervention is used, it must be benign and without deleterious side effects so it can be applied to all patients at high-risk for developing lung injury.

What is clinically needed to make this a reality is a reliable risk factor model that accurately identifies, with a high sensitivity and specificity, those patients who will develop ALI/ARDS. One model that may prove helpful in this regard is the Lung Injury Prediction score (LIPS). The LIPS score is calculated based on a set of predisposing conditions and risk modifiers that are catalogued before the onset of ALI including the presence of shock, sepsis, pneumonia, acute abdomen, smoke inhalation, lung contusion, multiple fractures and acidosis[31]. Benefits of the LIPS score include the use of clinical variables closely associated with lung injury that are easily available on hospital admission and are a usual part of the patient chart[31]. In addition, this model identifies at-risk patients before they are admitted to the intensive care unit (ICU) or suffer a "second hit" that can hasten the progression to ALI[31].

The only successful treatments thus far are those involving methods of protective mechanical ventilation instituted early in the disease course

Although a clinical predictive tool like the LIPS score may ultimately prove useful for identifying those patients at risk for developing ALI/ARDS, successfully preventing progression to lung injury has proven equally difficult to solve. To be sure, maximizing supportive care measures and following a standardized bundle of lung injury prevention measures is an important part of this process[15,22]. However, there is no clearly defined treatment to date, either pharmacologic or mechanical, that definitively prevents lung injury.

With this in mind, there is an increasing body of literature demonstrating the beneficial effects of early protective mechanical ventilation on halting the progression toward lung injury. For example, patients undergoing major abdominal, cardiac, or thoracic surgery represent a large patient population at risk for developing ALI[32-34]. The method and technique of mechanical ventilation during surgery, therefore, represent a potential therapeutic intervention for preventing the development of ALI/ARDS in these at-risk surgery patients. One constant across these studies is the following: Protective ventilation strategies in the operating room, using low tidal volume ventilation strategies (6-8 cc/kg), lower the risk of lung injury and pulmonary complications as compared to conventional mechanical ventilation with higher tidal volumes[34]. Employing selective positive end-expiratory pressure (PEEP) levels and using recruitment maneuvers in the operating room may provide further lung protection as well. For example, Futier *et al*[35] (add 35 here as well) demonstrated a 69% decrease in the number of patients requiring ventilatory support within the first seven days after major abdominal surgery. The ventilation strategy used in the operating room was low tidal volume ventilation (tidal volume 6-8 cc/kg) along with a PEEP of 6-8 cmH_2O and recruitment maneuvers every 30 min after intubation[35].

It is important to remember that these preemptive strategies of protective mechanical ventilation are not restricted to surgical patients or those patients undergoing major abdominal or thoracic surgery. For those patients with critical illness who are in the ICU setting, protective mechanical ventilation strategies may be of utmost importance as well. Specifically, Determann *et al*[36] compared the effect of conventional tidal volume ventilation (10 cc/kg of predicted body weight) *vs* low tidal volume ventilation (6 cc/kg of predicted body weight) in critically ill patients without ALI at the onset of mechanical ventilation. This trial was stopped prematurely as the development of lung injury was significantly higher in the conventional tidal volume group[36].

PREEMPTIVE, PROTECTIVE MECHANICAL VENTILATION INSTITUTED BEFORE THE DEVELOPMENT OF CLINICAL MANIFESTATIONS HAS THE POTENTIAL TO REDUCE THE INCIDENCE OF ARDS

It seems clear, therefore, that mechanical ventilation and the way it is implemented are key factors in determining whether or not patients at-risk for lung injury progress to ALI/ARDS. Thus, if used correctly, mechanical ventilation has the potential to dramatically decrease the incidence of ARDS. This brings up another important question: What method of mechanical ventilation provides the optimal protective breath-to-

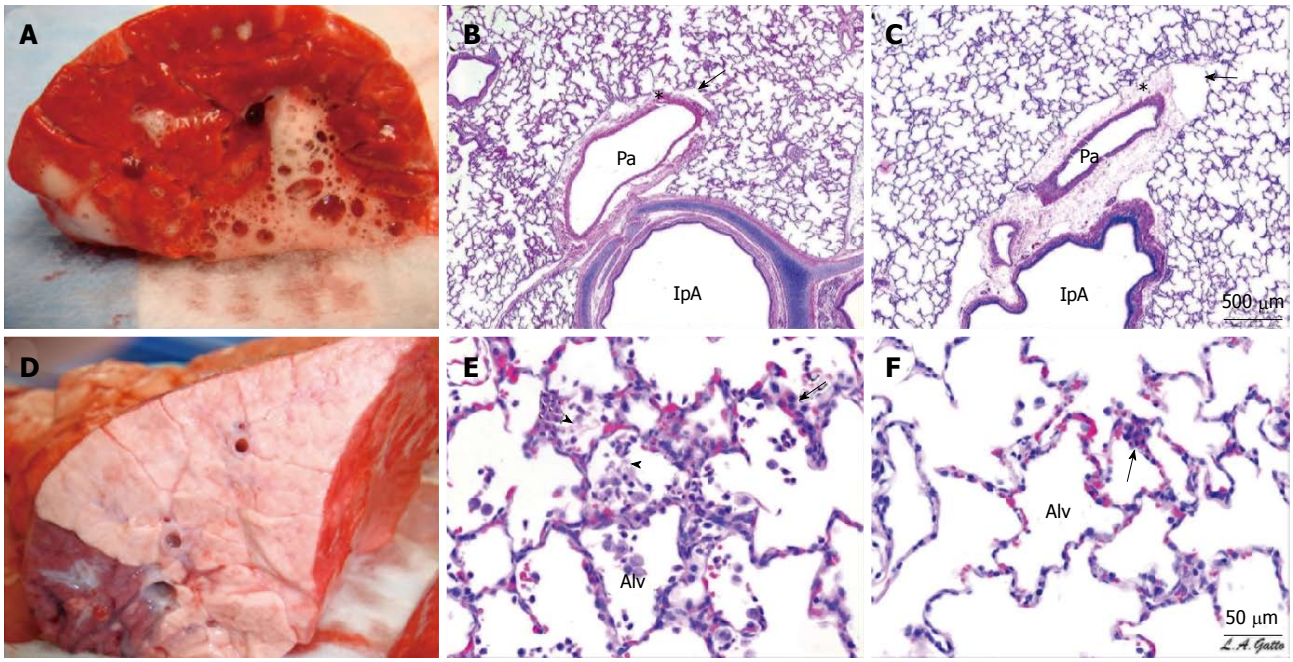


Figure 1 A gross and histological comparison between airway pressure release ventilation and nonpreventative ventilation. A and D: Gross pathology of the cut surface of the right lower lobe of the lung of representative animals from (A) the NPV and (D) the APRV group. The NPV shows severe inflammation, bronchial edema, and areas of hemorrhage. The APRV group demonstrates normal, pink, homogenously inflated lungs with little injury on gross appearance; B, C, E, F: Histological comparison of four pigs, two NPV (B and E) and two APRV (C and F) at low (B and C) and high (E and F) magnification. The NPV animals show classic stigmata of ARDS including atelectasis, fibrinous exudates, intra-alveolar hemorrhage, congested capillaries, thickened alveolar walls, and leukocytic infiltrates. The APRV animals demonstrate preservation of nearly normal pulmonary architecture. Published with permssion from Ref[38]. APRV: Airway pressure release ventilation; NPV: Nonpreventative ventilation; ARDS: Acute respiratory distress syndrome; Alv: Alveoli.

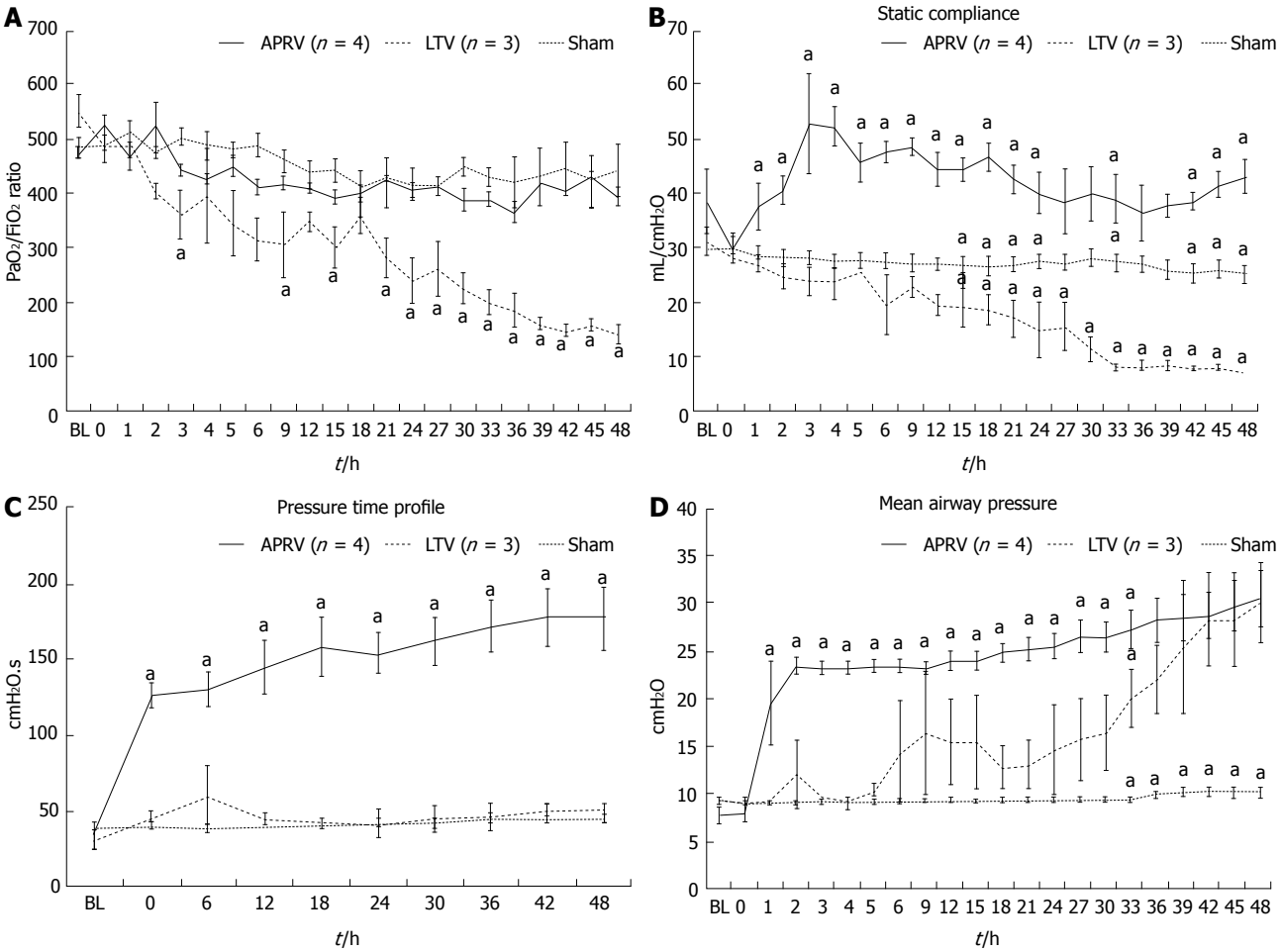
breath strategy for preventing lung injury?

Both basic science and clinical studies suggest that APRV is the ideal ventilation strategy for delivering the optimal protective breath

Work in our laboratory over the past several years has led us to the conclusion that APRV, using a specific MBP, may be the best method of mechanical ventilation for providing the optimal protective breath and ultimately preventing the progression to ALI/ARDS. Our laboratory specializes in a porcine model of secondary ARDS caused by an intestinal ischemia/reperfusion injury and peritoneal sepsis[37]. In 2012 we undertook a study to evaluate the effectiveness of APRV in preventing lung injury in this animal model. Yorkshire pigs were randomized to two mechanical ventilation groups: APRV (10-15 cc/kg tidal volume) and non-preventative ventilation (10 cc/kg tidal volume)[38]. Despite similar markers of systemic inflammation, the APRV group did not develop ARDS and displayed decreased pulmonary inflammation with increased preservation of surfactant proteins[38]. In addition, both the gross and histological appearance of the lungs demonstrated minimal lung injury in the APRV group, while the control group demonstrated significant lung injury and inflammation and progressed to fulminant ARDS (Figure 1)[38].

The significant difference in lung injury between groups prompted us to further evaluate APRV and its effectiveness in preventing lung injury. As the ARDSnet guidelines are the current standard of care for patients with ARDS, we decided to do a comparison study between APRV and the ARDSnet low tidal volume ventilation strategy with our porcine model of ARDS. As with our initial APRV experience, the APRV group in this study did not develop ARDS[39]. In addition, the APRV group demonstrated preservation of lung E-cadherin and surfactant protein A, suggesting APRV can attenuate lung permeability, edema, and surfactant degradation[39]. The ARDSnet ventilation group, on the other hand, developed significant lung injury and ARDS, based on pulmonary parameters along with both the gross and histological appearance of the lungs (Figure 2)[39]. It is important to keep in mind that in this study, low tidal volume protective ventilation was applied after lung injury had developed, similar to current clinical practice. We are currently conducting a study in which low tidal volume ventilation and APRV are both applied preemptively in an attempt to identify the optimally protective breath to block progressive ALI.

The results of these two former studies were clearly dramatic and prompted us to evaluate the mechanical breath profile of APRV to further elucidate its potential for lung protection. To examine the mechanical breath profile of APRV, we used a rat model of lung injury induced by polysorbate lavage[40]. Animals were randomized to one of two groups: A controlled mandatory ventilation group and an APRV group[40]. In the controlled mandatory ventilation group, different levels of PEEP (5, 10, 16,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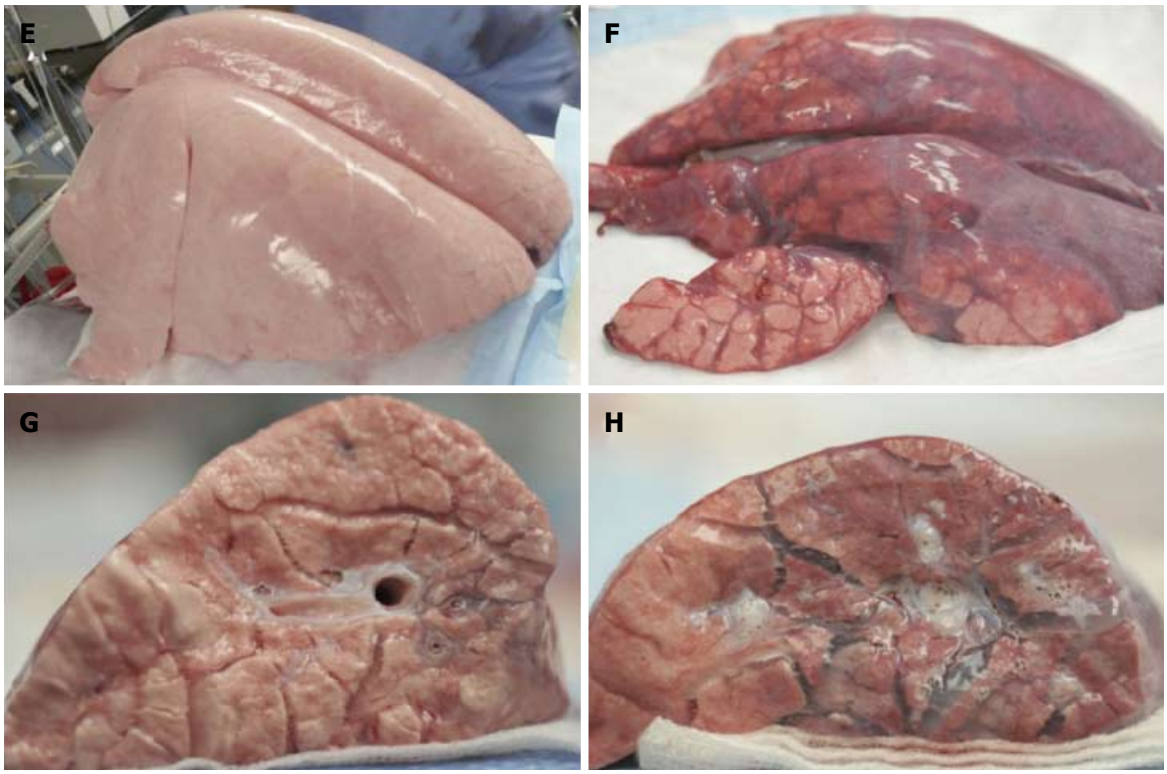
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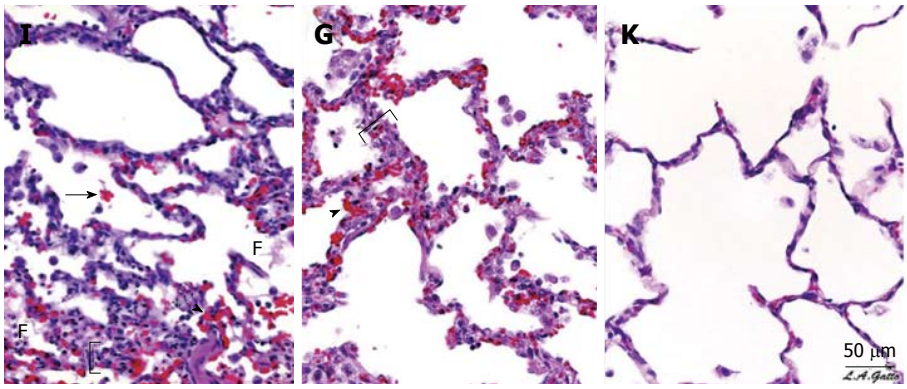

Figure 2 Pulmonary, gross and histologic representation between airway pressure release ventilation, LTV and sham animals. Top: Pulmonary data: A: P/F Ratio: APRV maintains a normal P/F ratio throughout the 48-h study with no significant difference from uninjured sham animals. Low tidal volume ventilation develops ALI (P/F G 300) by 19 h and ARDS (P/F G 250) by 33 h; ventilation strategy does not alter steady progression of increasing hypoxemia (P G 0.001 *vs* APRV and sham); B: Static compliance (Cstat): the APRV shows significant increase in Cstat after transition from volume- cycled mode to APRV (P G 0.001 *vs* sham and LTV ventilation). Sham maintained a normal Cstat level throughout the course of the study. In contrast, the LTV ventilation group developed progressive decreases in Cstat to less than 50% of BL; C: Mean airway pressure: sham group maintained normal Pmean throughout 48-h significantly different from both APRV and LTV ventilation (P G 0.001). Pmean was significantly higher in APRV than in both sham and LTV ventilation after transition from conventional ventilation at 1 h. Because of stepwise increases in PEEP per the ARDSnet protocol, the Pmean was identical from 39 to 48 h for LTV ventilation and APRV; D: Pressure-time profile (P/TP): APRV group had significantly higher P/TP than did both other groups as soon as the transition was made from volume-cycled ventilation (P G 0.001 *vs* sham and LTV ventilation). In the LTV ventilation group, P/TP remained low and did not change over the 48-h course of the study. Sham group animals also had low P/TP, which was not significantly different from the LTV ventilation group throughout the study; Middle: Gross appearance. Representative specimens of gross lungs and cut surface of gross lungs from LTV ventilation (F and H) and APRV (E and G) groups are shown. Bottom I-K: Histological appearance. Photomicrographs of representative lung sections of specimens from each treatment group at 40 × magnification are shown. F: Fibrinous deposit in the air compartment; arrow: Blood in alveolus; arrowhead: Congested alveolar capillary; bracket: Thickened alveolar wall. A: Sham: Animals received 48 h of mechanical ventilation and no injury. Specimen exhibits stigmata of lung injury including fibrinous deposits, blood in alveolus, congested capillaries, and thickened alveolar walls; B: Low tidal volume ventilation: animals received aforementioned ischemic injury along with peritoneal sepsis and LTV ventilation after onset of ALI. Specimen exhibits stigmata of lung injury including fibrinous deposits, blood in alveolus, congested capillaries, leukocyte infiltration, and thickened alveolar walls; C: Airway pressure release ventilation: animals received APRV 1 h following aforementioned ischmic injury and peritoneal sepsis. Specimen shows normal pulmonary architecture, alveoli are well expanded and thin walled, and there are no exudates. Republished with permission from Ref[39]. APRV: Airway pressure release ventilation; PEEP: Positive end-expiratory pressure; ALI: Acute lung injury.

20, 24 cmH_2O) were tested; in the APRV group, the T_{low} was set to achieve ratios of the end-expiratory flow rate to peak expiratory flow rate (EEFR to PEFR) of 10%, 25%, 50%, and 75% - the smaller this ratio is, the more time the lung is exposed to low pressure during the release phase[40]. A PEEP of 16 cmH_2O in the controlled mandatory ventilation group and an EEFR to PEFR ratio of 75% in the APRV group both minimized alveolar microstrain (*i.e.*, the dynamic change in alveolar size during tidal ventilation) in this study. However, alveolar recruitment was greater in the APRV group with an EEFR to PEFR ratio of 75% (Figure 3)[40].

From a purely clinical perspective, APRV has demonstrated tremendous potential in preventing ALI/ARDS as well. In particular, Dr. Nader Habashi's clinical work with APRV has demonstrated the benefits of utilizing APRV in trauma patients at risk for developing lung injury. In a systematic review published in 2013, outcomes for patients with early application of APRV at the R Adams Cowley Shock Trauma Center in Maryland from 2002 to 2005 were compared to patient populations at other trauma centers to evaluate rates of ARDS development and in-hospital mortality[11]. Relevant studies were identified through PubMed and MEDLINE searches from 1995 to 2012 using the keywords trauma and acute respiratory distress syndrome or ARDS and trauma and acute lung injury or ALI[11]. Sixteen studies met the inclusion criteria of being a prospective or retrospective observational studies or cohort studies enrolling 100 or more adult trauma patients with reported ALI/ARDS incidence and in-hospital mortality data[11]. Although the patients at the Shock Trauma Center were in the upper quartile for their injury severity scores, both the incidence of ARDS (1.3%) and the in-hospital mortality (3.9%) were the lowest for this group of patients in whom early APRV was applied (Figure 4)[11]. Although a prospective randomized controlled trial is needed to confirm these results, this systematic review provided convincing evidence that APRV may be precisely the protective mechanical ventilation mode that may be applied prophylactically to all patients as soon as they are intubated to prevent the progression to lung injury or ARDS. In addition, since APRV is a comfortable mode of mechanical ventilation with minimal negative side effects in patients with normal lungs, it can be applied prophylactically to all patients as soon as they are intubated (unpublished observations).

CONCLUSION

ARDS remains a troubling clinical entity with an unacceptably high mortality. Treating fulminant ARDS has proven futile for decades; there are currently no effective pharmacologic or mechanical ventilation strategies for curing ARDS, and treatment is relegated to aggressive supportive care measures. Thus, the key to

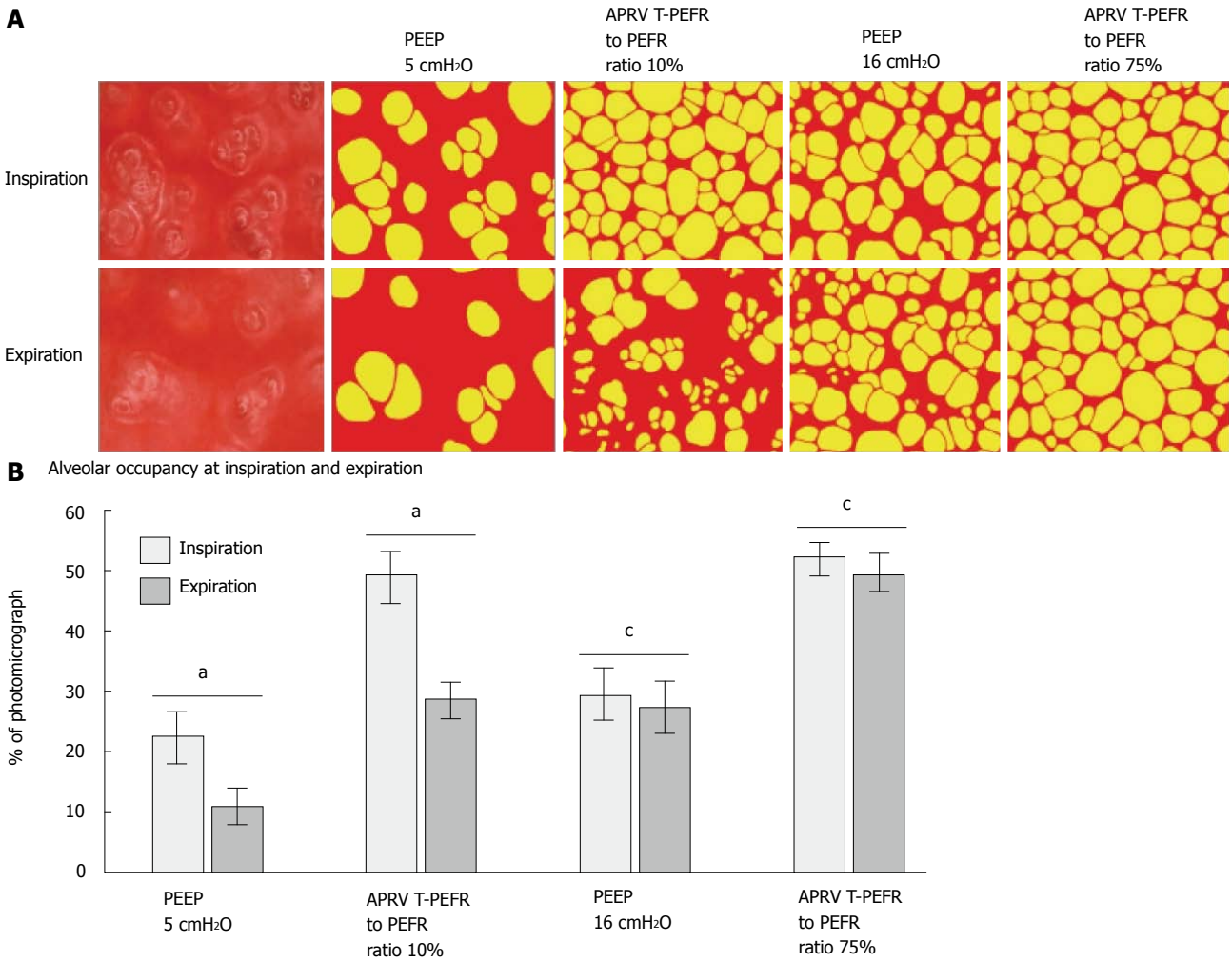

Figure 3 ***In vivo*** **photomicrographs and percentage of alveolar air space occupancy at inspiration and expiration.** A: *In vivo* photomicrographs at inspiration and expiration prior to coloring and for positive end-expiratory pressure (PEEP) of 5 cm H_2O, airway pressure release ventilation (APRV) ratio of termination of peak expiratory flow rate (T-PEFR) to peak expiratory flow rate (PEFR) of 10%, PEEP of 16 cm H_2O, and APRV T-PEFR to PEFR ratio of 75% (original magnification × 10). Alveoli are colored in yellow; nonalveolar tissue, red; B: Alveolar air space occupancy is expressed as a percentage of the photomicrograph containing inflated alveoli (yellow in A) at inspiration and expiration. Data are shown as the mean; error bars indicate standard error of the mean. $^{a}P < 0.05$ for PEEP of 5 cmH_2O *vs* APRVT-PEFR to PEFR ratio of 10%; $^{c}P < 0.05$ for PEEP of 16 cmH_2O *vs* APRV T-PEFR to PEFR ratio of 75%. Republished with permission from Ref[40].

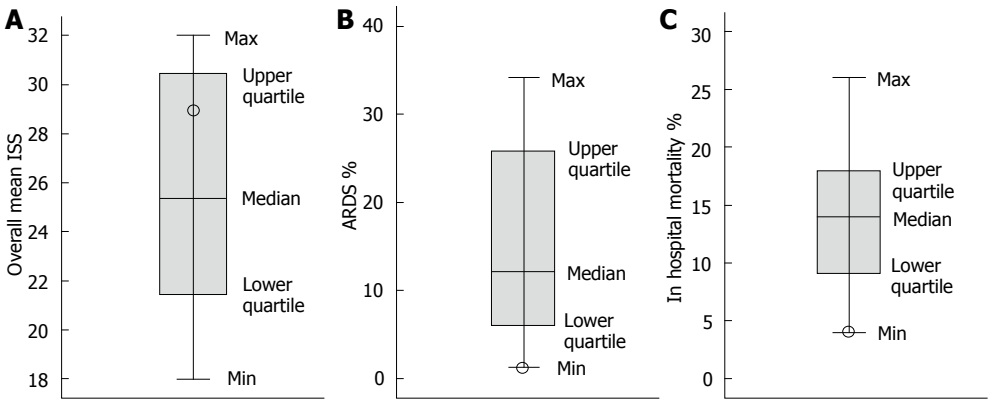

Figure 4 Boxplots for mean individual severity score (A), acute respiratory distress syndrome % (B), and in-hospital mortality % (C). Mean ISS shows the range and distribution of ISS scores reported by 16 authors; 50% of them reported ISS between 30.5 and 23.2, with the middle score of 25.4 (median). The mean ISS of 29 for the preemptive APRV group belonged to the upper quartile of the boxplot. ARDS incidence % shows the range and distribution of scores reported by 16 authors; 50% of them reported ARDS incidence between 22.5% and 6%, with the middle score of 11.95% (median). The incidence of ARDS in the preemptive APRV group represented the minimum score at 1.3%. Mortality % shows the range and distribution of mortality scores reported by 16 authors; 50% of them reported mortality between 18.2% and 9.2%, with the middle score of 13.9% (median). The preemptive APRV group scored the minimum mortality rate of 3.9%. Republished with permission from Ref[11]. ARDS: Acute respiratory distress syndrome; APRV: Airway pressure release ventilation; ISS: Individual severity score.

treating this highly morbid disease lies with preventing the disease from ever occurring. Indeed protective mechanical ventilation strategies are being employed in the operating room and in the intensive care unit before the development of lung injury. Moreover, data from both our laboratory and the clinical realm indicate that appropriately setting APRV generates a protective MBP that may be the most viable and accessible method of preventing lung injury and the subsequent progression to ARDS.

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MINIREVIEWS

Critical care of obese patients during and after spine surgery

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Abstract

Obesity is one of the most prevalent health problems facing the United States today, with a recent JAMA article published in 2014 estimating the prevalence of one third of all adults in the United States being obese. Also, due to technological advancements, the incidence of spine surgeries is growing. Considering these overall increases in both obesity and the performance of spinal surgeries, it can be inferred that more spinal surgery candidates will be obese. Due to this, certain factors must be taken into consideration when dealing with spine surgeries in the obese. Obesity is closely correlated with additional medical comorbidities, including hypertension, coronary artery disease, congestive heart failure, and diabetes mellitus. The pre-operative evaluation may be more difficult, as a more extensive medical evaluation may be needed. Also, adequate radiographic images can be difficult to obtain due to patient size and equipment limitations. Administering anesthesia becomes more difficult, as does proper patient positioning. Post-operatively, the obese patient is at greater risk for reintubation, difficulty with pain control, wound infection and deep vein thrombosis. However, despite these concerns, appropriate clinical outcomes can still be achieved in the obese spine surgical candidate. Obesity, therefore, is not a contraindication to spine surgery, and appropriate patient selection remains the key to obtaining favorable clinical outcomes.

Key words: Obesity; Spine sugary; Critical care

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Core tip: Obesity is one of the most prevalent health problems facing the United States today. Due to technological advancements, the incidence of spine surgeries is also growing. This is particularly true for spinal fusion procedures, as rates were noted to triple from 1990 to 2000. There are potential increased complication risks during and after spine surgery due to associated comorbidities. Spine surgery can be performed safely in obese patients with appropriate management of comorbidities and proper patient selection.

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INTRODUCTION

Obesity is one of the most prevalent health problems facing the United States today. Recent studies indicate that 32.2% of adult men and 35.5% of adult women in the United States are considered obese[1,2]. The prevalence of obesity has also increased, notably among adolescents and adult men[3]. Additionally, due to technological advancements, the incidence of spine surgeries is also growing. This is particularly true for spinal fusion procedures, as rates were noted to triple from 1990 to 2000[4]. Spinal fusion was the 19th most common inpatient procedure performed in 2003, rising from 41st in 1997[5]. The purpose of this article is to review the effects that obesity has on spinal surgery patients both during and after surgery and highlight the factors that must be taken into consideration when dealing with these surgeries in the obese.

OBESITY AND ASSOCIATED CO-MORBIDITIES

Most clinicians today define obesity according to a standardized formula known as the body mass index (BMI). This formula was created by Belgian statistician Adolphe Quetelet in 1832 and had been mostly abandoned[6]. It was then thrust to the front of obesity research in 1972 by Keys *et al*[7], who evaluated the methods available at the time for describing the relative weight of patients or populations. He chose the easiest and most reproducible method, which he renamed the BMI. This simple formula requires no special tools or data, as it is simply the patient's weight (kg) divided by the square of their height (m^2). From this information there have been guidelines set to classify patients as underweight, normal weight, overweight, obese, or morbidly obese (Table 1)[8].

Obesity has been shown to be closely correlated to multiple medical comorbidities such as increased rates of diabetes mellitus, hypertension, coronary artery disease, obstructive sleep apnea, and overall mortality[3,9-11]. This has specifically been shown in the surgical spine patient, as Vaidya *et al*[12] found averages of 5.1 and 8.1 comorbidities in obese and morbidly obese patients, respectively, that underwent posterior decompression and fusion with instrumentation. Thus not only does the presence of obesity play a role in the incidence of medical comorbidities, but the degree of obesity is also important. The increased rates of diabetes in these populations must also be carefully considered, as diabetic patients have been noted to have an increase in wound complications[13,14].

OBESITY AND THE PRE-OPERATIVE EVALUATION

The presence of obesity can also affect the diagnostic assessment of a patient being evaluated for spine surgery. Patients that undergo spinal surgery typically have multiple pre-operative imaging studies. These usually include plain radiographs, computed tomography (CT) scan and magnetic resonance imaging (MRI), which offer better detail of bone and soft tissue structures, respectively. All of these methods contribute to accurate diagnosis and appropriate pre-operative planning. Obtaining proper images, however, may be difficult in the obese patient. Plain radiographs are available in most clinics and are relatively easy for the patient to obtain. However, the presence of obesity may result in higher radiation doses and poorer image quality due to decreased tissue penetration. Digital imaging and good technicians can help minimize these issues.

Cross-sectional imaging modalities have special concerns related to patient size and weight. The tables required in these machines are finely calibrated and larger patients may "tweak" the table, resulting in decreased image quality. Additionally, a tube must be entered in order to obtain these images. CT scanners have traditionally been roomier, with apertures approximately 70 cm in diameter. MRI scanners, due to their magnets, are smaller, with standard machine diameters averaging around 60 cm. Obese patients may not fit into these confined spaces or may also have issues with claustrophobia. Due to these concerns standing, or "open", MRI has been developed. These machine diameters average about 70 cm, but also have reduced magnet sizes that may limit image quality. There are also some newer, traditional style MRI machines with table limits at or above 550 pounds with 70 cm diameter tubes. Unfortunately, availability of these machines may be limited[15].

Obesity and its commonly associated comorbidities alter the pre-operative medical evaluation necessary for surgical clearance. For instance, hypertension is a commonly present comorbidity which has been shown to lead to left ventricular hypertrophy. This may contribute to the development of ischemic cardiomyopathy and subsequent ventricular dysfunction. Furthermore, obesity increases the risk of arrhythmias likely through fatty and ischemic changes of the myocardium. Respiratory function may be altered as obese patients exhibit decreased chest wall compliance secondary to adiposity of the chest wall and abdomen. This results into a higher workload of breathing and a decreased functional residual capacity. Obese patients also have a high rate of obstructive sleep apnea. Other considerations include an increase in gastroesophageal reflux disease, fatty changes to the liver, endocrine and metabolic disturbances, including hypercholesterolemia and diabetes, and potential coagulopathies.

Table 1 Patient weight classification according to body mass index

Body mass index (kg/m^2)	Degree of obesity
Below 18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0-39.9	Obese
40.0 and above	Morbidly obese

Due to these factors the pre-operative evaluation require blood work that includes hemoglobin, electrolyte panel, liver function test, blood glucose level, and a clotting profile. A chest radiograph, pulmonary function tests, and electrocardiogram (ECG) are also recommended. If abnormalities are noted on the ECG further evaluation is likely needed, including an echocardiogram, cardiac stress test, and consultation with a cardiologist[16,17].

ANESTHESIA CONSIDERATIONS FOR SPINAL SURGERY IN OBESE AND MORBIDLY OBESE PATIENTS

Establishing intravenous access may be more difficult in an obese individual. Initial difficulties may be encountered with the administration of anesthesia. The decreased functional residual capacity of obese patients has important considerations for anesthesia. Patients with severely reduced functional residual capacity can develop premature airway closure and ventilation-perfusion mismatches, with resultant hypoxemia. During induction of anesthesia, these results into a shortened duration of nonhypoxic apnea, the period of time between paralysis and intubation before hypoxia occurs. Furthermore, large tongues and narrow airways, commonly seen in patients with obstructive sleep apnea, may make securing an airway more difficult, and fiber-optic intubation techniques may be necessary. Rapid induction of anesthesia is imperative in obese patients because of the high risk of aspiration. Esophageal reflux is common; 75% of obese patients have a high-volume, low-pH gastric residue that places them at risk for pneumonia. In severely obese patients, use of positive airway pressure during preoxygenation and induction may minimize hypoxia associated with the apneic phase of standard intubation. The increased adiposity provides a larger distribution area for certain anesthetic agents, which may make appropriate dosing more difficult[18].

CRITICAL CARE OF OBESE PATIENTS IN THE OPERATING ROOM

Due to higher rates of wound sepsis preoperative antibiotics is strongly recommended in obese patients. The current recommendations for the use of prophylactic antibiotics in spine surgery are: Cephalosporin (cefazolin 1-2 g; 2 g for patient weighing > 86 kg) and if B-lactam allergy, use clindamycin or vancomycin (dosing based on patient weight). It is recommended to start up to 60 min before incision, completed at the time of incision and re-dose antimicrobial intraoperatively every 4 h for prolonged procedure or significant blood loss. When using postoperative doses, discontinue within 24 h after wound closure as continuing of antibiotic prophylaxis longer than 24 h after wound closure has not proved to be beneficial; indeed, it may contribute to the development of antimicrobial resistance[19,20].

Patient positioning is more difficult, as many spine surgeries are performed prone. The degree of obesity plays a role, study showed that morbidly obese patients have longer surgical set up times[12]. Placement on the appropriate operative table is also crucial. Use of a closed frame table, such as a Wilson frame, may contribute to an increase in intra-abdominal pressures. This may cause elevation of the diaphragm, resulting in an increased intra-thoracic pressure, leading to a decrease in venous return[21]. This in turn can cause venous congestion, particularly along the epidural veins, and result in an increase blood loss. Due to these concerns it is often recommended to allow the abdomen to hang free using an open-frame table. Jackson spinal table (MIZUHO OSI, Union City, CA)® commonly used in spine surgery has a patient weight capacity of 500 lb (227 kg). A large abdominal pannus requires further modifications to allow for free passage of intra-operative fluoroscopy machines. Bariatric security straps are available that provide a comfortable hold of the pannus and accommodates up to 1000 lb (454 kg) patient (Figure 1)[22,23].

Peripheral nerve palsies have been noted in this population most likely secondary to increased pressure on contact points and difficulty with positioning[24]. Stretch injuries to the brachial plexus may occur with shoulder abduction more than 90°. Arm boards should be positioned to keep shoulder abduction less than 90° and this should be frequently checked by the anesthesia team during the surgical procedure. All bony prominence should all be carefully padded to avoid any pressure points.

Higher doses of radiation are also needed for adequate tissue penetration, thus exposing both the patient and the operative personnel to higher levels of radiation[25]. Larger patients require longer incisions, more extensive soft tissue dissection, and may present certain technical difficulties, such as obtaining the appropriate angles for pedicle screw placement[26]. Peng *et al*[27], evaluated different factors in obese and non-obese patients undergoing anterior lumbar surgery, concluding that obese patients required a longer duration of both exposure time and total surgical time. They also had longer incision lengths, as well as deeper skin to fascia and fascia to spine depths. Estimated blood loss, however, was not significantly different[27]. Rosen *et al*[28] noted no difference in the operative outcome between obese and non-obese patients that underwent minimally invasive spine surgery for lumbar fusion. This may be due to the tubular retraction system utilized in these procedures, which allows similar sized skin incisions in all patients[28]. Reducing operative times in spinal surgery is important, as longer times increase infection risk and the risk of blindness when the patient is prone,

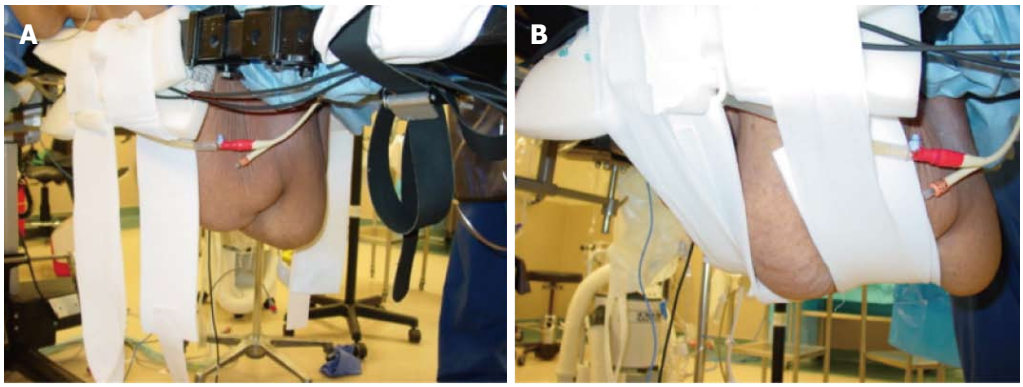

Figure 1 Patient in prone position on the Jackson spinal table. A: A large abdominal pannus will interfere with free passage of intra-operative fluoroscopy; B: Bariatric security straps are used to provide a comfortable hold of the pannus to the table. Foam is used to cover the metal edges of the table and protect the skin from pressure sores.

as this complication has been observed in long lasting surgeries[29,30].

OBESITY AND POST-OPERATIVE CARE AND COMPLICATIONS

The post-operative effects of obesity on surgical patients have remained controversial. Studies in general surgery patients indicated an increase in wound infections with open procedures, but no other differences[31]. Obese cardiac surgery patients were found to have an increased rate of superficial sternal and leg infections, as well as atrial dysrhythmias, but not in overall mortality[32]. Total hip and knee replacement patients have been found to have no difference in complications and post-operative course[33].

Post-operative pain and anesthesia will induce respiratory modifications which include atelectasis to due a restrictive syndrome and diaphragm dysfunction. This in turn can lead to hypoxemia and decreased pulmonary capacity. Jaber *et al*[34], stressed the importance of post-operative oxygenation using non-invasive ventilation in an effort to prevent acute respiratory failure. Several studies have shown that there is an increased mortality related to the complications of postoperative reintubation. Risk factors for such complication include COPD, age older than 60, ASA class of Ⅱ or greater, and obesity[34]. Therefore, post extubation it is of vital importance for adequate ventilation in the obese patients for optimizing surgical outcomes. A prospective study performed by Jaber *et al*[35] in 2005 showed that the use of non-invasive ventilation in patients with acute respiratory failure following extubation lowered the incidence of reintubation by 67%. Two methods of to avoid development of acute respiratory failure using non-invasive ventilation are positive end expiratory pressure and pressure support ventilation.

Post-operative pain control in obese patients also has its own specific challenges with a goal of decreasing the requirement for opioids to improve early rehabilitation and reduce the adverse effects of narcotics. With increased body fat, total body water, and plasma volume the pharmacokinetics of analgesics differs from that of those with ideal body weight diluting concentrations and therefore lowering the efficacy. Moreover, a study by Miscio *et al*[36] explored sensitivity to various noxious stimuli in obese subjects and compared those results to those with normal BMI of similar age. They discovered that obese non-diabetic subjects with a had a lower sensitivity to vibration, mechanical, and heat signals suggesting that obesity may affect the pain pathway and further complicate optimizing pain control[36]. Difficulty arises in the post-operative pain management due to the associated comorbidity of obstructive sleep apnea in obese patients and risk of respiratory depression with narcotics.

The development of deep venous thrombosis (DVT) is of particular concern in the post-operative period in this population, as both obesity and recent surgery are independent risk factors for DVT[37,38]. The post-operative spine patient, however, requires special consideration, as use of chemical prophylaxis in the acute post-operative period brings an increased risk of epidural hematoma and subsequent neurologic compression and deficits[39]. Due to this mechanical prophylaxis, such as compression stockings and sequential compression devices, is of the utmost importance. This should be started intra-operatively and continued throughout the post-operative hospital course. Proper fitting of such devices, however, may be difficult with an obese body habitus. Early ambulation is also important, with patients beginning to walk no later than post-operative day one.

The most frequently encountered complication in the obese spine patient is wound infection[40-42]. Other complications, however, have been noted more frequently in the obese. Patel *et al*[24] did find a correlation between BMI and a higher risk of major complications following elective thoracic and lumbar fusion procedures. Patients with a BMI of 25 were found to have a complication rate of 14%, while ones with a BMI of 30 were at 20%, and a BMI of 40 associated with a 36% rate[24]. Shamji *et al*[26] noted an increased transfusion requirement in thoracic and lumbar fusion patients, as well as an increase in the likelihood of discharge to an assisted living facility.

However, no differences were noted in length of stay, infection rates, or overall mortality[26]. Other studies have noted no difference in complication rates between obese and non-obese spine patients[43,44].

CONCLUSION

Obesity does not appear to be a contraindication for spinal surgery however it does pose a unique set of challenges in the perioperative time frame. It is important for the operative surgeon and anesthesia team to be aware of any special considerations that must be undertaken in preoperative evaluation, intraoperative and postoperative management. The potential for increased operative times, difficulties with anesthesia, operative positioning, higher blood loss, post-extubation complications, post-operative pain management, and increase in wound complications must be realized. However, it appears that with appropriate management of comorbidities and proper patient selection that spine surgery can be performed safely in obese patients.

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MINIREVIEWS

Corticosteroids for severe influenza pneumonia: A critical appraisal

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Abstract

Influenza pneumonia is associated with high number of severe cases requiring hospital and intensive care unit (ICU) admissions with high mortality. Systemic steroids are proposed as a valid therapeutic option even though its effects are still controversial. Heterogeneity of published data regarding study design, population demographics, severity of illness, dosing, type and timing of corticosteroids administered constitute an important limitation for drawing robust conclusions. However, it is reasonable to admit that, as it was not found any advantage of corticosteroid therapy in so diverse conditions, such beneficial effects do not exist at all. Its administration is likely to increase overall mortality and such trend is consistent regardless of the quality as well as the sample size of studies. Moreover it was shown that corticosteroids might be associated with higher incidence of hospital-acquired pneumonia and longer duration of mechanical ventilation and ICU stay. Finally, it is reasonable to conclude that corticosteroids failed to demonstrate any beneficial effects in the treatment of patients with severe influenza infection. Thus its current use in severe influenza pneumonia should be restricted to very selected cases and in the setting of clinical trials.

Key words: Influenza; Mechanical ventilation; Pneumonia; Corticosteroids; Respiratory failure

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Core tip: This review article presents a critical appraisal

to the use of corticosteroids in severe influenza infections covering the most relevant clinical studies, underlying mechanisms (pathophysiologic and pharmacologic aspects) and providing a scenario to help clinicians at bedside facing this challenging situation.

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INTRODUCTION

According to the World Health Organization, lower respiratory tract infections account for approximately 7% of deaths per year worldwide and viruses are a common cause of community-acquired pneumonia[1]. Among this wide group of species, influenza virus are of utmost importance and numerous interventions have been proposed for its management[2], especially after pandemic H1N1 influenza virus outbreak, which was associated with high number of severe cases requiring hospital and intensive care unit (ICU) admissions and resulted in ICU mortality rates ranging from 14% to 46%[3].

Systemic steroids are proposed as a valid therapeutic option due to their potential role in controlling host inflammatory response, inhibiting cytokine production and restoring the inappropriately low endogenous cortisol levels, compensating critical illness-related corticosteroid insufficiency[4]. Although widely used in H1N1 pandemics, the effect of corticosteroids is still controversial. The purpose of this review is to provide an overview of published data about steroid use and outcomes in severe influenza infection.

Influenza infection

Influenza viruses are enveloped negative-sense RNA viruses with segmented genomes that belong to the family *Orthomyoviridae*[5]. There are three antigenically distinct subtypes, A, B and C, which circulate among humans worldwide[6].

Three influenza pandemics occurred in the 20th century[5,7]: 1918 (Spanish influenza), 1957 (Asian influenza) and 1968 (Hong Kong influenza). Different antigenic subtypes of influenza A caused them, each resulting in more than a million deaths. In 2009, a pandemic H1N1 virus developed by reassortment among several influenza A strains. Over 18000 deaths were laboratory confirmed cases but experts agree that more than 250000 deaths may have resulted from H1N1 infection[8].

The 2009 H1N1 influenza pandemic originated a surge of research investigating the mechanisms of lung injury that develop in severe cases of influenza infection, complementing the work started six years before, after the SARS (Severe Acute Respiratory Syndrome) global outbreak.

Seasonal influenza is an acute respiratory disease that presents with sudden onset of high fevers, upper respiratory tract symptoms, chills, myalgia and gastrointestinal tract symptoms. Infection rarely induces symptoms of lower respiratory tract infections or severe lung injury. Pandemic H1N1 infected patients presented with fever, cough and sore throat and the most severe case rapidly developed bilateral pneumonia, severe ARDS, multiple organ failure and death[9,10]. It affected young individuals disproportionately and several epidemiological studies suggested that pregnant women and obese patients were more susceptible to severe infection[5].

Although molecular mechanisms underpinning these associations are not completely understood, it is known that adipocytes and macrophages from obese patients release higher quantities of interleukin (IL)-6 and tumor necrosis factor (TNF)-α when compared to non-obese patients[11]. Hypercytokinemia and a proinflammatory state are related to disease severity in influenza infections. Furthermore, the proinflammatory properties of lectin and anti-inflammatory properties of adiponectin may increase the risk of developing hypoxemic respiratory failure[11]. Biomarkers of endothelial injury (surfactant protein D and von Willebrand factor) were found to be elevated in obese patients with hypoxemic respiratory failure[12]. The likelihood of a combined influenza induced epithelial and endothelial injury is corroborated by pathology reports of pandemic H1N1 patients' lung specimens which showed extensive diffuse alveolar damage, variable degrees of pulmonary hemorrhage (with evidence of perivasculitis and microthrombi) and necrotizing bronchiolitis[13]. Persistence of viral shedding has recently been associated with poorer outcome and longer hospital stay both as a predisposing factor and as a complication of influenza infection[14].

Corticosteroid pharmacology

Corticosteroids are cyclic organic compounds physiologically secreted by zona fasciculata cells of the adrenal cortex. Under physiological circumstances, its synthesis and secretion are tightly regulated by the central nervous system, through the pituitary release of corticotropin (ACTH), which is very sensitive to negative feedback by the circulating cortisol and exogenous (synthetic) glucocorticoids[15]. Cortisol, the main human corticosteroid, has a half-life of 60 to 90 min which can be significantly increased with large steroid loads. The volume of distribution (Vd) also increases with higher steroid doses and both parameters are agent-specific[16]. Corticosteroids are metabolized through complexly regulated enzymatic transformations in the liver [through A-ring reductases (5β-reductase and 5α-reductase)] and kidney [through 11-β hydroxysteroid dehydrogenase type 2 (11β-HSD2)][17,18] that diminish their physiologic activity and increase water solubility to enhance their

urinary excretion[15]. Most of the known effects of the corticosteroids are mediated by nuclear receptors.

Corticosteroids in critical illness

Interest in the role of corticosteroids in the pathophysiology of critical illness has existed since the early decades of the 20th century[19] Every acute physical stress or noxious stimuli results in a coordinated systemic response classically referred to as stress response or general adaption syndrome. Among the physiological responses to stress, hypercortisolemia is proportionate to the severity of illness[20]. Such response has traditionally been attributed to activation of the hypothalamic-pituitary-adrenal (HPA) axis[21] with increased secretion from the paraventricular nucleus of the hypothalamus of corticotropin-releasing hormone which stimulates the production of ACTH by the anterior pituitary gland, causing a sustained increase in cortisol secretion. This increased corticotropin-driven cortisol production originates multiple effects (metabolic, cardiovascular and immune) aimed at restoring homeostasis during stress[17].

Since the late 90's a paradoxical dissociation between cortisol and corticotropin (slightly elevated or even normal to low levels of corticotropin with permanently high cortisol levels) has been observed during critical illness[22,23]. As a consequence, explanations for hypercortisolemia other than increased cortisol production due to HPA axis activation have been pursued. Proinflammatory cytokines (TNF-α and IL-6), neuropeptides and cathecolamines correlate positively with cortisol production and are independent of HPA axis[24]. The possibility of an increased sensitivity to corticotropin was formulated but considered unlikely because cortisol plasmatic levels were not consistently elevated after exogenous corticotropin stimulation[17,25]. The reduction of cortisol metabolism during critical illness emerged as an alternative or additional mechanism with recent data showing suppression of activity of cortisol metabolizing enzymes in critical care patients. Boonen *et al*[18] found evidence of impaired 11β-HSD2 function and reduction of A-ring reductases activity that may be mediated by bile acids, known competitive inhibitors and transcriptional suppressors of cortisol-metabolizing enzymes.

The possibility that reduced cortisol breakdown is a main contributor to hypercortisolemia during critical illness may changes our conceptual understanding of the stress response. It could mean that low cortisol metabolism with hypercortisolemia would have induced a negative feedback on the HPA-axis resulting in lower corticotropin levels and adrenocortical atrophy. Such effect implies the downregulation or functional inactivation of corticotropin receptors on adrenocortical cells, which would explain the low cortisol response to corticotropin stimulation. Moreover, reduced cortisol inactivation may also potentiate cortisol activity within the vital tissues that express inactivating enzymes[18], what suggests that corticosteroids stress doses in critically ill patients are at least three times too high. These facts imply that the concept of critical illness associated adrenal failure may not be real and question the pathophysiological principles of corticosteroids stress doses in acute injuries.

Observational studies

According to observational data, approximately one third of 2009 H1N1 pandemia cases reported were treated with corticosteroids[26] both as a primary therapy or as a rescue therapy for patients with severe ARDS[27,28]. Despite this, a standard steroid and dose regimen are not well established and its efficacy and safety are not entirely clear.

In general, therapy with steroids in severe infections has shown to be beneficial in a pair of clinical situations: bacterial meningitis in immunocompetent hosts[29] and Pneumocystis jiroveci pneumonia in HIV patients[30]. In other conditions, like severe CAP and ARDS (due to pneumonia or not), no positive impact on mortality has been shown, still being an unresolved matter that deserves further investigation[4].

A common pulmonary presentation of patients affected by pandemic (H1N1) influenza A infection is rapidly progressive pneumonia with bilateral alveolar infiltrates on chest radiography and ARDS, that might be linked to an abnormal immune response[31]. The role of steroids as adjunctive therapy in influenza is very attractive theoretical approach to try to modulate hypercytokinemia associated with the most severe presentation[4]. However, a balance must occur between this phenomenon and the possibility of prolonged viral replication, resulting in more direct cytopathic effect on the infected lungs[32].

The main observational studies on corticosteroid treatment in influenza infected patients are listed in Table 1. All but one[33] evaluate steroids use in H1N1 infections. Xi *et al*[34] retrospectively evaluated data from 155 adults with confirmed H1N1 infection in China, one-third (33.5%) were treated with steroids. In a multivariate analysis, the use of steroids was associated with a trend towards increased hospital mortality (OR = 3.6; 95%CI: 0.98-13.6; P = 0.052). Nevertheless, patients using steroids were often more severely ill.

Martin-Loeches *et al*[31], in an international registry of the European Society of Intensive Care Medicine included 220 patients with suspected or confirmed H1N1, 77.7% on mechanical ventilation and 57.3% with steroid use at ICU admission. A higher incidence of hospital-acquired pneumonia was noted in patients receiving early steroid therapy. These patients also had a higher ICU mortality, but after adjusting for disease severity and other confounding variables, this effect was no longer present.

Kim *et al*[35] in a retrospective analysis of the data from 28 hospitals in South Korea identified 245 critically ill patients with H1N1 infection, 136 of them met criteria for ARDS. The crude 90-d mortality for the 107 (43.6%) patients who received steroids was higher than in the patients who did not received steroids, which was confirmed by propensity adjusted analysis. Patients on steroids also had longer duration of mechanical ventilation

Table 1 Main observational studies evaluating steroid use in influenza infection

Ref.	Study design	Population	Steroid regimen	Outcomes
Bourdreault *et al*[33]	Retrospective cohort	143 hematopoietic cell transplant patients with seasonal influenza	Prednisone < 1 mg/kg per day (low dose) or prednisone > 1 mg/kg per day (high dose)	Steroid use not associated with lower respiratory disease, hypoxemia, need for MV or death
Brun-Buisson *et al*[36]	Retrospective cohort	208 patients with ARDS due to H1N1 pneumonia, 83 receiving steroids	Hydrocortisone 270 mg/d (median) for 11 d (median)	Steroid was associated with mortality in crude analysis (33% *vs* 18%, HR = 2.4; 95%CI: 1.3-4.3; P = 0.004) and after propensity score-adjusted analysis (HR = 2.82; 95%CI: 1.5-5.4; P = 0.002) Early therapy (≤ 3 d of MV) associated with increased mortality Steroid associated with bacterial pneumonia and prolonged MV
Confalonieri *et al*[44]	Case report	One patient with ARDS due to H1N1 infection, not responding to antiviral therapy	Methylprednisolone 1 mg/kg per day	Clinical improvement
Cornejo *et al*[40]	Case report	Two patients with H1N1 that developed organizing pneumonia	Methylprednisolone 500 mg/d for 3 d	Clinical improvement
Diaz *et al*[37]	Multicenter, prospective cohort	372 patients with primary H1H1 pandemic pneumonia, 136 receiving steroids	Not reported	Corticosteroid therapy was not significantly associated with mortality (HR = 1.06; 95%CI: 0.626-1.801; P = 0.825) after a regression analysis adjusted for severity and potential confounding factors
Han *et al*[45]	Multicenter, retrospective cohort	83 patients with H1N1 pneumonia with hospitalar admission, 17 with early glucocorticoid treatment	Median dose of methylprednisolone equivalent of 50 mg/d (use for fever reduction) to 61 mg/d (use for pneumonia)	Early steroid treatment (< 72 h) was associated with development of critical disease compared with who received late (> 72 h) or no steroid treatment: 71% vs 39% (HR = 1.8; 95%CI: 1.2-2.8), after adjustment for confounding variables
Kim *et al*[35]	Multicenter, retrospective cohort and case-control study	245 patients with H1N1 infection, 107 with steroid treatment	Median dose of prednisolone equivalent of 75 mg/d	90-d mortality rate higher in steroids group (OR = 2.2; 95%CI: 1.03-4.71), after propensity score Higher mortality both in cohort (58% *vs* 27%; P < 0.001) and case-control study (54% *vs* 31%; P = 0.004) Steroid group more likely to have secondary bacterial pneumonia, invasive fungal infection and prolonged intensive care unit stay
Luyt *et al*[46]	Multicenter, prospective cohort study	37 survivors of ARDS due to H1N1 infection, 20 with steroid treatment	Not reported	No relationship between steroid use and muscle weakness at 1-yr post-ICU discharge
Martin-Loeches *et al*[31]	Multicenter, prospective cohort study	220 patients with H1N1 infection, 126 with steroid treatment at ICU admission	Minimal equivalent dose of 24 mg/d (methylprednisolone) or 30 mg/d (prednisone)	Early use of steroids was not significantly associated with mortality by Cox regression analysis adjusted for severity and confounding factors: HR = 1.3; 95%CI: 0.7-2.4; P = 0.4 Early steroid use associated with an increased rate of HAP (OR = 2.2; 95%CI: 1.0-4.8; P < 0.05) by Cox regression analysis Similar results observed when only patiens with ARDS were analyzed Patients who received early steroid therapy were sicker than who did not receive them according to SAPS 3 (55.9 ± 16.8 *vs* 49.0 ± 14.5; P = 0.001)
Quispe-Laime *et al*[47]	Case series	13 patients with suspected H1N1 pneumonia and ALI-ARDS diagnosis	Methylprednisolone 1 mg/kg per day (severe ARDS) or hydrocortisone 300 mg/d. Duration of 21.2 ± 6.1 d	Twelve patients improved lung function, were extubated and discharged alive from the ICU By day 7 of treatment patients experienced a significant improvement in lung injury and multiple organ dysfunction scores (P < 0.001)

ALI: Acute lung injury; ARDS: Acute distress respiratory syndrome; HAP: Hospital-acquired pneumonia; HR: Hazard ratio; ICU: Intensive care unit; MV: Mechanical ventilation; OR: Odds ratio; SAPS: Simplified acute physiology score.

and ICU stay, and more bacterial pneumonia or invasive fungal infections.

Brun-Buisson *et al*[36] evaluated 208 patients with severe H1N1 infections and ARDS in a multicenter study in France. Steroids were administered to 39.9% and, after use of several analytical techniques to adjust for differences in steroid-treated *vs* non-steroid-treated patients to compare clinical outcomes, the association between steroid therapy and death remained significant, a fact that was more pronounced in patients receiving early steroid therapy.

Diaz *et al*[37], in a multicenter cohort composed by 372-patients with primary viral pneumonia due to H1N1, with 136 patients (36.6%) received corticosteroids, did not found any association between steroid therapy and mortality.

A systematic review and meta-analysis[3] composed by nine cohort studies (n = 1405) and 14 case-control studies (n = 4700) showed an increased mortality with corticosteroid treatment in influenza H1N1 infection (cohort studies RR = 1.85; 95%CI: 1.46-2.33; $P < 0.00001$; case-control studies OR = 4.22; 95%CI: 3.10-5.76; $P < 0.00001$). Subgroup and sensitive analysis were consistent with each other, suggesting that steroid treatment is associated with higher mortality. Nonetheless, corticosteroid tends to be used in the sickest case-patients.

None of these studies provided data on mechanical ventilation parameters. Lung protective ventilation is the standard of care for ARDS patients[38], and lack of data regarding this issue implies a dose of uncertainty about a major factor in determining which determines clinical outcomes[39]. The timing and dose of corticosteroid therapy were also not controlled in the study, and no specific drug regimen has been suggested in this context. Actually, several administration regimens, dosage and therapy duration are described in different studies, resulting in high heterogeneous strategies, adding complexity to systematic analysis. Observational - in particular retrospective - studies are potentially susceptible to bias, due to a lack of control of confounder variables, heterogeneity due to clinical diversity, and the fact that severe patients are more likely to receive corticosteroids than mild cases. Currently a conclusive trial on corticosteroids in severe H1N1 infection would be difficult or even not possible to perform. As a result it is reasonable to conclude from the available evidence that corticosteroids failed to demonstrate any clinical impact in severe influenza infection and, in addition, the data points to potential harm.

Case reports suggested beneficial use in specific contexts, such as organizing pneumonia[40], post-viral inflammatory pneumonitis[41] and H1N1 pneumonia in a pregnant woman[42].

Interventional studies

There is only one clinical trial addressing corticosteroid use in H1N1 influenza virus treatment. Wang *et al*[43] enrolled 38 patients with H1N1 pneumonia undergoing mechanical ventilation to be randomized to receive adjuvant treatment of corticosteroid either with sirolimus or without sirolimus for 14 d. In the sirolimus group, there was a shorter time spent on mechanical ventilation (7 d *vs* 15 d; P = 0.03), greater PaO_2-FiO_2 values on days 3 and 7 compared to the non-sirolimus group and improved SOFA score on day 3 and day 7. Sirolimus, as a mTOR inhibitor, could potentiate corticosteroid effect by limiting inflammatory cytokine production. The corticosteroid effect per se was not addressed in this small open-label randomized controlled trial as every patient enrolled received corticosteroids. As a consequence, no harmful or beneficial effect of steroids in H1N1 pneumonia can be inferred.

Critical analysis

Heterogeneity of published data regarding study design, population demographics, severity of illness, dosing, type and timing of corticosteroids administered constitute an important limitation for drawing robust conclusions. However, it is reasonable to admit that, as it was not found any advantage of corticosteroid therapy in so diverse conditions, such beneficial effects do not exist at all. Recent insights on a decrease in cortisol breakdown during critical illness questions the classic concept of adrenal failure with low cortisol production and constitutes a molecular argument against the use of corticosteroids as standard of care for patients with critical illness: The increased cortisol circulating levels and tissue activity make an additional synthetic corticosteroid dose either redundant or excessive and not devoid of deleterious effects.

Finally, it is reasonable to conclude that corticosteroids failed to demonstrate any beneficial effects in the treatment of patients with severe influenza infection. Its administration is likely to increase overall mortality and such trend is consistent regardless of the quality as well as the sample size of studies. Moreover it was shown that corticosteroids might be associated with higher incidence of hospital-acquired pneumonia and longer duration of mechanical ventilation and ICU stay. Thus its current use in Severe Influenza pneumonia should be restricted to selected cases and in the setting of clinical trials.

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MINIREVIEWS

Mild to moderate intra-abdominal hypertension: Does it matter?

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Abstract

This review summarizes the epidemiology, pathophysiological consequences and impact on outcome of mild to moderate (Grade Ⅰ to Ⅱ) intra-abdominal hypertension (IAH), points out possible pitfalls in available treatment recommendations and focuses on tasks for future research in the field. IAH occurs in about 40% of ICU patients. Whereas the prevalence of abdominal compartment syndrome seems to be decreasing, the prevalence of IAH does not. More than half of IAH patients present with IAH grade Ⅰ and approximately a quarter with IAH grade Ⅱ. However, most of the studies have addressed IAH as a yes-or-no variable, with little or no attention to different severity grades. Even mild IAH can have a negative impact on tissue perfusion and microcirculation and be associated with an increased length of stay and duration of mechanical ventilation. However, the impact of IAH and its different grades on mortality is controversial. The influence of intra-abdominal pressure (IAP) on outcome most likely depends on patient and disease characteristics and the concomitant macro- and microcirculation. Therefore, management might differ significantly. Today, clear triggers for interventions in different patient groups with mild to moderate IAH are not defined. Further studies are needed to clarify the clinical importance of mild to moderate IAH identifying clear triggers for interventions to lower the IAP.

Key words: Intra-abdominal pressure; Intra-abdominal hypertension; Pathophysiology; Epidemiology; Severity; Treatment

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Core tip: This review summarizes the epidemiology,

pathophysiological consequences and impact on outcome of mild to moderate intra-abdominal hypertension (IAH) and focuses on tasks for future research in the field. More than half of IAH patients present with IAH Grade Ⅰ and approximately a quarter with IAH grade Ⅱ. Even mild IAH can have a negative impact on tissue perfusion and be associated with impaired clinical outcomes. However, the impact of IAH and its different grades on mortality is controversial. Clear triggers for interventions in different patient groups with mild to moderate IAH are not defined.

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INTRODUCTION

Intra-abdominal hypertension (IAH) occurs in 20%-40% of intensive care patients and has a significant impact on outcome[1-3]. IAH is defined as intra-abdominal pressure (IAP) of 12 mmHg or above, whereas normal IAP is in the range of 0 to 11 mmHg[4]. The cut-off point of 12 mmHg for IAH was initially selected empirically[5,6], but is now supported by several epidemiological studies[1,5,7-11]. Based on severity, IAH is graded into four levels. Grade Ⅰ refers to IAP from 12 to 15 mmHg, grade Ⅱ 16 to 20 mmHg, grade Ⅲ 21 to 25 mmHg, and grade Ⅳ above 25 mmHg, respectively. The most severe form is abdominal compartment syndrome (ACS), defined as sustained IAP ⩾ 20 mmHg (with or without an abdominal perfusion pressure (APP) of ⩽ 60 mmHg) in association with the new onset or worsening of existing organ failure[4]. This is a life-threatening syndrome[6], which, however, seldom occurs in clinical practice[2,3,12]. In these cases, the deterioration of cardiac, respiratory and renal performance is usually clearly evident and determines the immediate need for life-saving treatment. The management of IAP below 20 mmHg is much more controversial[2,13] as there is no clear trigger for when and to what extent to initiate the treatment of IAH.

This review was undertaken to differentiate IAH grade Ⅰ and Ⅱ from higher grades of IAH regarding the pathophysiological changes and impact on outcome, and to discuss possible differences in management based on the severity of IAH.

EPIDEMIOLOGY AND OUTCOME OF IAH AND ITS DIFFERENT SEVERITY GRADES

There are several recent studies describing the epidemiology of IAH and investigating its impact on outcome[10,14,15].

Kim *et al*[15] included 100 consecutive patients in a prospective observational single-center study on a mixed intensive care unit (ICU) population. The overall incidence of IAH was 42%, while IAH grade Ⅰ occurred in 23%, grade Ⅱ in 14%, grade Ⅲ in 3% and grade Ⅳ in 2% of IAH patients (Figure 1). Patients with IAH had higher APACHE Ⅱ and Ⅲ scores, body mass index (BMI) and more sepsis on admission. However, there was no difference in the length of ICU stay or hospital mortality in patients with IAH (irrespective of the grade) *vs* patients without IAH.

Iyer *et al*[14] included 403 consecutive patients to investigate the incidence of IAH/ACS and to develop a screening tool for the early identification of patients requiring IAP monitoring. The incidence of IAH was 39% and of ACS, 2%. IAH grade Ⅰ occurred in 27%, grade Ⅱ in 9%, grade Ⅲ in 2% and grade Ⅳ in 1% (Figure 1). Regarding outcomes, patients with IAH had significantly longer duration of mechanical ventilation and, length of stay in the ICU and in the hospital. No difference in mortality was detected between the patients with or without IAH; however, patients with IAH of higher grades (Ⅱ-Ⅳ) had higher ICU mortality (13% *vs* 3.4%, P = 0.003)[14].

A recent systematic review and individual patient data meta-analysis reported distribution of IAP values among 1669 critically ill patients upon admission to ICU[10]. The mean IAP was 9.9 mmHg; whereas 27.7% of patients had IAH and 2.7% ACS on admission. Although the exact data on different IAH grades were not given, the IAP distribution histogram supports the studies discussed above (Kim *et al*[15] and Iyer *et al*[14]). Concerning the outcomes, the ICU length of stay, the ICU and the hospital mortality were significantly increased in the IAH group.

It is somewhat surprising that outcomes differ significantly when the data from Reintam *et al*[2], Malbrain *et al*[10] and Blaser *et al*[16] and our own earlier studies are compared to the results of Kim *et al*[15] or Iyer *et al*[14]. One possible explanation might be that the meta-analysis is based on studies published predominantly between 1995 and 2008. Almost two decades of research has very likely improved our understanding and management of IAH/ACS[12,17], and this may explain the decrease in morbidity and mortality. Moreover, most of the earlier studies (including the ones in the meta-analysis by Malbrain *et al*[10]) enrolled only selected patients (*e.g.,* patients with pancreatitis, trauma, mechanically ventilated or presenting other risk factors for IAH). Therefore, the patient groups are not entirely comparable. Furthermore, assigning patients with IAP of 12 to 15 mmHg to the same group as ACS most likely confuses the results in all the above-mentioned studies. As the incidence of ACS is decreasing and the outcome simultaneously improving[12,16,17], its impact to the overall group of IAH patients is diminishing.

Considering these factors, the clinical importance of IAH is much dependent on the severity (grade) of IAH, but these associations have been poorly studied.

EFFECT OF MODERATE IAH IN DIFFERENT PATIENT GROUPS

Next to the severity of IAH, the nature and course of

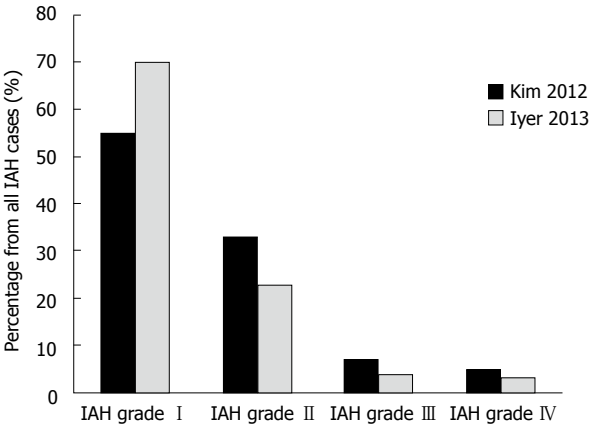

Figure 1 Prevalence of different grades of intra-abdominal hypertension in clinical studies performed in consecutive intensive care unit patients. IAH: Intra-abdominal hypertension.

underlying pathology needs to be taken into account. Higher grades of IAH may be less deleterious if the disease is cured (*e.g.,* after abdominal surgery), whereas moderate IAH may have additional aggravating effect on the patients with uncontrolled primary pathology (*e.g.,* shock with continuing need for fluid resuscitation).

In patients with pancreatitis or intra-abdominal infections already the mild IAH deserves close attention as a sign of increased oedema formation. In these patients development of IAH/ACS is primarily caused by the inflammatory process inside the abdominal cavity and may be further exacerbated by aggressive fluid therapy[18,19].

Intraperitoneal bleeding should be recognized promptly and therefore in trauma patients any increase of IAP, even at the low grades, deserves particular attention.

During pregnancy IAP increases physiologically, but the effect of the IAH has been poorly studied in this specific patient group. Recently, it has been postulated that the inability to adapt to the increasing intra-abdominal volume, reflected as sustained increase of IAP above 12 mmHg may be involved in the etiopathogenesis of pre-eclampsia[20].

Children, not specifically addressed in this review, require different approach. Organ dysfunction in paediatric patients has been reported to occur at the IAP 10 to 15 mmHg, and the ACS may develop already at the IAP of 16 mmHg[19,21,22].

In contrary, after elective abdominal hernia repair transient increase of IAP up to 18 mmHg may be well tolerated[23].

EFFECT OF IAH ON SPLANCHNIC BLOOD FLOW, MICROCIRCULATION AND METABOLISM

An experimental study on pigs demonstrated that a pneumoperitoneum-caused IAP of 12 mmHg combined with positive end-expiratory pressure of 10 cmH_2O decreases blood flow in the hepatic and mesenteric arteries and portal vein, impairs the hepatic and intestinal mucosal microcirculation, attenuates the hepatic pO_2 and intestinal mucosal pH, this all indicating to seriously disturbed splanchnic blood flow[24]. Olofsson *et al*[25] showed in pigs that increased IAP correlates with decreased gastrointestinal microcirculation measured by laser Doppler flowmetry, whereas microcirculation in mucosal layer was significantly less affected than in serosa. Cheng *et al*[26] demonstrated that, in rabbits, microvascular blood flow is decreased by 40% during IAP 15 mmHg for 2 h, and by 81% when the IAP was 25 mmHg for 6 h, while markers of intestinal injury increased significantly, in proportion to IAP and exposure time. After prolonged exposure to increased IAP, erosions and necrosis of the jejunal villi, mitochondrial swelling and discontinuity of intracellular tight junctions were microscopically observed[26]. These findings are clearly contrasted by recent study on mechanically ventilated sheep without sepsis, which demonstrated decreased renal blood flow and diuresis but preserved blood flow in superior mesenteric artery at IAP of 20 mmHg and no changes in microcirculatory variables. However, sheep with IAH received large amounts of fluids compared to sham and still developed relevant lactic acidosis. As shown by Dubin *et al*[27] in septic sheep, resuscitation was able to normalize mean arterial blood pressure, cardiac output, superior mesenteric artery blood flow and sublingual and serosal intestinal microvascular flow indexes, but not to restore percentage of perfused ileal villi, which could explain elevation of lactate. These different findings may be explained by several aspects: the level, mechanism and duration of the elevated IAP, presence or absence of sepsis, resuscitation strategy as well as the methodology of assessment of microcirculation all may play an important role.

In humans, the effect of IAP on gut perfusion is not well studied, but significant reduction of splanchnic blood flow has been demonstrated after the IAP increases from 7 to 14 mmHg[28]. As the splanchnic area is difficult to access in clinical setting, the monitoring of sublingual microcirculation might be considered for indirect evaluation of splanchnic microcirculation[29], although it is not clear whether this is well applicable in case of IAH where splanchnic bed is directly affected through the extravascular pressure.

So far, the associations between IAP and sublingual microcirculation have been evaluated in two studies[30,31]. No significant alterations in sublingual microcirculation were demonstrated at IAH grades Ⅰ and Ⅱ, neither in elective surgery nor in critically ill patients. In elective laparoscopic surgery the microcirculatory perfusion indices were relatively low at the baseline and did not improve during the study period[30].

In heterogeneous group of critically ill patients, the moderate but prolonged increase of IAP (median 14.5 mmHg) for up to 24 h exhibits a negligible influence on the sublingual microcirculation[31]. Ten out of 15 of these patients were in circulatory shock, and it is somewhat

surprising that no significant alterations in the sublingual microcirculation were detected[31]. Observed positive correlations between microvascular flow index, MAP and APP, however, may support the importance of APP in clinical management of this situation[31].

Relevant alterations in microcirculation should result in the increased anaerobic metabolism and this hypothesis has led to studies investigating influence of IAP on tissue metabolism[30-35]. The findings suggest that the deterioration of tissue metabolism in the abdominal area may occur well before IAH-related organ dysfunction become evident[30-35].

In animal experiments, tissue microdialysis has been increasingly used to evaluate metabolic status in different vascular beds and in different conditions. By this method, Meier *et al*[35] were able to demonstrate the accumulation of metabolites of anaerobic glycolysis in the rectus abdominis muscle (RAM) of rats subjected to IAH. The RAM is surrounded by a tight sheet of fascia, which makes the muscle-fascia compartment relatively non-compliant. The pressure in the intra-abdominal cavity directly influences the muscle tissue and its perfusion. This muscle is easily accessible and makes the RAM microdialysis minimally invasive; therefore the RAM serves as a good model of intra-abdominal organ[32].

We performed RAM microdialysis in elective laparoscopic surgery (median IAP 12.5 mmHg) and in critically ill patients (median IAP 14.5 mmHg)[32,33]. In both groups the RAM tissue metabolism was seriously disturbed when compared to the baseline before surgery or to the references from other studies[36]. Elevated lactate, lactate-to-pyruvate ratio, and glutamate levels indicated anaerobic metabolism during moderately raised IAP. The correlation analysis revealed a negative correlation of APP, pyruvate and glycerol, supporting the relevance of APP as a resuscitation end-point when setting the targets for MAP and vasopressor therapy[33].

Considering these factors, some experimental studies indicate that increased IAP results in impaired splanchnic microcirculation and metabolism. Limited data suggests that similar changes may occur also in humans although direct assessment of the splanchnic area would be desirable to confirm these findings. Setting the APP or any other macrocirculatory variable as a resuscitation endpoint in patients with IAH remains controversial.

PITFALLS IN MANAGEMENT RECOMMENDATIONS

The Abdominal Compartment Society management algorithm suggests initiating medical treatment at IAP of 12 mmHg or higher and tailoring treatment to keep IAP below 15 mmHg[4]. Several mechanisms may lead to IAH: increased baseline IAP (*e.g.,* obesity), increased intra-abdominal volume (*e.g.,* ascites or oedema), and decreased abdominal wall compliance (*e.g.,* tight abdominal closure after hernia repair)[6,37]. It is clear that these different mechanisms require different therapeutic approaches. However, the severity of IAH (grade of IAH) should also guide the selection of the best management option in these different situations. It is not clear whether in some cases lower grade IAH could merely be observed, whereas in others it should be aggressively treated with, *e.g.*, sedatives and muscle relaxants. Current IAH/ACS guidelines suggest stepwise IAH treatment: From medical and minimally invasive techniques to aggressive surgical decompression[4]. A stepwise approach in general is definitely wise. However, different grades of IAH and different patient groups are not considered. As most of the options for IAP reduction are not without risks (*e.g.*, drainages) and side effects (*e.g.,* sedation, muscle relaxation), it is important not to apply these strategies without clear indication. It is possible that not treating moderate IAH could impair the outcome in one patient, whereas aggressive treatment (*e.g.,* muscle relaxation) could be harmful in the other.

Future studies should form the basis for more detailed recommendations, whereas currently these decisions should be made during careful bedside evaluation, and require deep knowledge and experience.

FUTURE STUDIES

Based on existing evidence, it is likely that lower grades of IAH are relevant in terms of both pathophysiology and clinical consequences. However, the relationships are most likely complex, and the influence of IAP depends on patient characteristics (*e.g.,* obese *vs* non-obese; ventilated *vs* spontaneously breathing, critically ill *vs* ward patients), concomitant macro- (dependent on MAP) and microcirculation and disease characteristics (*e.g.,* pancreatitis *vs* pneumonia). As IAH has been often assessed as a yes-or-no variable, these issues are not yet clarified. Accordingly, there are several issues that should be studied more closely in future studies.

IMPORTANCE OF IAH GRADES IN DIFFERENT PATIENT GROUPS

Normal IAP in critically ill patients is thought to be between 5-7 mmHg[4], but there is not enough data to identify normal values in spontaneously breathing patients. Moreover, "normal" or expected IAP levels in patients with abdominal pathology, *e.g.,* after elective major abdominal surgery, are unknown.

Signs of organ dysfunction, duration of mechanical ventilation, ICU length of stay and ICU mortality seem to increase in patients with elevated IAH, whereas in most cases, IAP ranges between 12-16 mmHg. Dalfino *et al*[11] showed that elevated IAP and low APP are associated with the development of acute renal failure (ARF) in critically ill patients after shock and identified a cut-off IAP of 12 mmHg for increasing the risk of ARF. A cut-off value of 12 mmHg for IAH is also supported by several other studies[1,5,7-10]. However, it is not clear whether the current IAH grading system can be

translated to gradually increasing mortality or worsening organ function.

Spontaneously breathing patients

None of the studies has specifically addressed IAH in spontaneously breathing patients. Therefore, it is not known, whether 12 mmHg is also applicable to this subset of patients. Moreover, the likelihood of more unstable measurement conditions in spontaneously breathing patients may lead to wide variations, and muscle tonus may play an important role.

Patients with chronically elevated IAP

Obesity and pregnancy are chronic states of low-graded IAH to which the patient has adapted[6,38]. Both conditions develop relatively slowly, and the human organism adapts to these (patho) physiological changes, but there is still an issue if such patients need to be admitted to an ICU. IAP levels that trigger specific treatment should be most likely higher, but how much so, remains unclear.

Patients after abdominal surgery

Post-operative complications after abdominal surgery are frequent and are associated with increased morbidity and mortality[39-42]. Intra-abdominal hypertension and its pathophysiological consequences may contribute to the development of postoperative complications[43,44], but no specific data are available thus far. Therefore, a cut-off that triggers interventions directed to lower IAP and/or to increase APP in such patients is warranted.

CONCOMITANT CHANGES IN MACRO- AND MICROCIRCULATION DURING IAH

Ideally, the management of hemodynamics should ensure normal microcirculation and organ function in different vascular beds. We currently lack reliable tool(s) to assess microcirculation at the bedside, and the clinical signs (diuresis, mottled skin) and macrohemodynamic variables (MAP, cardiac output) rather than microcirculatory changes direct the patient management in clinical practise. However, in the case of increased abdominal pressure, "normal" MAP and cardiac output might be insufficient to assure the adequate perfusion of abdominal and retroperitoneal organs. Moreover, due to heterogeneous aspects of microcirculatory perfusion, effect of classical hemodynamic interventions on microcirculation will most likely be limited[45]. Whether microcirculatory measurements may be supportive for hemodynamic management during IAH remains to be elucidated.

The identification of patient groups where even mild IAH leads to microcirculatory dysfunction with anaerobic metabolism would be desirable for the more precise adjustment of management suggestions.

MANAGEMENT OF IAH

Higher grades of IAH are infrequent; most patients with IAH qualify as grade Ⅰ of IAH. Therefore, further studies should focus on mild to moderate IAH to clarify, which patients should be treated aggressively and which patients can simply be observed. Studies are needed to allow revision of the algorithm based on evidence. More specific recommendations including treatment triggers in spontaneously breathing patients, obese patients, patients after abdominal surgery and other specific groups, are warranted.

CONCLUSION

IAH occurs in about 40% of the ICU population. More than half of these patients present with IAH grade Ⅰ and approximately a quarter with IAH grade Ⅱ. Patients with IAH have a significantly longer duration of mechanical ventilation and, longer length of stay in the ICU and in the hospital. The impact of IAH and its different grades on mortality is controversial.

Preliminary data suggest that grades Ⅰ and Ⅱ IAH has a negative impact on tissue perfusion and microcirculation. Further studies are needed to clarify whether and in which particular sub-group of patients the occurrence of mild to moderate IAH should trigger immediate interventions directed at lowering the IAP.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Prognostic factors associated with hospital survival in comatose survivors of cardiac arrest

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Data sharing statement: Data presented in this manuscript is anonymised and the risk of identifying any individual patient is very low. No additional data available for this study beyond that stated in the manuscript.

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Abstract

AIM: To identify patient, cardiac arrest and management factors associated with hospital survival in comatose survivors of cardiac arrest.

METHODS: A retrospective, single centre study of comatose patients admitted to our intensive care unit (ICU) following cardiac arrest during the twenty year period between 1993 and 2012. This study was deemed by the Human Research Ethics Committee (HREC) of Monash Health to be a quality assurance exercise, and thus did not require submission to the Monash Health HREC (Research Project Application, No. 13290Q). The study population included all patients admitted to our

ICU between 1993 and 2012, with a discharge diagnosis including "cardiac arrest". Patients were excluded if they did not have a cardiac arrest prior to ICU admission (*i.e.*, if their primary arrest was during their admission to ICU), or were not comatose on arrival to ICU. Our primary outcome measure was survival to hospital discharge. Secondary outcome measures were ICU and hospital length of stay (LOS), and factors associated with survival to hospital discharge.

RESULTS: Five hundred and eighty-two comatose patients were admitted to our ICU following cardiac arrest, with 35% surviving to hospital discharge. The median ICU and hospital LOS was 3 and 5 d respectively. There was no survival difference between in-hospital and out-of-hospital cardiac arrests. Males made up 62% of our cardiac arrest population, were more likely to have a shockable rhythm (56% *vs* 37%, $P < 0.001$), and were more likely to survive to hospital discharge (40% *vs* 28%, $P = 0.006$). On univariate analysis, therapeutic hypothermia, regardless of method used (*e.g.*, rapid infusion of ice cold fluids, topical ice, "Arctic Sun", passive rewarming, "Bair Hugger") and location initiated (*e.g.*, pre-hospital, emergency department, intensive care) was associated with increased survival. There was however no difference in survival associated with target temperature, time at target temperature, location of initial cooling, method of initiating cooling, method of maintaining cooling or method of rewarming. Patients that survived were more likely to have a shockable rhythm ($P < 0.001$), shorter time to return of spontaneous circulation ($P < 0.001$), receive therapeutic hypothermia ($P = 0.03$), be of male gender ($P = 0.006$) and have a lower APACHE Ⅱ score ($P < 0.001$). After multivariate analysis, only a shockable initial rhythm (OR = 6.4, 95%CI: 3.95-10.4; $P < 0.01$) and a shorter time to return of spontaneous circulation (OR = 0.95, 95%CI: 0.93-0.97; $P < 0.01$) was found to be independently associated with survival to hospital discharge.

CONCLUSION: In comatose survivors of cardiac arrest, shockable rhythm and shorter time to return of spontaneous circulation were independently associated with increased survival to hospital discharge.

Key words: Cardiac arrest; Hypothermia; Hyperthermia; Arrhythmia; Resuscitation

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Core tip: Admission to intensive care after cardiac arrest is increasing. With the improvements in intensive care practice the survival to hospital discharge is being reported in up to 50% of patients. This study, one of the largest series published so far, was aimed to identify any association between patient factors, cardiac arrest characteristics and post-cardiac arrest management strategies with survival to hospital discharge. The results of this study confirm that of all the factors studied, shockable rhythm and shorter time to return of spontaneous circulation were independently associated with increased survival to hospital discharge.

Sathianathan K, Tiruvoipati R, Vij S. Prognostic factors associated with hospital survival in comatose survivors of cardiac arrest. *World J Crit Care Med* 2016; 5(1): 103-110 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/103.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.103

INTRODUCTION

Cardiovascular disease accounts for 37% of deaths in Australia, the majority being due to cardiac arrest, with an incidence of 148 per 100000[1]. Unconscious survivors of primary cardiac arrest are at high risk of death and neurological injury[2,3]. Hospital survival rates of up to 50% have been described[4,5].

Recent focus on the hospital management of patients following cardiac arrest has been on therapeutic hypothermia, or targeted temperature management (TTM). Therapeutic hypothermia has been described in human survivors of cardiac arrest as early as the 1950's[6]. Animal studies were undertaken in the early 1990's[7], followed by feasibility studies on humans[8-10]. Two landmark trials published in 2002[3,11] demonstrated therapeutic hypothermia improved survival and neurological recovery in comatose survivors of out-of-hospital VF arrest. In 2011, two systematic reviews[12,13] showed no benefit of therapeutic hypothermia over normothermia, and in 2013, the "TTM" trial[4] showed no benefit (or harm) between a targeted temperature of 33 ℃ and a targeted temperature of 36 ℃. All TTM trial subjects were also maintained below 37.5 ℃ for the first 72 h following cardiac arrest, even after rewarming, however this was not the standard practice for our hospital. A higher temperature prior to cooling has already been associated with greater survival[5], however we chose to use the time frame described in the TTM trial (see "MAX-TEMP" below).

A range of different cooling regimes have been described, including "moderate" hypothermia (33 ℃ for 12 h), 33 ℃ for 24 h, and "mild" hypothermia (32-34 ℃ for 24 h)[3,9-11]. Multiple methods have been described for inducing cooling, maintaining cooling and rewarming[3,9,11,14-16]. The optimal approach to inducing and maintaining a targeted temperature remains uncertain[5].

Dandenong Hospital has over twenty years' experience in the management of comatose survivors of cardiac arrest, providing a large pool of patient data to allow for identification of any association between patient factors, cardiac arrest characteristics and post-cardiac arrest management strategies with survival to hospital discharge.

MATERIALS AND METHODS

We undertook a single centre retrospective study at the intensive care unit (ICU) of Dandenong Hospital (DDH).

DDH is a 530 bed metropolitan teaching hospital affiliated with Monash University. The emergency department sees 58000 patients per annum, and the hospital has 48000 acute admissions per annum. The ICU is a 14 bed level 2 general ICU with 1100 annual admissions and 8.6% mortality.

This study was deemed by the Human Research Ethics Committee (HREC) of Monash Health to be a quality assurance exercise, and thus did not require submission to the Monash Health HREC (Research Project Application No. 13290Q). The study population included all patients admitted to our ICU between 1993 and 2012, with a discharge diagnosis including "cardiac arrest". Patients were excluded if they did not have a cardiac arrest prior to ICU admission (*i.e.*, if their primary arrest was during their admission to ICU), or were not comatose on arrival to ICU.

Patients were identified using the ICU database. Acute physiology and chronic health evaluation (APACHE) data (APACHE Ⅱ and Ⅲ) were obtained from the ICU database. APACHE data were only available for patients admitted from July 1999. Further patient information was extracted from the hospital medical records. The baseline characteristics collected were age, gender, admission diagnosis, location of cardiac arrest (*i.e.*, in-patient *vs* out-of-hospital), initial rhythm, time to return of spontaneous circulation, hospital admission source and ICU admission source. Information collected describing management were documentation of therapeutic hypothermia plan, decision to institute cooling, location of initial cooling, method of initiating cooling, method of maintaining cooling, targeted temperature, time taken to achieve target temperature, time at target temperature (both planned and actual), method of rewarming and the maximum temperature reached in the first 72 h following cardiac arrest (MAX-TEMP). The "MAX-TEMP" variable was created to investigate any association between hospital survival and hyperthermia within the first 72 h following cardiac arrest, using the same 37.5 ℃ cut-off used in the TTM trial.

Primary outcome measure was survival to hospital discharge. Secondary outcome measures were ICU length of stay (LOS), hospital LOS and the patient, cardiac arrest and management factors associated with survival to hospital discharge.

IBM SPSS Statistics (release 22.0.0.0, IBM Corp., Armonk, NY, United States) was used to analyse our data. Continuous data were presented as mean [standard deviation (SD)] and compared using student *t*-test. Parametric data were presented as median [interquartile range (IQR)] and compared using Mann-Whitney test. Nominal data were analysed using Chi-squared test. Binary logistic regression analysis was used to identify independent associations with hospital survival. *P*-values less than 0.05 were considered significant.

RESULTS

The ICU database search identified 728 patients admitted to our ICU between 1993 and 2012 with a discharge diagnosis including "cardiac arrest" (Figure 1). 109 patients were excluded for not having a cardiac arrest prior to ICU admission and a further 37 patients for not being comatose on arrival to ICU, leaving a total of 582 patients. There were no APACHE data available for patients admitted prior to July 1999 (n = 155, 26.6%). These patients were excluded from further analysis involving APACHE data, but were still included for all other analyses.

Overall survival to hospital discharge was 35%, with median ICU and hospital length of stays (LOS) of 3 and 5 d respectively (Table 1). Table 2 separates our patients into survivors and non-survivors, identifying statistically significant differences in initial rhythm, time to return of spontaneous circulation, APACHE Ⅱ score, gender and the institution of therapeutic hypothermia. There was no survival difference between in-hospital and out-of-hospital cardiac arrests. Males made up 62% of our cardiac arrest population (Table 1), were more likely to have a shockable rhythm (56% *vs* 37%, $P < 0.001$) (data not presented), and were more likely to survive to hospital discharge (40% *vs* 28%, $P = 0.006$) (Table 2).

On univariate analysis, therapeutic hypothermia, regardless of method used (*e.g.*, rapid infusion of ice cold fluids, topical ice, "Arctic Sun", passive rewarming, "Bair Hugger") and location initiated (*e.g.*, pre-hospital, emergency department, intensive care) was associated with increased survival (Table 2). There was however no additional difference in survival associated with target temperature, time at target temperature, location of initial cooling, method of initiating cooling, method of maintaining cooling or method of rewarming (data not presented). There was greater survival associated with MAX-TEMP higher than 37.5 ℃ (41% *vs* 27%, $P < 0.001$) (data not presented).

Comparing patients that presented before and after 2002 (Table 3), the second decade had statistically significant increases in non-shockable rhythms, time to return of spontaneous circulation, out-of-hospital cardiac arrests, prescription of therapeutic hypothermia and APACHE Ⅱ scores. Patients in this group took longer to cool and were cooled for a longer period of time. There was a statistically significant decrease in mean age and a non-significant decrease in survival in the second period. There was a statistically significant increase in ICU LOS, but a non-significant decrease in the hospital LOS in the second period. There was also a statistically significant increase in the implementation of therapeutic hypothermia over the course of the study period (Figure 2).

Binary logistic regression analysis identified only a shockable initial rhythm (OR = 6.4, 95%CI: 3.95-10.4; $P < 0.01$) and a shorter time to return of spontaneous circulation (OR = 0.95, 95%CI: 0.93-0.97; $P < 0.01$) to be independently associated with survival to hospital discharge (Table 4).

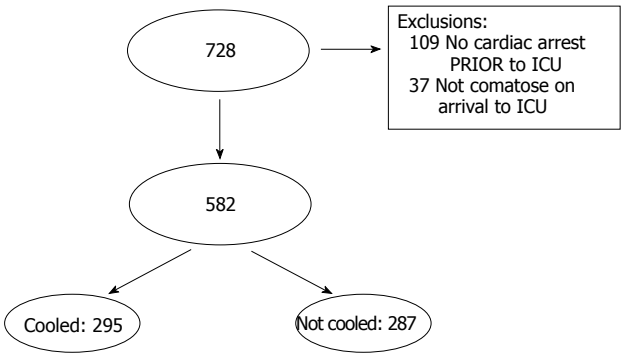

Figure 1 Flow diagram of all patients.

Table 1 Demographics, cardiac arrest details and management of included patients

Variable	All patients *n* = 582
Patient	
Age (yr) - mean (SD) (*n* = 581)	63 (16)
Gender (male) - *n* (%) (*n* = 579)	361 (62)
Cardiac arrest	
Time to ROSC (min) - mean (SD) (*n* = 571)	23 (15)
Presenting rhythm (shockable) - *n* (%) (*n* = 582)	286 (49)
Location of arrest (OHCA) - *n* (%) (*n* = 582)	408 (70)
Apache 2 score - mean (SD) (*n* = 427)	28 (8.4)
Apache 3 score - mean (SD) (*n* = 427)	78 (37.8)
Management	
Cooled - *n* (%) (*n* = 582)	295 (51)
Target temperature (℃) - median (IQR) (*n* = 290)	33 (33-33)
Time to temp[1] (h) - mean (SD) (*n* = 288)	2.1 (3.0)
Time at temp[2] (h) - median (IQR) (*n* = 290)	24 (12-24)
Outcome	
Survived to hospital discharge - *n* (%) (*n* = 582)	206 (35)
ICU LOS (d) - median (IQR) (*n* = 582)	3 (1-5)
Hospital LOS (d) - median (IQR) (*n* = 581)	5 (2-14)

[1]Time to temp = time taken to reach target temperature (hours); [2]Time at temp = time at target temperature (hours). LOS: Length of stay (days); ROSC: Return of spontaneous circulation (minutes); OHCA: Out of hospital cardiac arrest; IQR: Interquartile range.

DISCUSSION

This twenty year retrospective study identified multiple patient factors, cardiac arrest characteristics and post-cardiac arrest management strategies that were associated with increased survival to hospital discharge in comatose survivors of cardiac arrest.

A shockable rhythm, and a shorter time to return of spontaneous circulation were both associated with increased survival (Table 2). The Victorian Ambulance Cardiac Arrest Register (VACAR)[17] showed there was a higher chance of survival in patients found with a shockable rhythm. In addition, patients found with a shockable rhythm were more likely to have an earlier return of spontaneous circulation and survive to hospital admission[18,19]. These variables were the only two factors identified in our study to be independently associated with survival to hospital discharge following multivariate analysis.

Table 2 Comparison of survivors and non-survivors

Variable	Died *n* = 376 (65%)	Survived *n* = 206 (35%)	*P* value
Patient			
Age (yr) - mean (SD) (*n* = 581)	64 (17)	63 (15)	0.28
Gender (male) - *n* (%) (*n* = 579)	218 (58)	143 (70)	0.006
Cardiac arrest			
Time to ROSC (min) - mean (SD) (*n* = 571)	26 (14.5)	18 (14.3)	< 0.001
Presenting rhythm (shockable) - *n* (%) (*n* = 582)	134 (36)	152 (72)	< 0.001
Location of arrest (OHCA) - *n* (%) (*n* = 582)	269 (72)	139 (67)	0.3
Apache 2 score - mean (SD) (*n* = 427)	30 (7.6)	24 (8.5)	< 0.001
Apache 3 score - mean (SD) (*n* = 427)	79 (37.9)	77 (37.8)	0.5
Management			
Cooled - *n* (%) (*n* = 582)	178 (47)	117 (57)	0.03
Target temperature (℃) - median (IQR) (*n* = 290)	33 (33-33)	33 (33-33)	0.44
Time to temp[1] (h) - mean (SD) (*n* = 288)	1.8 (2.9)	2.5 (3.1)	0.04
Time at temp[2] (h) - median (IQR) (*n* = 290)	24 (12-24)	24 (12-24)	0.84
Outcome			
ICU LOS (d) - median (IQR) (*n* = 582)	2 (1- 4)	4 (2-7)	< 0.001
Hospital LOS (d) - median (IQR) (*n* = 581)	3 (1-6)	15 (8-27)	< 0.001

[1]Time to temp = time taken to reach target temperature (hours); [2]Time at temp = time at target temperature (hours). LOS: Length of stay (days); ROSC: Return of spontaneous circulation (minutes); OHCA: Out of hospital cardiac arrest; IQR: Interquartile range.

The association between male gender and increased survival to hospital discharge (Table 2) was expected, as men are more likely to have an out-of-hospital cardiac arrest[20], are more likely to survive to hospital admission[21] and are more likely to survive to hospital discharge[19,20]. Men are also more likely to have coronary artery disease and to have a shockable rhythm, both resulting in better survival following cardiac arrest[20,22].

There was a statistically significant association between lower APACHE Ⅱ scores and increased survival, but not with APACHE Ⅲ. The original APACHE score included 34 physiological variables[23], which was reduced to 12 with APACHE Ⅱ, along with inclusions of age, chronic health and surgical procedures[24]. APACHE Ⅲ was later introduced with 17 physiological variables, increased chronic health categories, less weighting for chronic health and a section for ICU admission source[25]. APACHE Ⅳ has subsequently been released, however due to its complexity, APACHE Ⅱ and APACHE Ⅲ are still used in mainstream practice[26]. Of the above, only APACHE Ⅱ measured at 24 h has been shown to correlate with mortality in patients following cardiac arrest[27]. The alteration in the chronic health section and the different weighting given to it, may explain the lack of correlation between the APACHE Ⅱ and APACHE Ⅲ scoring systems in our study population.

In addition to the TTM trial[4], there have been many other trials from Scandinavia looking at the management of patients following cardiac arrest[28-31]. Initially, because patients were selected for cooling based on "hypothermia after cardiac arrest" (HACA) inclusion criteria[3], only

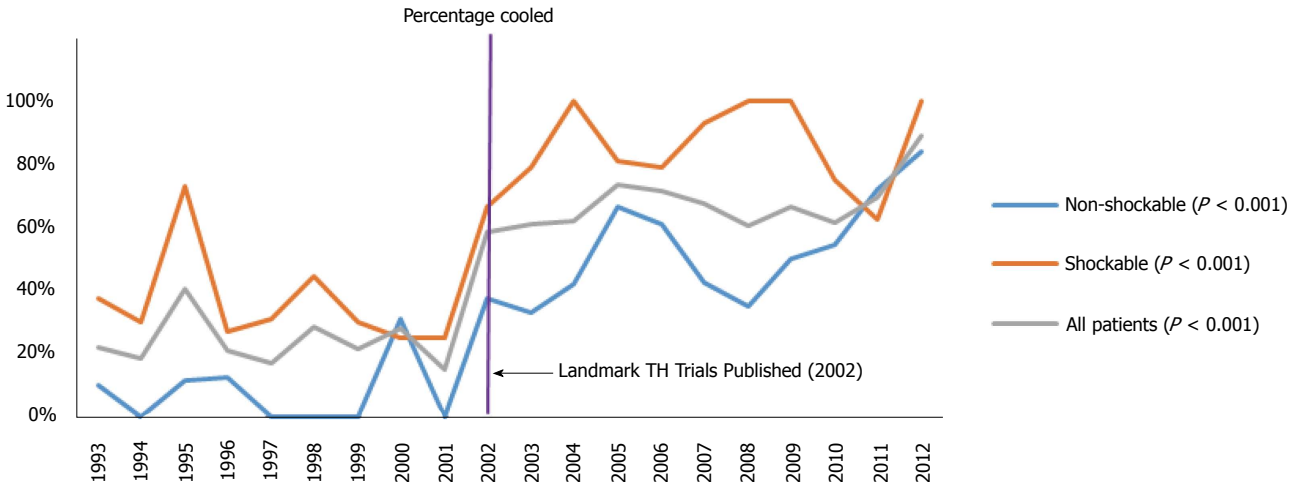

Figure 2 Percentage of patients cooled over time.

Table 3 Comparison of patients before and after 2002

Variable	1993-2002 *n* = 257 (44%)	2003-2012 *n* = 325 (56%)	*P* value
Patient			
Age (yr) - mean (SD) (*n* = 581)	65 (15)	62 (16)	0.04
Gender (male) - *n* (%) (*n* = 579)	161 (63)	200 (62)	0.73
Cardiac arrest			
Time to ROSC (min) - mean (SD) (*n* = 571)	21 (14)	24 (15)	0.02
Presenting rhythm (shockable) - n (%) (*n* = 582)	151 (59)	135 (42)	< 0.001
Location of arrest (OHCA) - *n* (%) (*n* = 582)	165 (64)	243 (75)	0.006
Apache 2 score - mean (SD) (*n* = 427)	26 (8.3)	29 (8.3)	0.007
Apache 3 score - mean (SD) (*n* = 427)	75 (35.9)	79 (38.2)	0.23
Management			
Cooled - *n* (%) (*n* = 582)	73 (28)	222 (68)	< 0.001
Target temperature (℃) - median (IQR) (*n* = 290)	33 (33-33)	33 (33-33)	0.62
Time to temp[1] (h) - mean (SD) (*n* = 288)	1.3 (2.2)	2.4 (3.2)	0.04
Time at temp[2] (h) - median (IQR) (*n* = 290)	12 (12-24)	24 (12-24)	0.56
Outcome			
Survived to hospital discharge - *n* (%) (*n* = 582)	99 (38)	107 (33)	0.16
ICU LOS (d) - median (IQR) (*n* = 582)	2 (1-4)	3 (1-6)	0.008
Hospital LOS (d) - median (IQR) (*n* = 581)	6 (2-15)	4 (2-13)	0.18

[1]Time to temp = time taken to reach target temperature (hours); [2]Time at temp = time at target temperature (hours). LOS: Length of stay (days); ROSC: Return of spontaneous circulation (minutes); OHCA: Out of hospital cardiac arrest; IQR: Interquartile range.

28% received therapeutic hypothermia[28]. However, as with our study, the percentage of patients receiving therapeutic hypothermia increased over time (28% in 2007[28], 44% in 2012[29], and 61.7% in 2013[30]) (Figure 2).

Our study identified no association between survival and the location of cooling, method of initiating cooling, method of maintaining cooling or method of rewarming. This may have been confounded by our lack of information on the efficacy of the different cooling strategies implemented. The RICH trial previously documented that pre-hospital cooling added no survival benefit over in-hospital cooling[16]. Other studies have documented the ability of various devices to achieve and maintain a specified temperature[14,15], however it is unclear whether improved efficacy directly translates to improved survival. Despite advances in cooling technology, patients that presented in the second half of the study took longer to achieve target temperature compared to those in the first half (Table 3).

The time of publication of the two practice-changing therapeutic hypothermia trials[3,11] evenly divided our study period into two ten year intervals. Looking at these two periods, there was no statistically significant difference in survival to hospital discharge (Table 3). In fact, there was a non-significant trend to worsening survival (38% *vs* 33%, *P* = 0.16), despite a higher percentage of patients being cooled and a younger group of patients. There are a number of explanations for this. To begin with, the latter group had sicker patients, as indicated by a higher mean APACHE Ⅱ score, which has previously been associated with worse outcomes following cardiac arrest[27]. There was also an increase in non-shockable rhythms and a higher mean time to return of spontaneous circulation, both of which have been associated with worse hospital survival[18,19]. This non-significant decrease in survival also came with the cost of a statistically significant increase in ICU length of stay.

The finding that survival was associated with a higher maximum temperature in the first 72 h (MAX-TEMP) following cardiac arrest (37.4 ℃ *vs* 37.9 ℃, *P* = 0.003) was unexpected. Fever is present in 42%-52% of patients post cardiac arrest[32,33], and has previously been associated with a poor outcome[34,35]. A multicentered observational cohort study from Canada,

Table 4 Final model of logistic regression analysis

Variables	B	SE	Wald	df	Sig.	OR	95%CI	
							Lower	Upper
ROSC	-0.048	0.009	27.588	1	0.000	0.953	0.937	0.971
Shockable rhythm	1.860	0.248	56.222	1	0.000	6.422	3.949	10.441
APACHE II	-0.001	0.003	0.156	1	0.693	0.999	0.993	1.005
Therapeutic hypothermia	0.088	0.248	0.126	1	0.722	1.092	0.672	1.775
Gender	-0.456	0.247	3.388	1	0.066	0.634	0.390	1.030
Constant	-0.210	0.410	0.263	1	0.608	0.810		

ROSC: Time to return of spontaneous circulation.

however, identified that a higher temperature prior to cooling was associated with greater survival (35.6 ℃ *vs* 36.1 ℃, $P < 0.0001$)[5]. We are uncertain whether a difference of only 0.5 ℃ in mean temperatures prior to cooling, or maximum temperatures following cardiac arrest, are significant enough to justify having an effect on outcome. In our study, a lower MAX-TEMP was associated with a shorter median ICU LOS (1 d *vs* 4 d, $P = 0.016$) implying that many patients in our study may have died while still in the cooling process. In addition, for those regaining consciousness, fever may have been tolerated by the treating team, but we were unable to support this statement with the data available.

Another unexpected finding was the association between a longer time to target temperature and greater survival. We found a difference of 42 min (1.8 h *vs* 2.5 h, $P = 0.04$) between the mean time to target temperature of the survivors and non-survivors. This was also noted in the Canadian study mentioned previously, where the difference in means between survivors and non-survivors was 54 min (3.4 h *vs* 4.3 h, $P = 0.001$)[5]. We are unsure whether a difference of less than an hour to achieve a target temperature is sufficient to influence survival. Our finding may have been confounded by our study period overlapping with the start of the RINSE trial[36], resulting in the introduction of non-selective pre-hospital cooling and increased number of patients presenting to ICU who were already hypothermic.

Our study had a number of limitations. We undertook a study that was retrospectively analysed and only involved a single site, raising concerns regarding causality and generalizability. Our primary endpoint was hospital survival, and did not include data on functional outcome, nor follow-up post discharge. Our data lacked many peri-arrest details, preventing us from using Utstein reporting. We lacked APACHE data for patients admitted prior to July 1999. Even though our twenty years of study data enabled comparison before and after the practice changing papers, there were also many other major changes, not only in the management of patients following cardiac arrest, but also in ICU management overall. In addition, this period overlapped with many therapeutic hypothermia studies[9,11,16,36], resulting in changes to therapeutic hypothermia protocols, including the introduction of pre-hospital cooling.

Over the twenty years during which this study encompassed, there was no appreciable change in survival to hospital discharge for comatose survivors of cardiac arrest admitted to our ICU. Increased survival to hospital discharge was found to be independently associated with a shockable initial rhythm and a shorter time to return of spontaneous circulation.

A similar study will need to be repeated following the translation of the TTM Trial findings into clinical practice.

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COMMENTS

Background

The intensive care management of patients following cardiac arrest is variable. This is particularly the case with regard to temperature management. Therapeutic hypothermia has been used in patients following cardiac arrest since the 1950's. However, more than 6 decades later, its role in the management of patients following cardiac arrest, and the parameters targeted, still remain up for debate.

Research frontiers

The targeted temperature management (TTM) trial has made us review our original thoughts on the use of therapeutic hypothermia in patients following cardiac arrest, leading to a new era in TTM. These new strategies have now been incorporated into international post-resuscitation guidelines.

Innovations and breakthroughs

This study looks at a twenty-year time period of the treatment of patients following cardiac arrest in a single institution enabling an insight into the practice changes that have occurred.

Applications

The study was conducted using retrospective data, allowing us to make a number of associations. Using out findings, further studies can be designed to not only look at temperature as a means of therapy, but potentially also as potential prognostic indicator for patients following cardiac arrest.

Terminology

"TTM" is a medical therapy where a patient's core body temperature is actively controlled to maintain a desired level; "Therapeutic hypothermia" is a subset

of TTM where the desired core body temperature is set to a target below 35 ℃; "Cardiac arrest" is the failure of the heart to pump blood, resulting in cessation of circulation; "Shockable rhythm" is an electrical cardiac rhythm causing a cardiac arrest that may be responsive to cardiac defibrillation, such as ventricular fibrillation and ventricular tachycardia'; "Non-shockable rhythm" is an electrical cardiac rhythm causing a cardiac arrest that is not responsive to cardiac defibrillation, such as asystole and pulseless electrical activity.

Peer-review

This is an interesting article describing the experience of a single center on the outcomes of cardiac arrest patients admitted to the intensive care unit.

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