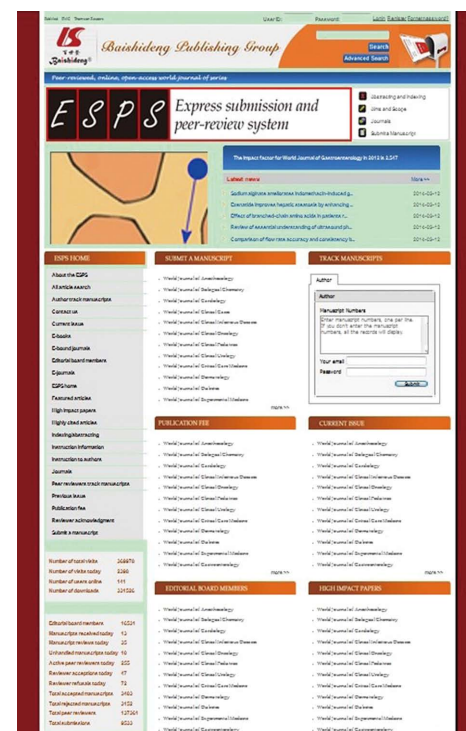
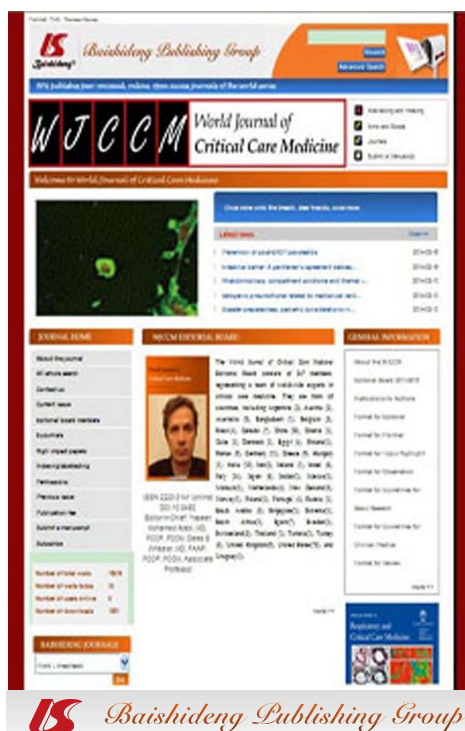
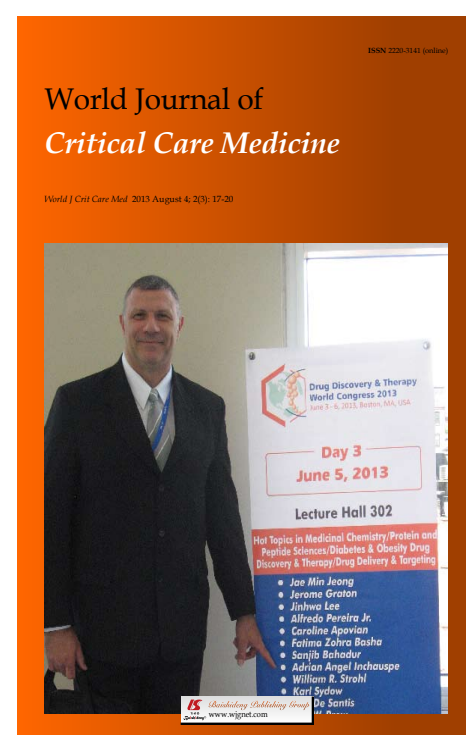
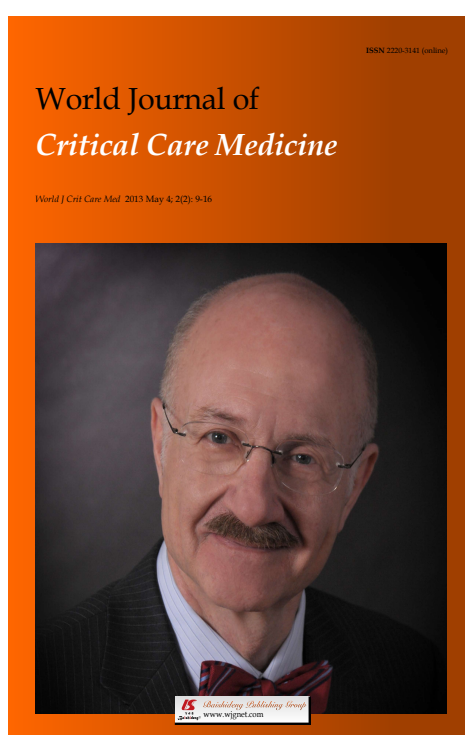


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Intraperitoneal wound in abdominal surgery

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Abstract

The intraperitoneal wound is often forgotten after transperitoneal surgery. This review is a on the peritoneum and the implications of peritoneal injury after surgery. This review will focus on the intraperitoneal wound response after surgical injury.

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Key words: Peritoneum; Vagus nerve; Abdominal surgery; Cytokine; Laparoscopy; Inflammation

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INTRODUCTION

An abdominal operation combines a somatic abdominal wall wound with a second wound to the peritoneal cavity and viscera. Little attention has been paid the peritoneal wound that communicates directly to the brain by the vagus nerve. Traditionally most interventions have focused on producing relief from the physiological burden created by the somatic abdominal wall wound. However recent research indicates that the “forgotten” intraperitoneal wound may be clinically important especially in

those who undergo extensive transperitoneal injury.

PERITONEUM

The peritoneum is a serous membrane that lines the abdominal cavity and the intra-abdominal viscera. This dynamic cellular membrane has important functions^[1]. It provides a frictionless environment for movement of abdominal organs and is a metabolically active sheet of tissue that envelops the majority of the abdominal viscera and is protected by macrophage scavengers. These scavengers play a key role in the local immune response by producing local mediators such as interleukin-6 (IL-6), tumor necrosis factor (TNF- α) and oxygen radicals^[2]. Furthermore the peritoneum is unique compared to surrounding organs in that it carries a lower level of anti-inflammatory pathways resulting to a greater adhesion forming pathways after injury compared to the regeneration that occurs in other organs^[3]. The peritoneum is highly metabolically involved and active, enveloping the majority of the abdominal viscera^[4].

Because the entire peritoneal cavity is linked *via* transcoelomic spread of immuno-humoral factors in the peritoneal fluid, it exhibits a coordinated response to injury which is generalised and not limited to the localised area of insult^[5,6]. This is supported by the fact that there are much higher cytokine concentrations in peritoneal fluid than in plasma after gastrointestinal surgery suggesting that cytokine production occurs in a compartmentalised fashion within the abdominal cavity^[7,8].

The nerve supply to the peritoneum is conveyed along the autonomic nervous system from the parasympathetic and sympathetic system. It can convey sensory fibres via the cranial nervous system, namely the sub-diaphragmatic vagus afferents. The sub-diaphragmatic vagal afferents, about 50000 in number are almost all made from low threshold unmyelinated (C) fibres. They convey background sensations such as mechanical stretch, satiety, fullness, nausea and vomiting sensations^[9]. Afferent vagal inputs originating from the peritoneum and abdominal viscera have great potential to modulate and regulate

behaviour in humans^[10,11]. Furthermore, 90% of the subdiaphragmatic vagus is entirely afferent in nature, indicating a critically important role in direct peritoneal to central nervous system signal transmission and modulation of inflammatory processes arising from the peritoneum^[10,12,13].

Spinal afferent also supply the parietal peritoneal lining and mesentery of the gastrointestinal tract, and have cell bodies located in the dorsal root ganglion projecting to the dorsal horn of the spinal cord. They follow the paths of the sympathetic (splanchnic) and parasympathetic (pelvic) efferents to the gut wall^[14]. All of the visceral afferents combined make no more than 7%-10% of all afferent inflow to the spinal cord^[12,14].

SURGICAL TRAUMA TO THE PERITONEUM

Comparative studies of cellular immunity after laparoscopic and conventional trans-peritoneal surgery have demonstrated immunologic advantages conferred by reducing the somatic abdominal wall wound by performing minimal access laparoscopy^[15]. In these animal models there appears to be a biological peritoneal advantage after laparoscopy when compared to open surgery. Authors have hence argued, that the peritoneal immune response after laparoscopic surgery is better preserved^[15]. This mechanism is uncertain but has been thought to arise from smaller peritoneal incisions minimizing peritoneal stress, reduced exposure of peritoneum to solubilized pathogens in air, and minimal manipulation and handling of the organs.

A large component of the intra-abdominal afferent system (40%-45% in the colon and bladder) are by fibres normally unresponsive to stimuli that become activated only in the presence of inflammation and injury^[16]. These “silent nociceptors” are different in that they are mainly concerned with tissue injury rather than mechanical stimuli such as stretch. One theory is that these class of nociceptors lead to abnormal autonomic regulations by insult which produces dramatic changes in the environment that surrounds the nerve endings with potential to excite distant nociceptors not affected by the initial insult^[17]. What is also concerning about intraperitoneal nociceptors is that as they are not normally active, discharge after inflammation and injury may be greater in magnitude and duration than the discharges produced by acute injurious stimuli, which potentially makes the central effects even greater than the initial insult^[18]. Transcoelomic spread of pro-inflammatory cytokines may activate areas of the peritoneum distant from the site on intraperitoneal injury. Thus downstream effects may persist for a long duration even after the initial injury is near or complete resolution.

The abdominal wall wound can be reduced significantly in size, by minimally access techniques, such as laparoscopy. When one considers procedures where the incision is the cause of the predominant metabolic insult to the patient, the benefits would appear to be obvious

and of a significant clinical magnitude. For example in cholecystectomy the metabolic response is thought to be from the abdominal wall wound itself^[19]. Therefore it can be postulated that this should translate into a lesser magnified sickness response and hence quicker recovery. The benefits of laparoscopic cholecystectomy are evident when compared to classic open colectomy^[20] but not as obvious when compared to the small or “mini” laparotomy version of the same operation^[21]. Therefore there may be a threshold size effect where further benefits are not seen.

However what is interesting is that in humans the peritoneal cytokine response is similar in laparoscopic and open colonic surgery^[22,23]. Also the systemic pro-inflammatory concentrations after both surgical approaches represent only a small fraction of what is generated from the peritoneum. This suggests that the two intra-abdominal approaches are locally equally traumatic to the peritoneal cavity^[22,24]. Thus it seems plausible that laparoscopic surgery does not confer an additional clinical advantage if we concentrate on peritoneal wound disruption. The intraperitoneal disruption is still the same no matter how access to the cavity is gained. A recent review on this topic in an optimized recovery setting has clinically confirmed that similar clinical outcomes can be reached between modalities^[25]. Hence what seems to be rather important in abdominal surgery is whether the peritoneum as an entity is entered, dissected, and manipulated. This is demonstrated in clinical studies of aorta aneurysm repair, with trans-peritoneal aneurysmal repair resulting in significantly higher inflammatory response corresponding to slower clinical recovery compared to the extra-peritoneal approach where this is possible^[26].

Operating on many organs such as colonic resection necessitates intraperitoneal injury and hence extra-peritoneal approach is not an option. In Part II of this series we will focus on possible new methods to manipulate the intraperitoneal wound in order to reach improved clinical endpoints.

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Intravenous glutamine for severe acute pancreatitis: A meta-analysis

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Abstract

AIM: To evaluate the efficacy of intravenous glutamine on the patients with severe acute pancreatitis (SAP).

METHODS: The Cochrane Library, PubMed, EMBASE, and EBM review databases were searched up to June 2012. Randomized controlled trials (RCTs) that compared non-glutamine nutrition with intravenous glutamine supplemented nutrition in patients with SAP were included. A method recommended by the Cochrane Collaboration was used to perform a meta-analysis of those RCTs.

RESULTS: Four RCTs involving a total of 190 participants were included. Analysis of these RCTs revealed the presence of statistical homogeneity among them. Results showed that glutamine dipeptide has a positive effect in reducing the mortality rate (OR = 0.26, 95%CI: 0.09-0.73, $P = 0.01$), length of hospital stay (weighted mean difference = -4.85, 95%CI: 6.67--3.03, $P < 0.001$), and the rate of complications (OR = 0.41, 95%CI: 0.22-0.78, $P = 0.006$). No serious adverse effects were found.

CONCLUSION: Current best evidence demonstrates that glutamine is effective for SAP. Further high quality trials are required and parameters of nutritional condition and hospital cost should be considered in future RCTs with sufficient size and rigorous design.

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Key words: Glutamine; Severe acute pancreatitis; Meta-analysis

Core tip: Glutamine dipeptide was given to patients with severe acute pancreatitis (SAP) in order to improve their nitrogen balance and immunonutrition. This meta-analysis aims to enhance our understanding of the clinical and economical validity of glutamine dipeptide for patients with SAP. We report the meta-analysis of four randomized controlled trials involving a total of 190 participants. Results showed that glutamine dipeptide has a positive effect in reducing the mortality rate, length of hospital stay, and the rate of complications. No serious adverse effects were found.

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INTRODUCTION

Acute pancreatitis is a common and sometimes fatal disease that places a significant financial burden on society^[1,2]. The mortality rate ranges from 10% to 15% in patients who are diagnosed with severe acute pancreatitis (SAP)^[1,3]. The use of enteral nutrition (EN) for SAP was associated with a significant reduction in infectious morbidity, mortality, hospital length of stay, and a trend toward reduced organ failure morbidity^[4]. However, the most common

complications of enteral feeding is diarrhea, which can be detected up to 20%-30% of patients. Thus, parenteral nutrition (PN) is still a choice for the patients suffering from the SAP initially.

Glutamine (Gln) is the most abundant free amino acid in the body and plays a vital role in amino acid transport and nitrogen balance. Gln is also a primary fuel for rapidly dividing cells such as enterocytes and lymphocytes, which protect mucosa barrier and enhance immune functions^[5]. The results of previous studies have shown that glutamine-enriched total PN (TPN) formulas improve the prognosis of acute pancreatitis^[6,7]. It was given to patients with SAP in order to improve their nitrogen balance and immunonutrition^[8-11]. Therefore, it is worth knowing whether routine supplementation of glutamine dipeptide is benefit for clinical outcomes. This meta-analysis aims to enhance our understanding of the clinical and economical validity of glutamine dipeptide for patients with SAP.

MATERIALS AND METHODS

Study selection criteria

The titles and abstracts of all citations identified by the literature search were reviewed. Selection criteria were then applied to all potentially relevant studies. The meta-analysis included clinical randomized controlled trials (RCTs) of patients with SAP. The trials compared standard isonitrogen PN (or EN) and PN (or EN) intravenously supplemented with glutamine dipeptide. Editorials and expert opinions, reviews without original data, case reports and studies lacking control groups were excluded.

Search strategy for identification of studies

Trials were identified by searching the Cochrane Library (Issue 1 2012), PubMed (June 2012), EMBASE (June 2012), and CBM (Chinese Biomedical Literature Database). The query was constructed by using the combination of the following keywords: (SAP or acute pancreatitis) and (glutamine or glutamine dipeptide). Articles published in any language were considered. Abstracts of the articles selected from each of these multiple searches were reviewed and those meeting the criteria were recorded. In the case of duplicate reports, or studies obviously reporting results from the same study population, only the latest published results were used.

Data collection

Data were extracted independently by two reviewers and decided by the research team. The quality of included studies was assessed independently by two authors and discrepancies were resolved by involving the third author. The quality of the studies was assessed using the scores proposed by Cochrane handbook 5 standards: randomization, allocation, concealment, blinding (participants, investigators, outcomes assessors, and data analysis), and completeness of follow-up. The following data were extracted: quantity and group dividing of patients, different doses

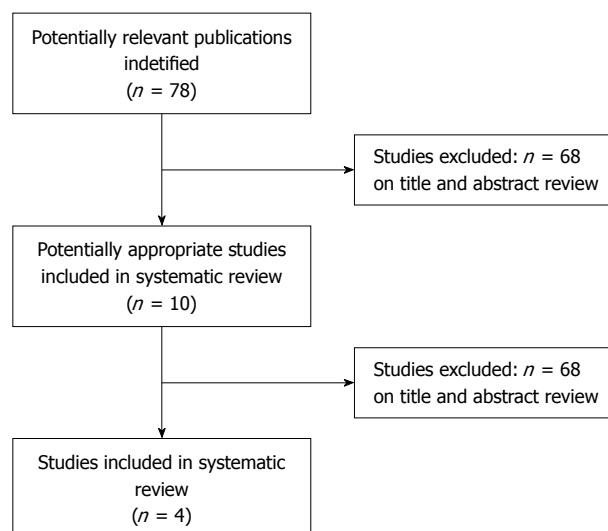


Figure 1 Flow diagram of the study selection process.

and days of glutamine dipeptide used, and the baseline of trials. Outcome variables included: mortality rate, length of hospital stay, and rate of complications.

Statistical analysis

The statistical analysis was performed by RevMan5.0 software, which was provided by the Cochrane Collaboration. P value < 0.05 was considered statistically significant. Heterogeneity was checked by the χ^2 test meta-analysis was done with fixed effects model when results of the trials had no heterogeneity. If the results had heterogeneity, random effects model was used and causes were analyzed. The result was expressed with an OR for the categorical variable and weighted mean difference (WMD) for the continuous variables, and with 95%CI.

RESULTS

Search results

There were 78 papers relevant to the searching words. Through the steps of screening the title, reading the abstract and the entire article, only four RCTs involving 190 patients were included (Figure 1). There were three papers published in English and one in Chinese. Data regarding characteristics of the studies, including patients, baseline characteristics and quality assessment of the studies are summarized in Table 1, respectively.

Mortality rate

Four RCTs (involving 190 patients) reported mortality rate. There was no heterogeneity ($P = 0.84$). Combined analysis indicated that the use of glutamine dipeptide reduced the mortality rate (OR = 0.26, 95%CI: 0.09-0.73, $P = 0.01$) (Figure 2A).

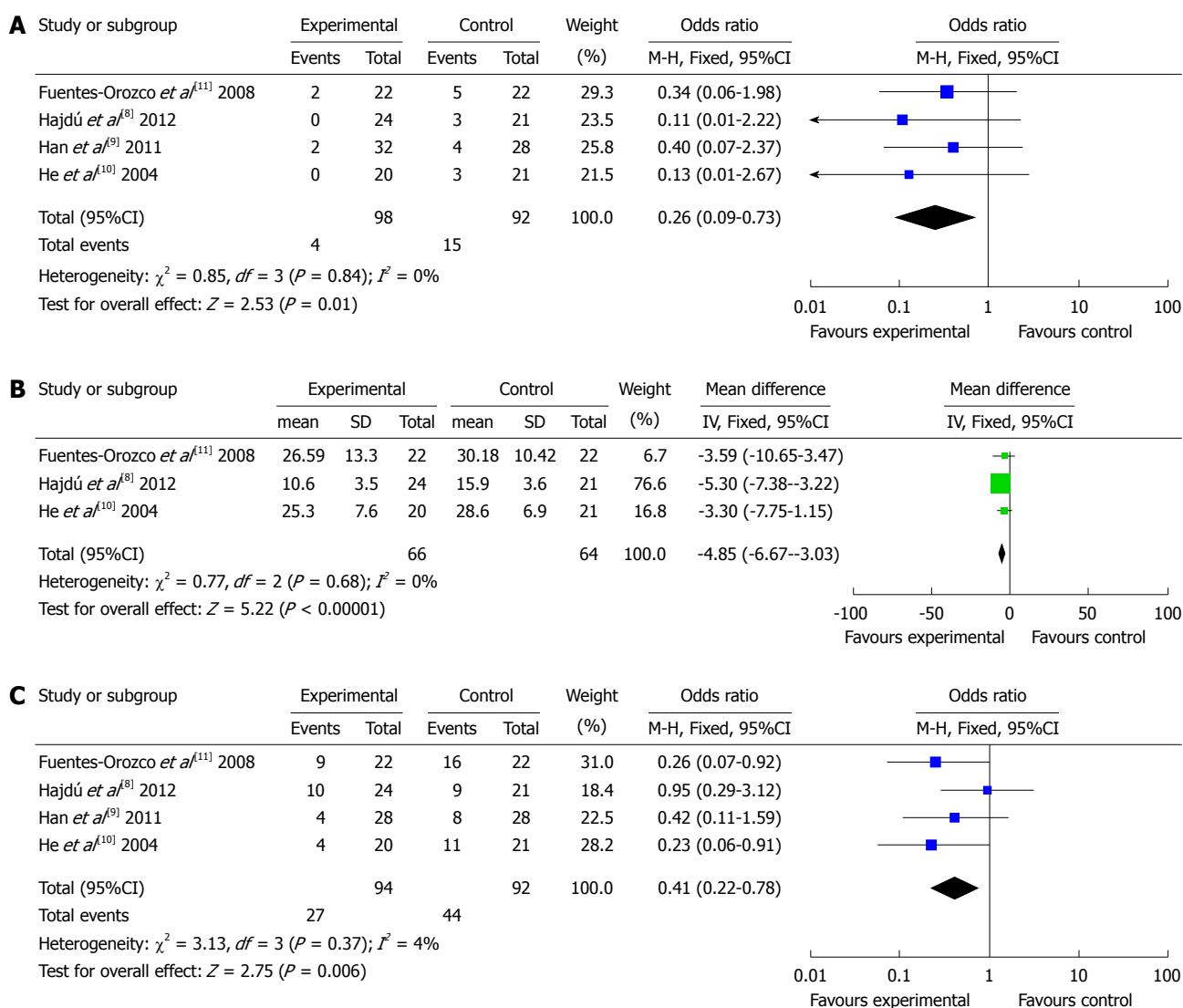
Length of hospital stay

Three RCTs (involving 130 patients) reported length of hospital stay. There was no heterogeneity ($P = 0.77$).

Table 1 Characteristics of the studies included in meta-analysis on glutamine dipeptide for severe acute pancreatitis

| Study | Hajdú <i>et al</i> ^[8] | Han <i>et al</i> ^[9] | He <i>et al</i> ^[10] | Fuentes-Orozco <i>et al</i> ^[11] |
|--------------------------------------|-----------------------------------|---------------------------------|---------------------------------|---|
| No. of patients included | 45 | 60 | 41 | 44 |
| Mean age | No significant difference | No significant difference | No significant difference | No significant difference |
| Male/female | No significant difference | No significant difference | No significant difference | No significant difference |
| Body mass index on admission | No significant difference | No significant difference | No significant difference | No significant difference |
| Plasma glutamine levels on admission | No significant difference | No significant difference | No significant difference | No significant difference |
| Patients (Gln/Con) | 24/21 | 32/28 | 20/21 | 22/22 |
| Gln dipeptide | 0.5 g/kg per day, intravenously | 20 g/d, intravenously | 0.4 g/kg per day, intravenously | 0.4 g/kg per day, intravenously |
| Days of Gln (d) administration | 7 | 7 | 14 | 10 |
| Randomization | Yes | Yes | Yes | Yes |
| Allocation concealment | Yes | Yes | Yes | Yes |
| Double blinding | Yes | Yes | Yes | Yes |
| ITT analysis | Yes | Yes | Yes | Yes |

Gln: Glutamine.

**Figure 2** Effect of glutamine dipeptide. A: On mortality for severe acute pancreatitis (SAP); B: On length of hospital stay for SAP; C: On rate of complications for SAP.

Combined analysis indicated that the use of glutamine dipeptide reduced the length of hospital stay (WMD = -4.85, 95%CI: -6.67--3.03, $P < 0.001$) (Figure 2B).

Rate of complications

Four RCTs (involving 190 patients) reported the rate of complications. There was no heterogeneity ($P = 0.37$).

Combined analysis indicated that the use of glutamine dipeptide reduced the rate of complications (OR = 0.41, 95%CI: 0.22-0.78, $P = 0.006$) (Figure 2C).

DISCUSSION

The current meta-analysis demonstrated that the use of glutamine dipeptide could improve the outcome better than standard PN or EN. The use of glutamine dipeptide reduced the mortality rate, length of hospital stay, and the rate of complications. The inclusion criteria of the four RCTs were similar. There was no significant heterogeneity between any of the groups. At the same time, no serious adverse effects were found in all the included studies.

Glutamine is used as a major fuel and nucleotide substrate for rapidly dividing cells such as intestinal mucosal cells and the gut-associated immunocytes^[12-14]. Glutamine can prevent atrophy of the intestinal epithelial cells through HSP 70 generation^[15] and improve the intestinal immune barrier^[16-18]. The deficiency of glutamine is the main cause for protein metabolism disorder, intestinal mucosal injury, enteral wall permeability destruction, bacterial translocation and immunosuppression. All these increase the secondary infection risk and hinder the recovery. A meta-analysis had revealed that glutamine could reduce the infectious morbidity and mortality in critical illness^[19]. Another meta-analysis suggested that glutamine dipeptide-supplemented PN was beneficial to postoperative patients by shortening the length of hospital stay and reducing the morbidity of postoperative infectious complications^[20].

In the early stage of SAP, the patients tend to be hypermetabolic due to occurrence of SIRS and subsequent multiple organ dysfunction syndromes, resulting in the greatly increased demand for nutrition^[21-23]. A study had revealed that plasma glutamine levels were negatively correlated with the severity of acute pancreatitis^[24]. The facts that EN is most likely superior to PN in preventing septic complications of acute pancreatitis, it may also eliminate some complications of PN (catheter sepsis, pneumothorax, and thrombosis), and costs less than TPN, make it an increasingly accepted treatment modality. According to the studies enrolled in our analysis, intravenously administered glutamine with TPN is beneficial in the prevention of infectious complications and reduce mortality rate^[9-11]. At the same time, the recent RCT revealed that intravenously administered glutamine was able to achieve the same effect with early EN as well^[8].

One of the disadvantages of this meta-analysis was that only four RCTs were included. All four studies had high methodological quality and generalizability, nonetheless, there may still have been bias in the final results. Besides, we didn't analyse the parameters of nutritional condition such as concentrations of serum albumin and body weights after the use of glutamine because there is only one RCT has the data. Therefore, more multicenter cooperative studies with prospective design are needed.

In conclusion, PN supplemented glutamine dipeptide with or without EN is effective and safe to reduce the

mortality rate, occurrence of complications, and length of hospital stay in patients with SAP. The encouraging outcomes in this analysis may demonstrate a notion in nutritional supplementation of the patients who are diagnosed with SAP. Further high quality trials are required. Parameters of nutritional condition and hospital cost should be considered in future RCTs with sufficient size and rigorous design.

COMMENTS

Background

Glutamine (Gln) is involved in a wide variety of metabolic and synthetic biochemical processes and acts as nitrogen and ammonium carrier to the liver and kidney. In conditions of excessive demand of Gln during episodes of severe diseases, endogenous Gln production may not be sufficient to meet the increased requirements.

Research frontiers

The results of previous studies have shown that glutamine-enriched total parenteral nutrition formulas improve the prognosis of acute pancreatitis, however, there is no previous meta-analysis confirm the clinical validity and safety of glutamine dipeptide for patients with severe acute pancreatitis (SAP).

Innovations and breakthroughs

Authors performed a meta-analysis of four randomized controlled trials that compared non-glutamine nutrition with intravenous glutamine supplemented nutrition in patients with SAP. Authors' results suggested that parenteral nutrition supplemented glutamine dipeptide with or without enteral nutrition is effective and safe in patients with SAP.

Applications

The encouraging outcomes may demonstrate a notion in nutritional supplementation of the patients who are diagnosed with SAP and provide a practical evidence for the use of Gln.

Terminology

Gln is the most abundant free amino acid in the body and plays a vital role in amino acid transport and nitrogen balance. Deficiency of glutamine increases the secondary infection risk and hinder the recovery. Acute pancreatitis is a common disease with a very varied outcome. Patients with SAP have worse outcomes than those with mild acute pancreatitis. The two major complications of SAP are organ failure and infection, which are both considered as two major reasons for death.

Peer review

This is a well written meta-analysis on the effect of intravenous glutamine in SAP. Mainly the authors systematically summarized and analyzed four randomized trial evidences regarding intravenous glutamine for SAP, and drew the conclusion that glutamine dipeptide has a positive effect in reducing the mortality rate, length of hospital stay, and the rate of complications. No serious adverse effects were found. Therefore the contribution of this meta-analysis is to provide a better knowledge of the benefits of glutamine infusion in SAP.

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- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

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- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean \pm SD or mean \pm SE.

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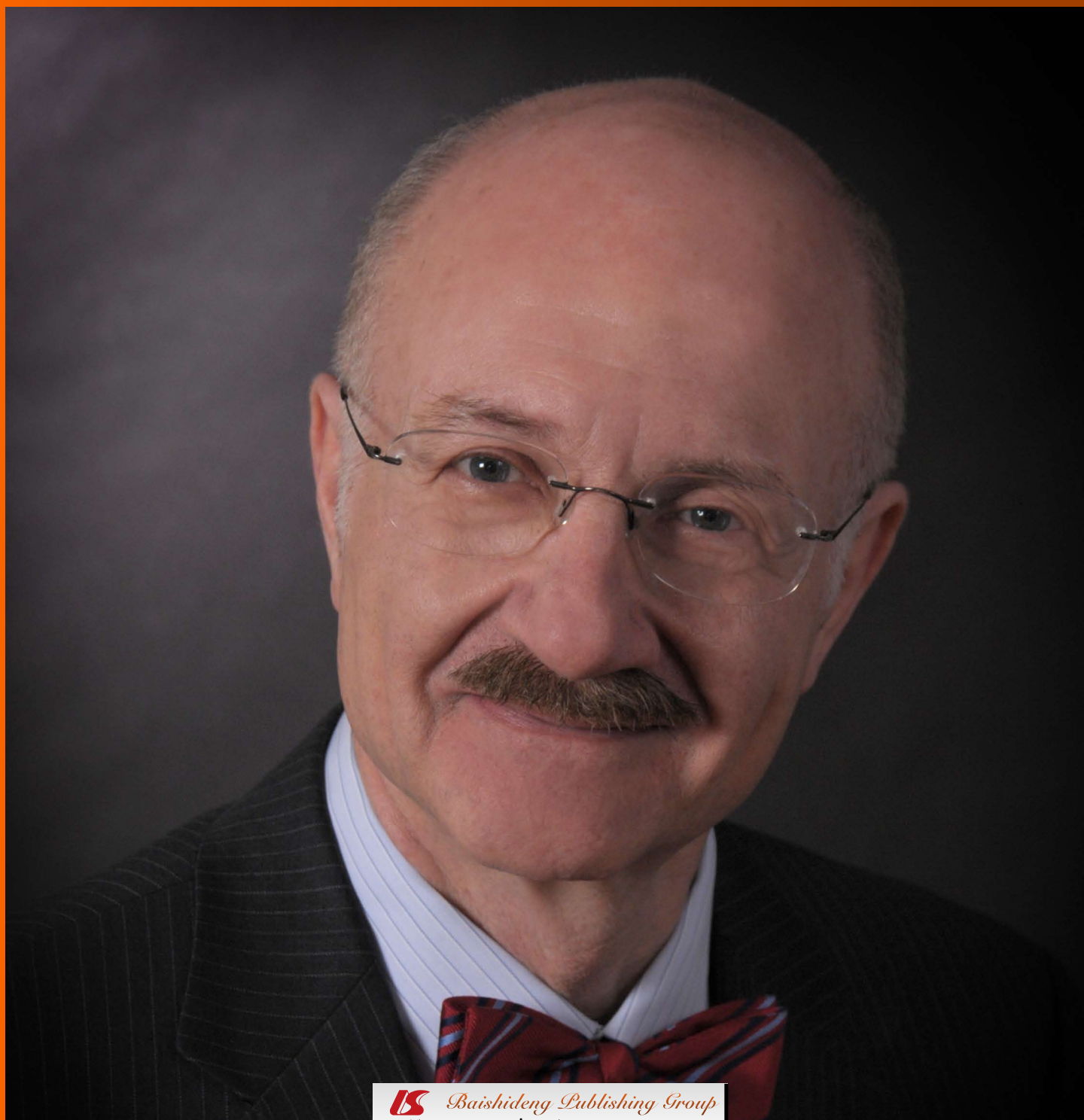
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Gaidukov KM, Raibuzhis EN, Hussain A, Teterin AY, Smetkin AA, Kuzkov VV, Malbrain MLNG, Kirov MY

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Effect of intra-abdominal pressure on respiratory function in patients undergoing ventral hernia repair

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Abstract

AIM: To determine the influence of intra-abdominal pressure (IAP) on respiratory function after surgical repair of ventral hernia and to compare two different methods of IAP measurement during the perioperative period.

METHODS: Thirty adult patients after elective repair of ventral hernia were enrolled into this prospective study.

IAP monitoring was performed *via* both a balloon-tipped nasogastric probe [intra-gastric pressure (IGP), CiMON, Pulsion Medical Systems, Munich, Germany] and a urinary catheter [intrabla-der pressure (IBP), UnoMeterAbdo-Pressure Kit, UnoMedical, Denmark] on five consecutive stages: (1) after tracheal intubation (AI); (2) after ventral hernia repair; (3) at the end of surgery; (4) during spontaneous breathing trial through the endotracheal tube; and (5) at 1 h after tracheal extubation. The patients were in the complete supine position during all study stages.

RESULTS: The IAP (measured via both techniques) increased on average by 12% during surgery compared to AI ($P < 0.02$) and by 43% during spontaneous breathing through the endotracheal tube ($P < 0.01$). In parallel, the gradient between PaCO_2 and EtCO_2 [P(a-et)CO_2] rose significantly, reaching a maximum during the spontaneous breathing trial. The $\text{PaO}_2/\text{FiO}_2$ decreased by 30% one hour after tracheal extubation ($P = 0.02$). The dynamic compliance of respiratory system reduced intraoperatively by 15%-20% ($P < 0.025$). At all stages, we observed a significant correlation between IGP and IBP ($r = 0.65-0.81$, $P < 0.01$) with a mean bias varying from -0.19 mmHg (2SD 7.25 mmHg) to -1.06 mmHg (2SD 8.04 mmHg) depending on the study stage. Taking all paired measurements together ($n = 133$), the median IGP was 8.0 (5.5-11.0) mmHg and the median IBP was 8.8 (5.8-13.1) mmHg. The overall r^2 value ($n = 30$) was 0.76 ($P < 0.0001$). Bland and Altman analysis showed an overall bias for the mean values per patient of 0.6 mmHg (2SD 4.2 mmHg) with percentage error of 45.6%. Looking at changes in IAP between the different study stages, we found an excellent concordance coefficient of 94.9% comparing ΔIBP and ΔIGP ($n = 117$).

CONCLUSION: During ventral hernia repair, the IAP rise is accompanied by changes in P(a-et)CO_2 and $\text{PaO}_2/\text{FiO}_2$ -ratio. Estimation of IAP *via* IGP or IBP dem-

onstrated excellent concordance.

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Key words: Intra-abdominal pressure; Gastric pressure; Bladder pressure; Intra-abdominal hypertension; Hernia; Oxygenation; Respiratory function

Core tip: The surgical repair of ventral hernia is accompanied by a rise of intra-abdominal pressure, a deterioration of CO₂ elimination and a decrease in arterial oxygenation. The measurements of intra-abdominal pressure using nasogastric tube and urinary catheter demonstrate a close agreement between both methods; thus, both these methods can be used in clinical practice.

Gaidukov KM, Raibuzhis EN, Hussain A, Teterin AY, Smetkin AA, Kuzkov VV, Malbrain MLNG, Kirov MY. Effect of intra-abdominal pressure on respiratory function in patients undergoing ventral hernia repair. *World J Crit Care Med* 2013; 2(2): 9-16 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v2/i2/9.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v2.i2.9>

INTRODUCTION

Abdominal wall reconstruction during ventral hernia repair can be associated with perioperative intra-abdominal hypertension (IAH), respiratory dysfunction and complications^[1-3].

The relationship between intra-abdominal pressure (IAP) and respiratory function was demonstrated for the first time in 1863^[3]. Today the negative effects of IAH on respiratory system have been investigated in a large number of studies^[2,4]. Development of IAH decreases chest wall compliance and functional residual capacity, shifts the end-expiratory position of the diaphragm, and leads to development of atelectases. Thus, it may affect blood oxygenation and carbon dioxide elimination^[2,5]. The abdominal compartment syndrome (ACS) is defined as a sustained increase in IAP exceeding 20 mmHg with the presence of new organ dysfunctions that is associated with significant morbidity and mortality^[6-8]. Therefore, in patients with risk factors for IAH it is necessary to measure IAP with simultaneous evaluation of respiratory function^[1,9-13].

There are direct and indirect methods for the measurement of IAP^[14]. The direct technique involves estimation of IAP through the placement of intraperitoneal catheter. This method however is invasive and thus not applicable in most clinical situations^[15]. Many simple and less invasive indirect methods are most often used in routine clinical practice for IAP estimation. These methods include measurement of pressure in hollow organs of the abdomen or pelvis cavity such as bladder, stomach, intestine, and uterus^[9,14,16,17]. Among them, the intrablad-

der technique using Foley catheter has been forwarded as the “gold” standard for IAP estimation in the consensus definitions report of the World Society on Abdominal Compartment Syndrome (WSACS, www.wsacs.org)^[6,7]. Another indirect technique is the measurement of IAP *via* nasogastric probe^[16,18-21].

The increase of the gradient between PaCO₂ and EtCO₂ [P(a-et)CO₂] can reflect changes in respiratory function. Moreover, the P(a-et)CO₂ value demonstrates an association with dead space volume and severity of pulmonary ventilation-perfusion mismatch due to IAH^[5,22]. In 1984, Murray *et al*^[23] suggested that P(a-et)CO₂ might be a more sensitive indicator in the search of the optimal positive end-expiratory pressure (PEEP) than changes in lung shunt or PaO₂. Later, it has been shown that monitoring of dead space and P(a-et)CO₂ was useful for detecting lung collapse^[24]. In a porcine model of IAH, it has been demonstrated that assessment of P(a-et)CO₂ might help to evaluate the severity of atelectasis during laparoscopic surgery; however these findings still need to be validated in different clinical settings^[5].

Today, there are a number of concerns regarding indirect evaluation of IAP. The intrabladder pressure measurements can be unreliable in case of low intrinsic bladder compliance (as in patients with chronic renal failure and anuria), and bladder trauma^[9,14,17,25]. The intragastric estimation of IAP can be incorrect during intestinal obstruction with large volume gastric aspirate and partial or total gastric resection^[26]. Therefore, these methods need validation in selected categories of patients at risk for IAH.

Thus, the goals of our study were to determine the influence of IAP on respiratory function after surgical repair of ventral hernia and to compare two different methods of IAP measurement during the perioperative period.

MATERIALS AND METHODS

The study was approved by the Medical Ethics Committee of Northern State Medical University, Arkhangelsk, Russian Federation. Written informed consent was obtained from every patient or next of kin.

This prospective study was performed in a 900-bed university hospital (City Hospital#1 of Arkhangelsk). From June 2011 to March 2012, we enrolled 30 adult (age > 18 years) patients (10 males and 20 females) after elective incisional ventral hernia repair, using an open technique. The patients were excluded from the study if they were above 75 years of age, were pregnant or required simultaneous operation, other than ventral hernia repair, or participated in other clinical investigations. Before the procedure all patients received standard premedication with diazepam and omeprazole according to a standard protocol.

All patients received monitoring of IAP *via* both intragastric pressure (IGP) with a balloon-tipped nasogastric probe (CIMON, Pulsion Medical Systems, Germany) and intrabladder pressure (IBP) with a urinary catheter system

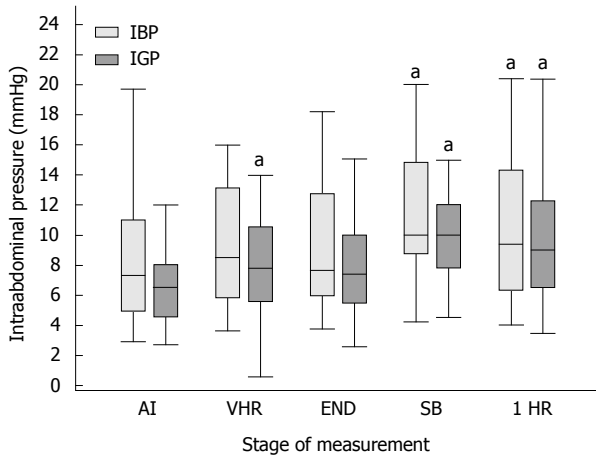


Figure 1 Changes in intra-abdominal pressure in ventral hernia repair: both methods of measurement are presented. ^a $P < 0.05$ vs after tracheal intubation (AI) values using Wilcoxon's signed-rank test with Bonferroni correction. Box plots present median, interquartile interval, and minimum–maximum. VHR: After ventral hernia repair; END: End of surgery; SB: During spontaneous breathing through the endotracheal tube; 1 HR: One hour after extubation; IBP: Intrablauder pressure; IGP: Intra gastric pressure.

(UnoMeterAbdo-Pressure Kit, UnoMedical, Denmark). The abdominal perfusion pressure (APP) was calculated by subtracting the IAP from mean arterial pressure for each method of IAP estimation. The measurements also included arterial blood gases (ABL 550, Radiometer, Denmark) and end-tidal CO_2 (Et CO_2 , Oridion MicroCap, Israel). The combined anesthesia consisted of total intravenous anesthesia (propofol 4–8 mg/kg per hour, fentanyl 0.05–0.1 mg/kg per hour, atracurium 0.2–0.6 mg/kg per hour) and epidural anesthesia at Th 8–10 level (ropivacaine 0.4–0.6 mg/kg). Mechanical ventilation was performed in a pressure-controlled mode (Fabius GS, Dräger, Germany) with FiO_2 0.5, tidal volume 7–8 mL/kg, PEEP 5 cm H_2O and respiratory rate of 12–14/min. After surgery, the level of FiO_2 during data collection was 0.21. The measurements were done during the five consecutive stages: (1) after tracheal intubation (AI); (2) after ventral hernia repair; (3) at the end of surgery; (4) during a spontaneous breathing trial *via* the endotracheal tube; and (5) one hour after tracheal extubation.

Statistical analysis

The SPSS 16.0 software package was used for statistical analysis. We have used non-parametric tests because of small number of observations and non-normal data distribution. Data are presented as a median (25th–75th percentiles). Intragroup comparisons were performed using Wilcoxon signed-rank test. A P -value < 0.05 was considered as significant. For multiple comparisons, we used Bonferroni correction. The Spearman correlation coefficient (ρ) and Bland-Altman analysis were used to determine the agreement between the two techniques of IAP measurement and to calculate the percentage error. We compared the mean values with SD per patient ($n = 30$) and computed the Pearson correlation coefficient. Two methods may

be used interchangeably if r^2 (Pearson correlation coefficient) is > 0.6 , if the differences between bias and limits of agreement (1.96 SD) are not clinically important and if the percentage error is less than 35%. Finally, the ability of IGP to track changes or trends in IBP was assessed by plotting ΔIBP against ΔIGP during the same time interval (four quadrants trend plot). The concordance coefficient is calculated as the percentage of pairs with the same direction of change. Based on clinical relevance, the concordance should be $> 90\%$ when pairs with both a ΔIBP and $\Delta\text{IGP} \leq \pm 2.5$ mmHg are excluded for analysis.

RESULTS

The median age was 61 (53–69) years, weight 89 (73–103) kg, and body mass index (BMI) 31 (29–36) kg/m^2 , respectively. The median size of incisional hernia was 244 (170–415) cm^2 . The fluid balance for the first day after operation was 1700 (1325–2000) mL. According to both techniques of measurement, during surgery IAP increased on average by 12% from AI ($P = 0.013$ and $P = 0.002$ for IBP and IGP, respectively; Figure 1). The maximal increase of IAP by 43% was observed during spontaneous breathing through the endotracheal tube: up to 10 (9–15) mmHg for IBP and 10 (8–12) mmHg for IGP ($P = 0.001$). At the end of the investigation, IAP still exceeded the AI values ($P = 0.003$ and $P = 0.006$ for IBP and IGP, respectively). The abdominal perfusion pressure (APP), blood gases (Pa CO_2 and Et CO_2) and arterial lactate concentrations are presented in Table 1. The values of APP rose significantly after transfer to spontaneous breathing ($P < 0.001$ for both IBP and IGP) in parallel with the increase in Pa CO_2 and Et CO_2 ($P < 0.013$). The gradient between Pa CO_2 and Et CO_2 also rose significantly reaching a peak during spontaneous breathing trial ($P = 0.02$) (Figure 2A). The mean arterial lactate concentration did not change significantly and did not exceed 1 mmol/L throughout the study.

The oxygenation index (Pa O_2/FiO_2) was decreased by 30% one hour after tracheal extubation ($P = 0.02$ vs AI; Figure 2B). These changes were delayed as compared to the increase of IAP and P(a-et) CO_2 .

Tidal volume during the study did not change significantly (not shown). However, the dynamic compliance of the respiratory system decreased with 15%–20% both after hernia repair and at the end of surgery ($P < 0.025$; Table 1).

At all stages, we found a significant correlation between the two methods of IAP measurement ($r = 0.65$ – 0.81 , $P < 0.01$). The mean bias between gastric and urinary methods of IAP monitoring varied during the study from -0.19 mmHg (2SD 7.25 mmHg) to -1.06 mmHg (2SD 8.04 mmHg) (Table 2). Taking all paired measurements together ($n = 133$), the median IGP was 8.0 (5.5–11.0) mmHg and the median IBP was 8.8 (5.8–13.1) mmHg. In total, 4 outliers, related to measurement error, or abdominal muscle contraction or migrating motor complex activity (2 paired measurements each in 2

Table 1 Changes in abdominal perfusion pressure, blood gases, arterial lactate and dynamic compliance during different study stages

| Study stage | AI | VHR | END | SB | 1 HR |
|---|---------------|-------------------------|-------------------------|-------------------------|-------------------------|
| APP = MAP - IBP | 75 (63-82) | 74 (66-85) | 82 (68-96) | 92 (77-98) ^a | 85 (77-96) ^a |
| APP = MAP - IGP | 74 (65-82) | 78 (67-85) | 74 (65-82) | 90 (78-97) ^a | 85 (77-96) ^a |
| PaCO ₂ (mmHg) | 36 (34-39) | 36 (33-42) | 37 (34-42) | 40 (38-49) ^a | 37 (35-40) |
| EtCO ₂ (mmHg) | 32 (29-35) | 30 (27-35) | 33 (28-36) | 36 (31-39) ^a | 33 (30-35) |
| Arterial lactate (mmol/L) | 0.9 (0.7-1.0) | 0.7 (0.6-0.8) | 0.8 (0.7-1.0) | 1.0 (0.7-1.4) | 0.9 (0.8-1.4) |
| Dynamic compliance (mL/cm H ₂ O) | 32 (26-38) | 27 (22-32) ^a | 26 (22-30) ^a | | |

Data are presented as median and interquartile interval. ^a $P < 0.05$ vs AI values using Wilcoxon's signed-rank test with Bonferroni correction. AI: After intubation; VHR: After ventral hernia repair; END: End of surgery; SB: During spontaneous breathing through the endotracheal tube; 1 HR: One hour after extubation; APP: Abdominal perfusion pressure; MAP: Mean arterial pressure; IBP: Intrablauder pressure, IGP: Intra gastric pressure; PaCO₂: Partial pressure of carbon dioxide in arterial blood; EtCO₂: End-tidal partial pressure of carbon dioxide.

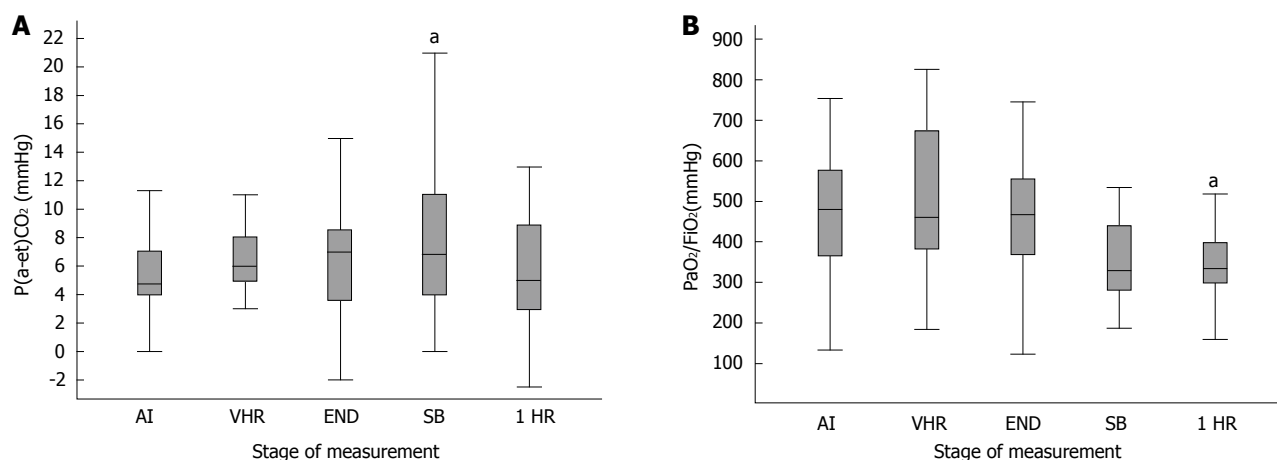


Figure 2 Changes in arterial to end-tidal CO₂ gradient (A) and oxygenation index (PaO₂/FiO₂) (B) during and after ventral hernia repair. ^a $P < 0.05$ vs after tracheal intubation (AI), Wilcoxon's signed-rank test. Box plots present median, interquartile interval, and minimum-maximum. VHR: After ventral hernia repair; END: End of surgery; SB: During spontaneous breathing through the endotracheal tube; 1 HR: One hour after extubation.

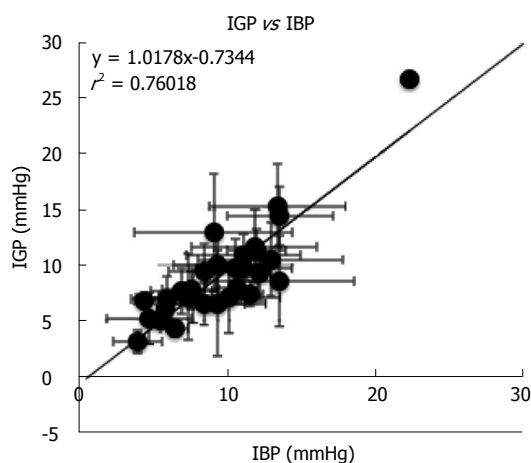


Figure 3 Regression analysis of intrablauder and intra gastric pressure. Patient averages ($n = 30$) with mean \pm SD deviation of intrablauder pressure (IBP) and intra gastric pressure (IGP).

patients) were excluded from further analysis. Pearson correlation coefficient comparing mean IBP and IGP values ($n = 30$) showed a r^2 of 0.76 ($P < 0.0001$). Figure 3 demonstrates the regression analysis between mean IBP

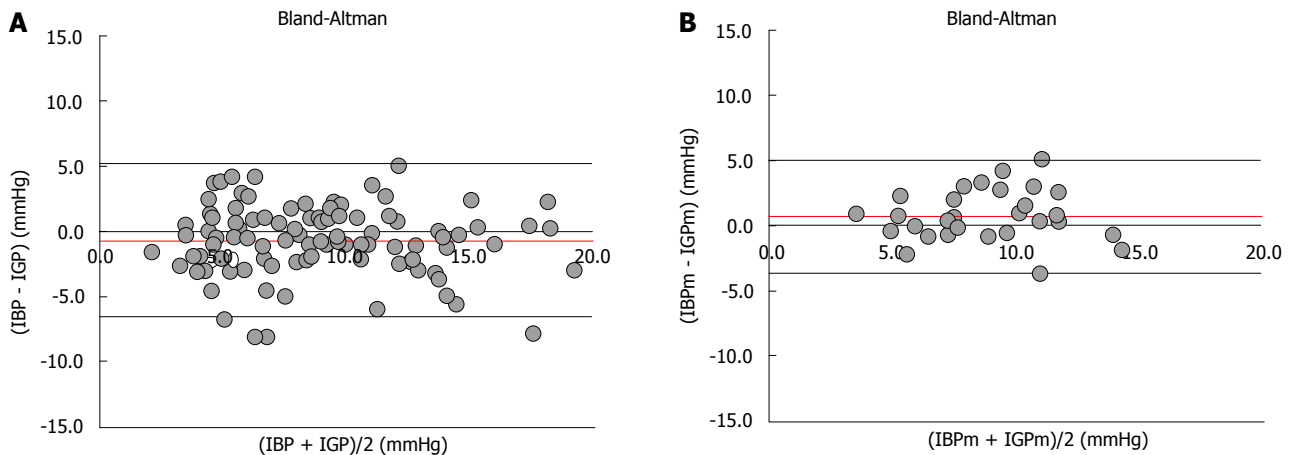
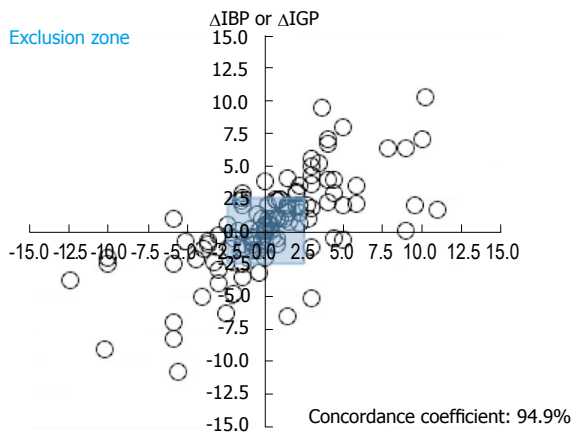
and IGP values per patient. Bland-Altman analysis of all paired measurements ($n = 128$) showed an overall bias of -0.7 ± 2.9 mm Hg (with limits of agreement from -6.6 to 5.2 mmHg) with percentage error of 65.5% (Figure 4 A). When analyzing the mean values per patient ($n = 30$), we found an overall bias of 0.6 ± 2.1 mm Hg (with limits of agreement from -3.7 to 4.8 mm Hg) with percentage error of 45.6% (Figure 4B). Concordance correlation coefficients of the IAP measurements during the study are shown in Table 3. The precision and accuracy of IAP measurements during study stages varied within 0.63-0.85 and 0.95-0.98, respectively. The four quadrants trend plot is shown in Figure 5. From the 117 initial paired measurements, 55 pairs were excluded because either Δ IBP or Δ IGP were $\leq \pm 2.5$ mmHg or because Δ IBP or Δ IGP were equal to zero. The calculated level of concordance was 94.9%.

DISCUSSION

This study demonstrates that the increase in IAP during surgical repair of ventral hernia and the early postoperative period is accompanied by deterioration of CO₂ elimination followed by a decrease in arterial oxygenation. These

Table 2 Agreement between the two techniques of intra-abdominal pressure measurement

| | Number of patients | Mean intra-abdominal pressure | Correlation analysis | | Bland-Altman analysis | |
|---|--------------------|-------------------------------|----------------------|----------|-----------------------|-----------|
| | | | <i>r</i> | <i>P</i> | bias | Precision |
| After tracheal intubation | 29 | 7.83 | 0.65 | 0.002 | -1.06 | 4 |
| After ventral hernia repair | 28 | 9.22 | 0.73 | 0.001 | -0.57 | 2.8 |
| At the end of surgery | 26 | 8.91 | 0.75 | 0.001 | -0.46 | 4.1 |
| During spontaneous breathing through the end of tracheal tube (spontaneous breathing trial) | 23 | 11.48 | 0.75 | 0.002 | -0.19 | 3.6 |
| At 1 h after tracheal extubation | 27 | 9.7 | 0.81 | 0.001 | -1.00 | 3.3 |

**Figure 4** Bland-Altman analysis of all paired measurements ($n = 128$, A) and of paired measurements of mean intrablaider pressure and mean intragastric pressure ($n = 30$, B). IBP: Intrablaider pressure; IGP: Intragastric pressure; IBPm: Mean intrablaider pressure; IGPm: Mean Intragastric pressure.**Figure 5** Four quadrants trend plot. Plot for 117 paired measurements of Δ IBP and Δ IGP. From the 117 initial paired measurements, 55 pairs were excluded because either Δ IBP or Δ IGP were $\leq \pm 2.5$ mmHg or because Δ IBP or Δ IGP was equal to zero (exclusion zone). The calculated level of concordance was 94.9%. See text for explanation. IBP: Intrablaider pressure; IGP: Intragastric pressure.

changes reflect the impairment of respiratory function after the procedure and could guide possible interventions.

The rise in IAP during abdominal surgery observed in our study can be explained by the stretch of abdominal wall following hernia repair^[3,26]. The peak of IAP increase was observed during spontaneous breathing after reversal of the effects of muscle relaxants and seda-

tive agents^[11,26,27]. Despite the rise in IAP, APP remained above 60 mmHg during all study stages, and this was accompanied by normal arterial lactate concentrations, reflecting adequate organ perfusion^[9,28]. Previous studies considered an APP < 60 mmHg to be the indicator of abdominal hypoperfusion, moreover, APP has been shown to correlate well with survival from IAH and ACS^[29,30].

The increase in IAP during and after repair of ventral hernia together with effects caused by general anesthesia can lead to deterioration of respiratory function. Thus, the rise in PaCO₂, EtCO₂ and P(a-et)CO₂ in parallel with reduction in respiratory compliance in our study may be caused by atelectasis formation in the basal lung areas, although we did not perform radiological imaging. The increase of the CO₂ gradient can occur when mixed venous blood passes the pulmonary circulation through shunt vessels without delivering CO₂ to alveolar air that is typical for atelectasis. Moreover, when ventilated lung areas are compromised by the cranial displacement of the diaphragm caused by IAH, a shift of ventilation can be anticipated so that regions ventilated normally before the insult are becoming over-ventilated in relation to their perfusion^[5].

In addition, increased P(a-et)CO₂ can result from a decrease of cardiac output. The linear relationship between changes in EtCO₂ and cardiac output observed in animals has supported the necessity of clinical studies

Table 3 Concordance between the two intra-abdominal pressure measurements during different study stages

| | All measurements | AI | VHR | END | SB | 1 HR |
|-------------------------------------|------------------|-----------|-----------|-----------|-----------|-----------|
| Number of measurements | 133 | 29 | 28 | 26 | 23 | 27 |
| Concordance correlation coefficient | 0.74 | 0.61 | 0.84 | 0.62 | 0.81 | 0.69 |
| 95%CI | 0.65-0.80 | 0.33-0.79 | 0.69-0.92 | 0.34-0.80 | 0.63-0.90 | 0.45-0.84 |
| Precision | 0.75 | 0.63 | 0.85 | 0.65 | 0.84 | 0.73 |
| Accuracy | 0.98 | 0.96 | 0.98 | 0.95 | 0.96 | 0.95 |

Precision: Pearson's correlation coefficient; Accuracy: bias correction factor; AI: After intubation; VHR: After ventral hernia repair; END: End of surgery; SB: During spontaneous breathing through the endotracheal tube; 1 HR: One hour after extubation.

to determine whether a change in EtCO₂ would be useful as a noninvasive, continuous indicator of a change in cardiac output during anesthesia or intensive care^[31]. In line with this hypothesis, McSwan *et al*^[32] have shown that the P(a-et)CO₂ gradient increased in parallel with a rise in physiologic dead space (V_d). It is known that poor pulmonary perfusion from low cardiac output or hypotension can elevate V_d fraction^[33] due to peripheral carbon dioxide production, which increases P(a-et)CO₂ in case of a persistent decreased blood flow^[34].

In spite of decreased cardiac output as one of the reasons for the rise in P(a-et)CO₂, we suggest that the pivotal role in this process belongs to atelectasis formation. This speculation is confirmed by the delayed deterioration of arterial oxygenation in relation to the increase of IAP and P(a-et)CO₂. Similar findings were obtained by Strang *et al*^[5]. During atelectasis formation, even a transient increase in PaO₂ might occur, due to a decreased intrapulmonary shunt (Q_s/Q_t). Consequently, oxygenation may not adequately reflect the severity of lung collapse during IAH^[5], and hypoxemia usually develops later than changes in CO₂. The decrease in PaO₂/FiO₂ and atelectasis after the hernia repair may also be related to discontinuation of PEEP following extubation. Thus, Pelosi *et al*^[2] recommended the application of PEEP to prevent atelectasis formation related to IAP in morbidly obese patients during general anaesthesia.

The difference between gastric and urinary methods of IAP estimation observed in our study may be caused by the physical characteristics of the wall of bladder. This wall is not merely a membrane that transfers pressure from the intra-abdominal space to the bladder content^[14,16,17]. Bladder wall compliance differs between patients and depends on several factors such as age, presence of chronic renal failure, BMI, filling status, fluid balance and bladder perfusion/ischemia. Moreover, several patients in our study had peritoneal adhesions, which might limit the transduction of abdominal pressure during measurement. Thus, IAP measured at one point cannot always be considered to be the pressure in the whole abdominal cavity^[16, 25,35]. Body anthropomorphic data may also have an impact on IAP measured at different sites^[36,37]. We found that the measurement of IAP through the nasogastric probe correlates well with the results of the intrabladder measurement with mean difference between methods around -0.7 mmHg (with IGP being consistently lower than IBP). However, the mean percentage error of

all measurements of IAP was 45.6%, thus in ventral hernia repair, both methods for the estimation of IAP can be used interchangeably keeping in mind the possibility of large data variations and the limitations of monitoring techniques. Moreover, both methods were able to keep track of changes in IAP during the different study stages as demonstrated by the concordance coefficient above 90%. In addition, Malbrain *et al*^[16] concluded that in some patients, IAP estimation *via* nasogastric probe and IAP estimation *via* urinary catheter may differ significantly and this may have clinical implications. This situation can occur due to localized ACS, thus clinicians should be aware of this possibility. In order to identify risk factors and to recommend treatment for localized ACS, further studies of simultaneous intragastric and intrabladder IAP measurements are needed. In conclusion, this study fulfilled the minimal requirements for IAP measurement and validation studies as suggested by the "Recommendations for research by the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome"^[38]. More than 20 relevant patients were included with a broad range of IAP from normal to high. At least 50% of the measurements demonstrated IAP ≥ 12 mmHg and at least some measurements an IAP > 20 mmHg (5%). When looking at the mean values per patient, the bias was ≤ 1 mmHg with a precision close to 2 mmHg, good accuracy, reasonable limits of agreement and excellent concordance.

The surgical repair of ventral hernia is accompanied by a rise IAP and a parallel increase of PaCO₂, EtCO₂, and arterial to end-tidal gradient of CO₂, followed by a decrease in arterial oxygenation. The measurements of IAP using nasogastric tube and urinary catheter demonstrate a close agreement between both methods with excellent concordance, although the percentage error was quite high suggesting that the abdomen may not always act like a fluid filled compartment. Thus, both these methods can be used in clinical practice.

COMMENTS

Background

Abdominal wall reconstruction during ventral hernia repair can be associated with perioperative intra-abdominal hypertension (IAH), respiratory dysfunction and complications.

Research frontiers

The methods for measuring intra-abdominal pressure (IAP) are integrating in

clinical practice but need validation in selected categories of patients at risk for IAH, including ventral hernia surgery.

Innovations and breakthroughs

The measurement of IAP through the nasogastric probe during hernia repair and postoperative period correlates well with the results of the intra-bladder measurement.

Applications

The study findings reflect the impairment of respiratory function after the surgery for ventral hernia that requires possible interventions, including measurement of IAP and correction of IAH.

Terminology

Intra-abdominal pressure: pressure in hollow organs of the abdomen or pelvis cavity such as bladder, stomach, intestine, and uterus. Intra-abdominal hypertension: intra-abdominal pressure exceeding 12 mmHg.

Peer review

The paper determined the influence of IAP on respiratory function after surgical repair of ventral hernia and compared two different methods of IAP measurement during the perioperative period. It's very well done study.

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Drawing the Yongquan protocol into the different stages of the cardiopulmonary resuscitation sequence

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Abstract

AIM: To introduce new applications into the ILCOR-cardiopulmonary resuscitation (CPR) "chain" sequence.

METHODS: Stages of the CPR sequence ("chain"): prior to the application of chest massage: assess the victim's state of consciousness and lung-heart failure; seek help (call 911), or in situations in which it is impossible to start the ILCOR protocol: (1) if the victim is trapped in car crash, overturned car, landslide, massive number of victims or catastrophe; or (2) delayed CPR. During chest compression: Yongquan is simultaneously stimulated by a third rescuer. During defibrillator application: activate K-1 Yongquan through needles before defibrillation. Unsuccessful CPR: "gold standard" for legal clinical death.

RESULTS: Implies comparing two hypotheses: Ho

(null hypothesis) demonstrates no association between the two variables studied; Ha (alternative hypothesis) implies some degree of relation between them. Difference between the two treatments is observed. If it is greater than the standard error multiplied by a coefficient of security, the difference is significant: Ha will be accepted and Ho rejected. First we will compare CPR without defibrillator (method "A") and K-1 Yongquan method (method "B"), using percentages of representative samples (treatment "A": 6.4% response, treatment "B": 85% response). If $|PA - PB|$ is greater than the product of 1.96 times the standard error, the difference is significant. Because $|PA - PB| = 0.786$ is greater than 0.098, the difference between 0.064 and 0.85 is statistically significant. Thus, we reject Ho and accept Ha as correct. Thus, it is improbable that chance was responsible for this association. This analysis shows that K-1 Yongquan method has a "quality guarantee". Second, we compare defibrillators ("A") with K-1 Yongquan method ("B") (treatment "A": 48%, treatment "B": 84%, $|PA - PB| = 0.36$; $|PA - PB| = 0.36$ is greater than $SE \times 1.96 = 0.0148$ and also statistically significant, demonstrating again the comparative value of the Yongquan method.

CONCLUSION: The Yongquan resuscitation manoeuvre is a non-invasive, non-tiring, costless, and easy-to-apply procedure that provides a second chance when other options fail.

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Key words: Yongquan; K-1 acupuncture point; Resuscitation manoeuvre; ILCOR protocol inclusion; Complementary life support

Core tip: As a result of 25 years of experience on the application of the "Lazarus Effect" in Acupuncture, a formalized protocol project is shown and submitted in order to integrate this maneuver into the cardiopulmo-

nary resuscitation (CPR) sequence. The K-1 maneuver is neither intended to replace nor to interrupt the CPR international protocol, but to provide an alternative way of upgrading heart stoppage mortality when the ILCOR-CPR protocol has failed.

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INTRODUCTION

After 25 years of research into the K-1 Yongquan resuscitation manoeuvre, called the “Lazarus phenomenon”, the main reasons for standardising this antidote point in situations in which cardiopulmonary resuscitation (CPR) is expected to be applied are introduced^[1-8].

Evidenced-based analysis of both basic and advanced CPR failure reveals that K-1 Yongquan resuscitation manoeuvre should be formally included in the different stages of the CPR sequence protocol.

MATERIALS AND METHODS

Material

Since 1987, 58 patients have been treated with the K-1 Yongquan manoeuvre after basic and advanced CPR failure^[3,4,9,10].

Thereafter, the classic action chain sequence for CPR changed, especially after the last H1N1 pandemic in 2009. It would not seem strange that a real fear of contagion may have influenced the public to reject the practice of mouth-to-mouth resuscitation. The change of the ILCOR-2010 sequence of application of life support manoeuvres, giving priority to thoracic compression over support for ventilation, does not appear to be due to chance.

Thus, the application method of the K-1 Yongquan point has been compared statistically with known conventional systems of resuscitation and then integrated with the ILCOR-2010 sequence to plan a contingency procedure before the possible failure of basic and advanced CPR.

Stages of the CPR sequence (“chain”)

Prior to application of chest massage: Assess the victim’s state of consciousness and lung-heart failure.

Seek help (call 911): there are many situations in which it is impossible to start ILCOR protocol, such as the following: the victim is trapped in a car crash, an overturned car, a landslide, a catastrophe with a massive number of victims; CPR is delayed for any reason.

During the application of chest compression: Yongquan could be simultaneously stimulated by a third rescuer, improving the CPR success.

During defibrillator application: Activate the K-1 Yongquan through needles before applying defibrillation to guide the shock to this acupuncture point.

Unsuccessful CPR

“Gold standard” for legal clinical death^[1-4]. Comparisons between the Utstein and Yongquan protocols are presented in Figure 1.

Statistical analysis

The performance of any applied method in medicine should demonstrate whether there is an association between different variables and whether this association is real or is the product of chance. The larger the sample, the greater is the precision, and the variability due to chance is reduced.

Although we apply statistical significance here, adapting it to the circumstances, the statistical significance does not resolve all of the questions that must be answered (because the results may not be clinically relevant). However, the term “statistically significant” indicates a guarantee of quality. The word “significant” implies using terms comparing two hypotheses. Ho (null hypothesis) represents an affirmation that there is no association between the two variables studied. Ha (alternative hypothesis) affirms that there is some degree of relation between the two variables.

Statistical analysis assists us in selecting the correct hypothesis. First, one observes the magnitude of the difference that exists between the two treatments being compared. If this magnitude is greater than the standard error multiplied by a defined coefficient of security, we conclude that there is a significant difference between both methods; thus, Ha will be accepted, and Ho will be rejected.

In our case, we will first compare CPR treatment without a defibrillator (method “A”) with K-1 Yongquan method (method “B”) using response percentages for these protocols, based on representative samples: treatment “A” yields a 6.4% response; treatment “B” yields an 85% response.

If $|PA - PB|$ is greater than the product of 1.96 times the standard error, we conclude that the difference is significant ($|PA - PB| = |0.064 - 0.85| = 0.786 < SE (0.05) \times 1.96 = 0.098$).

Because the difference $|PA - PB| = 0.786$ is greater than the value of 0.098, which is calculated by multiplying the standard error by the fixed constant, we conclude that the difference between 0.064 and 0.85 is statistically significant. Thus, we reject Ho (the null hypothesis) and we accept Ha (the alternative hypothesis) as most likely correct. In this manner, we state that it is highly improbable that chance was responsible for this association. Using this analysis, we show that K-1 Yongquan method has a “quality guarantee”.

Second, we compare the CPR method, this time with a defibrillator: treatment “A” with 48% (CPR with a defibrillator); treatment “B” with 84% (K-1 Yongquan method) ($|PA - PB| = |0.48 - 0.84| = 0.36 < SE (0.0076) \times$

A Cardiac Arrest Data Collection Form

Date of arrest: YYYY/MM/DD

Patient Identifier: (first name, last name, or ID Number)

Sex: _____

Age: _____ year (estimated) OR Date of Birth: YYYY/MM/DD

Cardiac arrest determined by _____

Cause of arrest _____

Treatment before EMS arrival _____

Bystander CPR

Defibrillation by bystander ☐ or implanted defibrillator ☐

Resuscitation attempted by EMS

Location of arrest: _____ out of hospital _____ in hospital

Witnessed _____ If witnessed, time of arrest HH:MM

Initial rhythm _____

Chest compressions _____

Defibrillation attempt _____

Ventilation _____

Drugs _____

Time of collapse HH:MM _____

Time of call receipt HH:MM _____

Time vehicle stop HH:MM _____

Time of first rhythm analysis HH:MM _____

Spontaneous circulation (on arrival in ED) _____

Hospital admission _____

Hospital discharge _____

Date of hospital discharge (or year) YYYY/MM/DD

Neurologic status of at discharge (CPC) _____

Revised Utstein cardiac arrest data collection form

B K1 - Yongquan protocolization into the different stages of the CPR sequence

ADDITIONAL MANEUVER RESUSCITATION OVER POINT K-1 YONGQUAN FORM FOR DATA COLLECTION

Whichever protocol you use to record cardiac arrest data, add the following data

Full Name: _____

Date: _____

No. Clinical History: _____

PROBABLE CAUSE OF CARDIAC ARREST: _____

Cardiac arrest / Stroke / Trauma / Choking / Poisoning / Other _____

Underlying disease: _____

INDICATIONS OF THE USE OF INTEGRATED K-1 YONGQUAN TO THE SEQUENCE OF CPR

PRIOR TO THE IMPLEMENTATION OF THE RCP → IMPOSSIBILITY TO APPLY CPR

- wrecked vehicle } Patient extrication by firemen/paramedics is required

- overturned vehicle }

- collapse }

- No. Massive victims → Physical impossibility to apply CPR, insufficient number of rescuers

DURING THE IMPLEMENTATION OF CPR

BASIC CPR (CAB) → application of the maneuver by a third rescue

Defibrillation (shock) → prior application of needles on the R-1 of each foot Yongquan

BASIC AND ADVANCED CPR FAILURE → R-1 Yongquan Stimulation

Start Time of complementary maneuver on R-1: _____

Duration (or application) of the maneuver: _____

CONSEQUENCES OF MANEUVER

A) Effect on heart rate (pulse, ECG) _____

B) Effect on recovery of consciousness _____

C) Final result _____

Time or completion of the life support maneuvers: _____

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Figure 1 Comparison between the Utstein and Yongquan protocols. A: Revised Utstein cardiac arrest data collection form; B: K1-Yongquan protocolization into the different stages of the cardiopulmonary resuscitation (CPR) sequence.

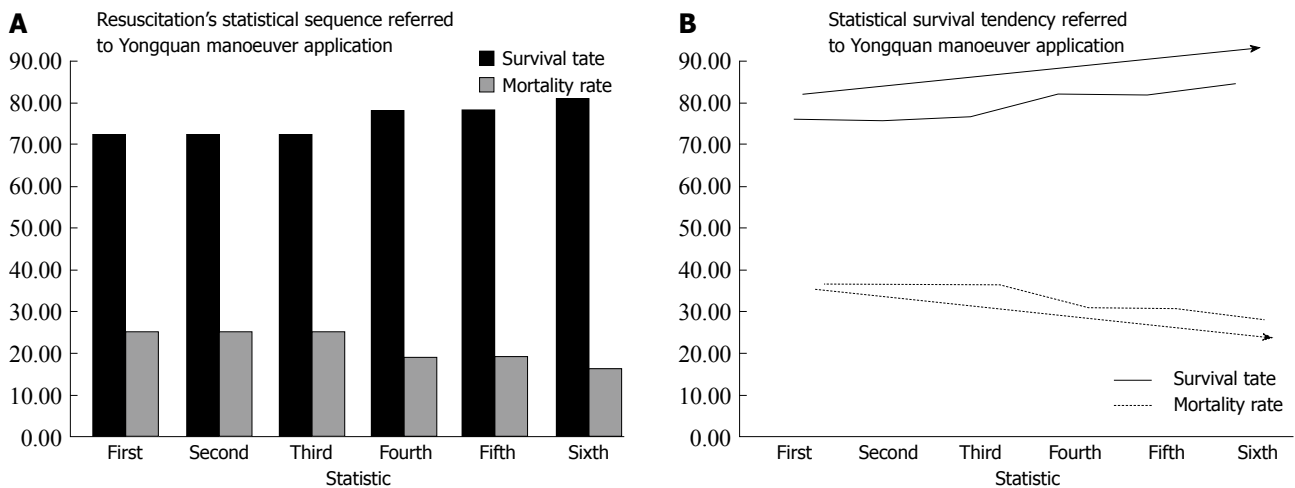


Figure 2 Progression of the presented statistics. A: Survival statistics; B: Tendency.

1.96 = 0.0148).

$|PA - PB| = 0.36$ is greater than 0.0148. The difference here is also confirmed to be statistically significant; thus, all of the considerations from the previous example are valid, demonstrating once more the comparative value of the Yongquan method.

RESULTS

Progression of the presented statistics

This progression was introduced as a Section C Poster Presentation (No.0100) during the 9th International Brain Injury Association Congress^[4], Edinburgh, March 23-26, 2012: first statistic: November 2005 (50th Argentina Acupuncture Society Congress 19, patients-five deaths, survival rate: 73.68%); second statistic: November 2009 (Lazarus Effect Video, 27 cases-seven deaths, survival rate: 74.07%); third statistic: January 2010 (Resuscitation Journal^[1], 30 cases-eight deaths, survival rate: 73.33%); fourth statistic: 8th IDDST Congress, Beijing^[7], 39 cases-eight deaths, survival rate: 79.48%; fifth statistic: InTech's,

44 cases-nine deaths^[3], survival rate: 79.53%; and sixth statistic: 9th International Brain Injury Congress^[4], 52 cases-nine deaths, survival rate: 82.69% (Figure 2).

The trial published in "resuscitation" four involved 30 patients treated with K-1 Yongquan stimulation after CPR protocol failure^[1-4,7,8]. After its application, approximately 79% survived, demonstrating that the protocol yields valuable results when there are no other options.

Today, 58 patients survived, yielding an 84.48% survival rate. This result indicates a consequent improvement of the survival tendency.

Despite a "non-resuscitation order", based on the law of each country, the Yongquan resuscitation maneuver will be useful as long as it is promptly applied, with the following considerations: (1) currently, approximately 95% of individuals undergoing cardiac arrest worldwide die before the arrival of assistance (an ambulance never takes less than 12 min to reach the accident site); (2) nearly 8000000 individuals worldwide die suddenly each year (neither earthquakes, tsunamis^[11], volcano eruptions, nuclear leaks, epidemics, nor pandemic diseases could

match this mortality rate)^[12,13]; (3) so-called “Cardiac Chaos” affects 1000 victims per day, and there were 350000 reported cases in the United States last year^[12,14]; (4) in Argentina, two people per hour (that is, 54 per day and more than 20000 per year) will experience sudden death; and (5) in infants, the sudden death mortality is over 98%^[15].

In conclusion, the Torsadogenic Index was recently introduced as a management tool for risk against pharmacologically induced sudden death due to torsadogenic drugs, whereas the K-1 Yongquan resuscitation complementary manoeuvre is a contingency measure against basic or advanced CPR failure. Both costless strategies, once universally implemented, can definitely improve survival rates after cardiac arrest. The Yongquan resuscitation manoeuvre is a non-invasive, non-tiring, costless, and easy-to-apply procedure that provides a second chance when other options fail.

COMMENTS

Background

As a result of 25 years of experience in the “Lazarus Effect” of acupuncture, a formalised protocol project is demonstrated for integrating this manoeuvre into the cardiopulmonary resuscitation (CPR) sequence.

Research frontiers

Actuarial statistics are presented to draw attention to the enormous mortality from cardiac arrests, without visible improvements due to classical CPR applications (less than 19% overall survival after cardiac arrest). This protocol increases the survival rate: over 84% resuscitation success. After the ILCOR protocol sequence's failure, in the absence of additional options from current science, the Yongquan resuscitation manoeuvre has become the “gold standard” for improving survival rates after an unsuccessful CPR rescue.

Innovations and breakthroughs

The K-1 Yongquan manoeuvre does not replace or interrupt any CPR protocol but, rather, offers an alternative to improve the mortality rates from cardiac arrest when the ILCOR-CPR method has failed.

Applications

Considering the lack of time for a successful rescue, K-1 Yongquan manual praxis is proposed for conditions in which application of the ILCOR-CPR manoeuvres is impossible. Only in situations of entrapment (landfalls or accidents with crashed or overturned cars), the K-1 Yongquan manoeuvre is suggested while waiting for firefighters to address the trauma scenario. During chest massage, a third rescuer can assist in stimulating the heart to bring victims back to life. For cases in which defibrillation is indicated (and prior to shock), needles positioned over the Yongquan points will provide additional power from the electric current to activate the point.

Peer review

It is interesting to clinicians if the protocol can be validated to a large number of the sample at multi-center setting.

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Computerized decision support in adult and pediatric critical care

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Abstract

Computerized decision support (CDS) is the most advanced form of clinical decision support available and has evolved with innovative technologies to provide meaningful assistance to medical professionals. Critical care clinicians are in unique environments where vast amounts of data are collected on individual patients, and where expedient and accurate decisions are paramount to the delivery of quality healthcare. Many CDS tools are in use today among adult and pediatric intensive care units as diagnostic aides, safety alerts, computerized protocols, and automated recommendations for management. Some CDS use have significantly decreased adverse events and improved costs when carefully implemented and properly operated. CDS tools integrated into electronic health records are also valuable to researchers providing rapid identification of eligible patients, streamlining data-gathering and analysis, and providing cohorts for study of rare and chronic diseases through data-warehousing. Although the need for human judgment in the daily care of critically ill patients has limited the study and realization of

meaningful improvements in overall patient outcomes, CDS tools continue to evolve and integrate into the daily workflow of clinicians, and will likely provide advancements over time. Through novel technologies, CDS tools have vast potential for progression and will significantly impact the field of critical care and clinical research in the future.

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Key words: Clinical decision support systems; Critical care; Computers; Computer-assisted decision making

Core tip: Computerized decision support (CDS) is increasingly utilized in both adult and pediatric critical care. Improvements in care have been shown in areas including guideline adherence and reduction of medical errors, but reports of meaningful improvements in patient outcome have been scarce to date. However, with technology improvements and widespread acceptance of tools, CDS has the potential to revolutionize critical care medicine with improved diagnosis, monitoring, risk prediction, and treatment. Improvements in multiple aspects of patient care through CDS tools can lead to better patient outcomes.

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INTRODUCTION

Decision support tools have been used by the medical profession for decades and evolved with technology to become largely computer based and widely accessible to all clinicians in the form of smart phone applications,

web-based search engines, online references and journal access, and bedside tools incorporated into daily clinical practice. The potential for further advancements in biomedical informatics to improve healthcare quality is vast and increasingly studied at the patient care level and in research^[1]. The goal of clinical decision support is to provide current and pertinent knowledge to clinicians to aid patient care at the exact time of care delivery^[2]. Computerized technology provides the tools to facilitate timely delivery of this knowledge to bedside clinicians. Computerized decision support (CDS) systems have been implemented by hospitals internationally targeting important goals including improved diagnostic accuracy, error reduction, delivery of preventative care, and better patient outcomes^[3]. As the field of medicine continues to increase in complexity, these tools are likely to become further integrated into patient care, as well as provide substantial resources for clinical research.

Intensive care unit (ICU) clinicians are in unique environments where vast amounts of information are collected and displayed by computerized systems, and where expedient, accurate diagnosis and treatment may profoundly affect quality of care and patient outcomes. ICU clinicians are tasked daily to manage large volumes of data from multiple sources and incorporate this data into patient-specific decisions. Given the unique position of ICU clinicians, CDS will likely become central to delivery of critical care in the coming years. However, inter-provider decision variability, lack of universal diagnostic and therapeutic protocols for many common diagnoses, and the demand for real-time individual variation at the bedside provide challenges for CDS design in critical care. In this paper, we give an overview of CDS history in clinical medicine, discuss different types of CDS tools, review some current applications in adult and pediatric critical care, address advantages and limitations to CDS tool use, and discuss the potential of CDS for critical care in the future.

HISTORY AND OVERVIEW OF COMPUTERIZED DECISION SUPPORT

CDS is the most efficient form of decision support and is designed to improve the quality of healthcare delivery, assist nurses and physicians in clinical decision making, and reduce variation^[1,2]. CDS tools have evolved over time in both content and theoretical design for many healthcare related functions commonly used today: alert, diagnosis, reminder, suggestion, interpretation, prediction, critique, and assistance^[4]. The concept of computer aided diagnosis in medicine was introduced as early as by Ledley *et al.*^[5]. Warner *et al.*^[6] presented a Bayesian theory based system for diagnosing congenital heart disease relying on inputted signs and symptoms. Design of CDS tools has evolved beyond rule-based tools to contain more complex mathematical models incorporating multiple static and dynamic factors rather than just the presence or absence of a variable. Despite the many advan-

tages of CDS tools, widespread acceptance by clinicians across healthcare disciplines remains variable.

Computerized order entry (CPOE) and electronic health records (EHR) represent forms of computer assistance used in healthcare systems worldwide. CPOE and EHR centralize information and CDS can be incorporated into these technologies. CPOE and EHR with integrated CDS enables provision of abnormal lab value and allergy alerts, antibiotic choice assistance, vaccination reminders, mortality prediction tools, compliance with protocols and care guidelines, and suggestions for therapeutic interventions at the bedside^[4,7,8]. The warehousing of information in EHR and other computer databases with CDS enables research advancement as databases can be linked and analysis of previously unrecognized relationships between patients and disease states explored^[9].

Bedside computer monitoring devices can also be considered a form of CDS and have evolved from display tools to alarm systems and clinical assistance tools. For example, electrocardiography machines now provide a tracing as well as an interpretation. This type of analysis, using various inputs and known associations to generate a weighted output, is known as a neural network and is commonly utilized in both waveform analysis and mortality risk assessment tools^[9]. Another type of CDS tool with increasing medical use is fuzzy logic; this permits use of ambiguous and imprecise data in logic control when constructing objective outputs. Applications include mechanical ventilation control, oxygen titration, and medication administration for blood pressure regulation^[9]. Belief networks, another type of CDS tool, are algorithms derived from probability trees describing relationships of variables in a system to each other. Belief networks often utilize one of three models: simulation, mathematical, or statistical^[10]. Belief networks can be designed to assist clinicians in real-time clinical decision making, and such belief networks have also been used to determine prognosis following head injury^[9]. Effective computer decision support tools require high data integration accuracy and quality meshed with error free logic, ease of use, and explicit communication^[11].

Experience with decision support and decision making in medicine

Current examples of accepted CDS tools include mortality prediction tools, such as the acute physiology and chronic health evaluation (APACHE) and pediatric risk of mortality (PRISM) scores. These have been validated and revalidated providing accurate mortality risk prediction and are routinely employed to generate risk adjusted mortality estimates to assess ICU performance^[12,13]. CDS tools used in outpatient care document improved adherence to recommended vaccine schedules and adherence to recommended asthma care^[14,15]. CPOE, with integrated CDS, decreases medical errors and improves pharmacy costs over time^[16-20]. CDS tools have improved care in time-sensitive disease states including septic shock^[21].

Table 1 Applications of computerized decision support in adult, pediatric and neonatal critical care

| Type of support tool | Example or subject |
|--------------------------------------|--|
| Adult critical care | |
| Diagnostic | DXplain ^[28] |
| Alert and reminder | Mortality and length of stay prediction ^[9,29] Ventilator induced lung injury ^[84] Blood pressure variability while on vasopressors ^[32] Adverse drug reactions ^[19] Drug induced thrombocytopenia ^[30] Epidural hematoma with neuraxial anesthesia ^[31] |
| Protocol/procedure | Acute respiratory distress syndrome ^[33-35] Sepsis ^[21] VTE prophylaxis and events in trauma patients ^[37] VTE prophylaxis ^[38,39] |
| Management | Tidal volume during mechanical ventilation ^[36] Ventilator fraction of inspired oxygen ^[41] Pressure support ventilation ^[42] Antibiotic recommendation ^[43,44] Blood glucose control ^[46-48] Sepsis ^[21] |
| Research | Heparin dosing after myocardial infarction ^[45] Mortality prediction ^[29] Prediction of fluid requirement ^[53] Predictive alerts for hemodynamic instability ^[49-51] Ventilator settings ^[76] Prediction of dialysis need ^[52] Insulin e-protocol ^[54,55] |
| Pediatric and neonatal critical care | |
| Diagnostic | ISABEL (www.isabelhealthcare.com) ^[59,86] SimulConsult (www.simulconsult.com) ^[87] MEDITEL pediatric diagnostic system ^[58] Outcome prediction and severity of illness ^[55-57] |
| Alert and Reminder | Drug interaction ^[62] Prescription errors and adverse drug events ^[18,61] Parenteral nutrition orders ^[61] NICU pulse oximeter ^[60] |
| Protocol/Procedure | Blood transfusions ^[63] Medications ^[61] Parenteral nutrition ^[64] |
| Management | Oxygen in ventilated newborns ^[68] Antibiotic recommendation ^[44,65] Blood glucose control ^[69] Medication information databases ^[88] Medication dosing calculators ^[61] Ventilator management in neonates ^[66,67] |
| Research | Virtual PICU (www.picu.net) ^[89] Pediatric cardiac care consortium ^[70] Acuity scoring systems for quality improvement ^[56,57] Ventilator settings in neonates ^[71] Neonatal seizure detection ^[72] Glycemic control ^[90] |

VTE: Venous thromboembolism; PICU: Pediatric intensive care unit; NICU: Neonatal intensive care unit.

Hunt *et al.*^[3] conducted a literature review on > 60 studies evaluating decision support tools to determine if these systems impacted patient care and found that CDS tools consistently enhanced performance for drug dosing and preventative care. Similarly, improvements in practitioner performance are noted in a review by Garg *et al.*^[22] with implementation of CDS systems.

Research on the effectiveness of CDS tools for more

advanced clinical decisions in disciplines such as critical care are limited. Decisions rely heavily on clinical judgment and provider knowledge, and in the ICU environment, decisions are often affected by uncertainty. Clinical uncertainty among diagnoses and therapies makes conclusive decisions challenging^[23]. Use of computer protocols or automated systems is still considered investigational; however, computers could assist clinicians' decisions by providing probabilistic estimates for diagnosis, choice of therapy, and survival^[10]. Additionally, little is known about physician and nurse utilization or opinions of CDS tools^[1]. To accurately assess the potential impact of a CDS tool by a clinical parameter, such as patient outcome, widespread tool use and acceptance is required^[11]. Currently, use of CDS remains variable across different healthcare professionals and clinical situations^[1,23,24]. Furthermore, an unappreciated challenge to CDS tools is that clinical decisions often incorporate patient and provider preferences. Some might term this phenomenon "the art of medicine." Therefore, it is not surprising that individual clinicians might resist incorporation of automated decision trees into their daily practice.

Despite advancements in the field, many pitfalls in both design and implementation of CDS tools occur and are multifactorial. In the review by Hunt *et al.*^[3] only 1 of 5 diagnostic aides showed a quantifiable benefit and in the review by Garg *et al.*^[22] only 4 of 10 diagnostic tools showed patient benefit. Diagnostic aides may be limited by variations within a diagnosis between patients and by the uncertainty of symptom variables collected from patients and inputted into systems. Also, measurement of meaningful outcomes in these studies is difficult when the intervention is designed to improve workflow and reduce barriers to guideline compliance. Other reports found no improvement or worsening in patient outcomes and costs after implementation of computerized systems^[25-27]. Many reports have suggested that failure of some CDS systems is related to problems with implementation and not to content. Several studies highlighted learned lessons from failed implementation and suggested strategies for improved success. Seamless integration with existing systems and clinician workflow, limiting alarms in a system to prevent alert fatigue, and proper training before and after implementation are particularly important^[1,7]. Additionally, the complex nature of human decision making adds confusion to measuring the effectiveness of CDS tools as many healthcare decisions are unstructured with high levels of uncertainty and depend on the judgment of the decision maker^[1].

CURRENT APPLICATIONS OF CDS IN ADULT AND PEDIATRIC CRITICAL CARE

CDS systems in critical care continue to advance and are beginning to show improvements in care for both adult and pediatric ICU patients. A large amount of data is available for each ICU patient, and CDS tools

are designed to assist the clinician in incorporating this multitude of data into patient specific therapeutic plans. Examples of CDS systems in adult critical care are provided in Table 1. Diagnostic support tools are available to assist in disease identification and also for using symptoms and patient condition on admission to predict outcome^[9,28,29]. Ranson's criteria and various APACHE models are examples that have been validated using real time data to predict mortality risk in critically ill patients^[29]. Alert support tools are used to improve workflow, warn practitioners of adverse drug reactions^[19,30], and to notify practitioners of potential adverse consequences of an ordered therapy, such as anticoagulation^[31,32]. This type of system decreases reported patient complications from drug-drug interactions and adverse drug events in the ICU following implementation^[19]. In the prospective cohort study by Bertsche *et al*^[19], implementation of a CDS program showed significant decreases in drug-drug interactions and in adverse events related to drug-drug interactions, including prolonged QT interval and hypokalemia. Additionally, CDS improves adherence to protocols for mechanical ventilation^[33-36], sepsis^[21], and venous thromboembolism prevention^[37-39], and can improve patient care. Such protocol use in critical care standardizes treatments of common physiologic states and is often central to quality improvement efforts in the ICU^[40]. Tafelski *et al*^[21] demonstrated significantly increased adherence to standard care protocols for sepsis following implementation of CDS, and additionally reported a significant association between mortality and adherence to those care protocols. CDS is also used to aide patient management independent of protocols by recommending suggestions for ventilator settings and weaning^[41,42], antibiotic assistance^[43,44], and medication dosing. Mungall *et al*^[45] found significant improvement in achieving desired anticoagulation goals when using a CDS tool for heparin dosing following tissue plasminogen activator treatment in myocardial infarction compared to the standard nomogram. Blood glucose control is a commonly investigated area for support tools, and studies report more consistent target glucose levels and few adverse events with these tools^[46-48]. CDS is also used for research in improving mortality risk estimation^[29], prediction of hemodynamic instability^[49-51], and in forecasting the need for therapies in the ICU, such as dialysis^[52,53]. CDS tools can also reduce variability of clinical decisions during critical care research, therefore enabling replicable experimental methods and reproducible results^[54].

Pediatric and neonatal ICUs are also utilizing CDS tools with increasing frequency, and specific examples are provided in Table 1. Multiple support tools are available to aide in diagnosis, classification of disease severity, and outcome prediction^[55-59]. ISABEL is one such diagnostic aide that is commercially available as a stand-alone product or for integration into existing EHR systems and has shown good sensitivity for common pediatric diagnoses^[59]. PRISM models and score for acute

neonatal physiology (SNAP) models are validated tools for mortality risk prediction in pediatric and neonatal patients^[55,56]. CDS alerts improve patient safety and are used to warn of drug interactions and adverse events and to improve the specificity of monitor alarms^[18,60-62]. Kadmon *et al*^[18] found alert CDS tools integrated with CPOE significantly decreased dosing order errors and potential adverse events in a pediatric ICU. Similarly, use of these tools reduced parenteral nutrition order errors in the neonatal ICU^[61]. Similar to adult tools, CDS in pediatrics provides improved adherence to care protocols for blood transfusion, parenteral nutrition, and medication orders^[61,63,64]. Adams *et al*^[63] found a significant reduction in pediatric blood transfusions, consistent with best practice guidelines, when CDS was added to CPOE. Pediatric CDS tools also assist patient care by providing antibiotic assistance^[65], medication dosing calculators^[61], and ventilator management suggestions^[66-68]. These management tools have improved attainment of target oxygen saturations in newborns and target blood glucose concentrations in critically ill children^[68,69]. CDS tools are also used for pediatric and neonatal research on a variety of topics, including seizure detection and quality improvement^[56,57,70-72].

BARRIERS TO WIDESPREAD ACCEPTANCE OF CDS IN THE ICU

CDS tools are not uniformly incorporated into critical care units. There are many barriers to widespread acceptance, including style of implementation, variability in provider preference, and perceived lack of generalizability to patient populations. Use of CDS tools is largely optional and determined by either provider preference or group consensus and a cultural shift must occur to ensure broad utilization^[11]. Additionally, the formation of CDS tools through integration of independent systems, such as EHR, with probability estimates from different ICUs is complex and dependent on the quality and generalizability of the data collected^[29]. Likewise, data used to create a protocol often rely on imperfect data, such as from meta-analyses, that individual clinicians may determine are not generalizable to their patients^[73,74].

Even the use of simple computer protocols for care items like ventilator weaning can ignite objection from clinicians who value the importance of individual patient specific decision making. Some argue CDS tools overly standardize medicine and fail to satisfy the complex nature of ICU decision making. Proponents cite the unique processing capabilities of computer networks and the advantages of analyzing several data points simultaneously^[29]. CDS tools also allow for programming models that can respond to patient specific states and data^[54]. CDS tools are meant to support, not replace, clinical decisions and can expand limited human recall by presenting several data points simultaneously. The successful use of CDS tools in the ICU relies heavily on the preferences of clinicians and on the specific contexts

and degree of uncertainty present for a given clinical decision^[1].

Additionally, some failures with CDS tools have been noted in the literature. Han *et al*^[27] reported an unexpected increase in mortality associated with implementation of a CPOE program with integrated CDS due to delays in medication ordering, dispensing, and administration to critically ill patients. These delays were linked to unanticipated delays in workflow with early implementation. The published failures highlight the importance of proper design, implementation, and deployment of CDS tools. Mitigation of changes to clinician workflow and widespread user acceptance are important to production of a successful CDS tool.

POTENTIAL FOR CDS IN CRITICAL CARE

Advancements in computer technology and mathematics have already led to improved technology for aides in critical care, but have the potential to enhance clinician performance and patient care even more. Bedside monitors collect vast amounts of information that are currently analyzed at discrete time periods by clinicians. Neural networks and fuzzy logic systems are two types of tools that can be integrated into these bedside alarms to provide continuous analysis and potentially identify patterns consistent with various diagnoses, such as cardiac ischemia and hypovolemia^[9]. Evaluation of hemodynamic data for prediction of instability and hypotension is an ongoing area of research that could translate into bedside tools in the future^[49-51].

Continuous electroencephalogram (EEG) is a commonly used critical care tool from which patients and clinicians may benefit from rapid identification of seizures or prediction of seizures before they occur. Retrospective evaluation of EEG data by various mathematical techniques has shown good detection of seizure and identification of pre-ictal states minutes to hours prior to onset of seizure activity; no prospectively evaluated models have proven effective, though new methods are being researched^[75]. Fuzzy logic controllers could also be used with bedside devices to provide automatic adjustment of ventilators or dialysis machines by integration of patient specific information and programmed logic controllers^[9].

CDS for mechanical ventilation in adults and children has already shown good agreement with clinician recommendations^[71,76,77]. In the future, these CDS tools could provide independent control of ventilator settings based on patient specific data. CDS tools also have the potential to manage decisions regarding titration of medications or weaning of support devices, thereby freeing the clinician's mind to direct the overall care of a patient. CDS incorporated into CPOE could also be used to decrease unnecessary testing or to enhance the proper selection of available tests, such as radiologic exams, based on patient information^[78]. Incorporation of belief networks and neural networks into existing EHR could also provide tools for identifying diseases or estimating

the probability a patient will develop a disease, such as sepsis or acute respiratory distress syndrome^[9]. As septic shock is a disease with time-sensitive implications for outcome, use of prediction tools could alert clinicians to high risk patients that may benefit from additional or different therapies^[79]. Additionally, the adoption of CDS linked into EHR systems could identify patients presenting to small facilities with time-sensitive diagnoses and disseminate ICU protocols to providers lacking in-house critical care specialists.

In addition to identification of disease for clinical support, CDS tools integrated into existing EHR or databases can rapidly identify patients for inclusion into research studies^[80]. Utilization of CDS in this way has the potential to increase recruitment numbers, especially among studies with time dependent inclusion criteria. CDS can also provide automatic data capture for research studies by tracking patient information and automatically transmitting it to a central data coordination center, saving coordinator time and potentially costs^[11]. This automatic capture can also be used to operate research protocols, potentially improving compliance^[11]. CDS can standardize co-intervention control during multicenter prospective clinical trials. Co-interventional control improves the signal to noise ratio on pertinent clinical questions, thereby standardizing clinical experimental methods and enhancing the probability of accurate trial results^[81,82]. Finally, increased use of CDS with EHR and data warehousing provides opportunities for collecting information across many institutions. This data provides cohorts for research on rare diseases or chronic diseases that could close existing gaps in medical evidence and improve care for patients^[83].

CONCLUSION

Computerized decision support systems are becoming increasingly common in medicine, though barriers to widespread acceptance continue to exist. Studies have shown benefits to their use in a variety of applications, but research regarding improvement in patient outcome is limited. Studies have also shown that careful and proper implementation is crucial to the success of these systems. Critical care physicians are in unique environments where the use of CDS could play a significant role in patient safety and outcome over the coming years. CDS has the potential to provide improved care standardization, faster diagnosis and treatment, reduced medical errors, improved health care costs, and unique research opportunities that could all translate into improved patient outcomes over time. Advancements are occurring in the field of CDS and promise to improve current technologies and to yield exciting new technologies for clinicians in the future.

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Extracorporeal membrane oxygenation for pediatric respiratory failure: History, development and current status

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over the past several decades. Additional risk factors associated with death include prolonged use of mechanical ventilation (> 2 wk) prior to ECMO, use of VA ECMO, older patient age, prolonged ECMO support as well as complications during ECMO. Medical evidence regarding daily patient management specifically related to ECMO is scant, it usually mirrors care recommended for similar patients treated without ECMO. Linkage of the Extracorporeal Life Support Organization dataset with other databases and collaborative research networks will be required to address this knowledge deficit as most centers treat only a few pediatric respiratory failure patients each year.

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Key words: Respiratory failure; Pediatrics; Extracorporeal life support; Veno-arterial; Veno-venous

Abstract

Extracorporeal membrane oxygenation (ECMO) is currently used to support patients of all ages with acute severe respiratory failure non-responsive to conventional treatments, and although initial use was almost exclusively in neonates, use for this age group is decreasing while use in older children remains stable (300-500 cases annually) and support for adults is increasing. Recent advances in technology include: refinement of double lumen veno-venous (VV) cannulas to support a large range of patient size, pumps with lower prime volumes, more efficient oxygenators, changes in circuit configuration to decrease turbulent flow and hemolysis. Veno-arterial (VA) mode of support remains the predominant type used; however, VV support has lower risk of central nervous injury and mortality. Key to successful survival is implementation of ECMO before irreversible organ injury develops, unless support with ECMO is used as a bridge to transplant. Among pediatric patients treated with ECMO mortality varies by pulmonary diagnosis, underlying condition, other non-pulmonary organ dysfunction as well as patient age, but has remained relatively unchanged overall (43%)

Core tip: Extracorporeal membrane oxygenation (ECMO) is a very important mode of support for patients of all ages with acute severe respiratory failure, non-responsive to conventional treatments. Goal of this review is to describe evolution of ECMO support for respiratory failure, changes and advances in technology, epidemiology, outcomes and care of pediatric respiratory failure patients. Also, we would like to describe changes in modes of support and although veno-arterial (VA) mode of support remains the predominant type used, veno-venous (VV) support is increasingly used especially in older children and adults. We described advantages and limitations of VV ECMO comparing to VA support.

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BACKGROUND

Extracorporeal membrane oxygenation (ECMO), a form of prolonged cardiopulmonary bypass (CPB), has been used to “rescue” patients suffering from severe cardiopulmonary failure unresponsive to conventional therapies for over 30 years. ECMO development has been guided by the Extracorporeal Life Support Organization (ELSO)^[1], an International Consortium of Health Care Centers that voluntarily contribute detailed data to a registry supporting the vast majority of ECMO clinical research. ELSO also develops and disseminates standards and guidelines for the member programs and sponsors medical education^[2,3]. In addition to supporting patients with acute, severe respiratory failure failing conventional management, there are new applications for ECMO recently reported. These include support of patients with chronic respiratory failure as a bridge to transplant^[4,5] as well as cardiopulmonary support for organ donation after circulatory determination of death both *in vivo*^[6] and *ex vivo*^[7]. Although ECMO is currently used in both adults and children, the pioneering initial application of ECMO was for neonates with severe respiratory failure.

This focus on newborns was because initial applications in patients with respiratory failure^[8] found that veno-arterial (VA) bypass dramatically improved survival in “moribund” infants, while the first randomized trial in adults with severe hypoxic respiratory failure reported dismal overall survival (9%) that was not improved by ECMO support^[9]. The initial success in newborns was because ECMO support could interrupt the spiral of unrelenting hypoxia and acidosis from severe pulmonary hypertension, while adults with hypoxic respiratory failure treated in the original study reported by Hardart *et al.*^[10] had already suffered severe ventilator induced lung injury (VILI) that was not reversible. Early recognition that ECMO support is only potentially effective, when implemented before irreversible organ injury develops, became the key to successful ECMO patient selection. Another lesson learned from early reports was that potential candidates should not have high risk of severe bleeding complications. Premature newborns with gestational age < 35 wk suffered high rates of severe of intraventricular hemorrhage that continues to limit ECMO use for premature infants.

EPIDEMIOLOGY OF NEONATAL RESPIRATORY FAILURE AND ECMO

In the 2013 ELSO international summary 26205 of 53190 (49%) of all patients treated with ECMO reported to ELSO were neonates with respiratory failure, and patients less than a month of age comprised 60 percent of patients treated with ECMO if neonates with cardiac failure (9%) or failed cardiopulmonary resuscitation (3%) are also considered^[3].

However, ECMO use to treat severe neonatal respiratory failure peaked in 1992 and steadily declined since,

as advances in other less invasive therapies occurred^[11,12] such as high frequency oscillatory ventilation^[13-15], inhaled nitric oxide^[15-20], surfactant^[21,22] and maternal antibiotic therapy^[23,24]. In 2011, neonatal respiratory failure accounted for 24% of cases reported to ELSO. The neonatal respiratory failure population for whom the annual cases treated with ECMO have remained relatively unchanged over time are infants with congenital diaphragmatic hernia and unfortunately approximately 40%-50% mortality persists among these patients^[3,25-27]. Understanding the contribution of reversible pulmonary hypertension relative to lung hypoplasia in these newborns continue to complicate prognosis assessment.

EPIDEMIOLOGY OF PEDIATRIC RESPIRATORY AND ECMO

ELSO annual reports of ECMO use to support pediatric patients with respiratory failure have remained fairly stable over last 5 years (300-500 cases/year) with some transient increases during years of severe influenza outbreaks^[3,28-31]. Compared to neonates much less ECMO experience involves pediatric respiratory failure and no clinical trials have established efficacy in this patient group. A United States study led by James Fackler^[32] was initiated, but concurrent changes in critical care practices resulted in lower pediatric mortality from acute hypoxic respiratory failure and providers were largely unwilling to enroll patients in an ECMO trial. However, studies of pediatric hypoxic respiratory failure found that centers with ECMO available had lower mortality among patients with respiratory failure compared to centers treating patients without ECMO available for select cases^[32]. Furthermore, recent randomized trial in adult ARDS patients reported by Peek *et al.*^[33] found that adults transferred to a centralized ECMO center died less frequently when both standardized conventional care and “rescue” ECMO was available compared to patients treated at multiple centers with only conventional care as a treatment option.

Trials in the United Kingdom in both neonates^[34,35] and adults^[33] have shown that ECMO is an effective treatment for severe respiratory failure compared to conventional support with acceptable cognitive and functional status. The remaining studies in this review refer to children treated with ECMO for respiratory failure but lack key information including: the number of children with a given pulmonary process at risk for severe respiratory failure compared to the number treated with ECMO. The unanswered questions are would a child with a unique set of clinical and demographic features survive without ECMO yesterday, today and tomorrow?

ORIGINAL TECHNOLOGY

Initial ECMO support relied exclusively on VA support typically with arterial (carotid) and venous (internal jugular) cannula in the neck with the distal end of the carotid artery permanently ligated (Figure 1). The cannula

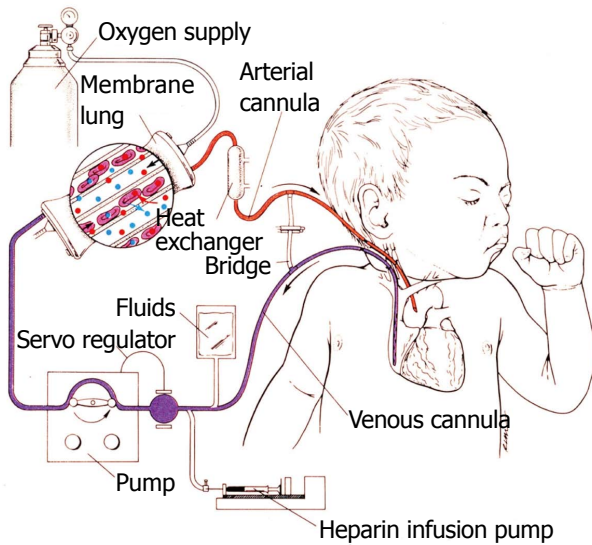


Figure 1 Classic veno arterial extracorporeal membrane oxygenation in an infant with cannulation of the right internal jugular vein draining blood by gravity to a roller pump that generates non pulsatile flow to a membrane oxygenator. Oxygenated blood is returned to the aorta by a catheter inserted in the right internal carotid artery.

drained venous blood by gravity into a reservoir (bladder) and a roller pump provided non-pulsatile propelled blood flow through an oxygenator and returned blood to the infant's aorta. With this configuration, venous drainage can be augmented by elevating the patient on multiple cushions to increase the pressure gradient between the patient and the ECMO bladder enhancing circulating volume. Systemic anti-coagulation was primarily monitored with activated clotting times. The blood moved through a circuit, and diffusion of gases occurred across a semi-permeable membrane with oxygenation limited by time in the oxygenator membrane, so larger membranes are required to support larger patients. A blood primed bridge existed in the circuit so that flow could be diverted away from the patient to preserve the circuit from clotting when testing to see if the patient was ready for ECMO support to be removed.

TECHNICAL PROBLEMS

The technical limitations to early ECMO primarily revolved around complications due to inadequate flow and oxygen delivery, hemolysis, and anti-coagulation (clot and bleeding complications). Arterial cannulation for infants is primarily limited to either accessing the heart and great vessels either *via* a sternotomy or open cannulation of the carotid because extremity vessels are inadequate until the child is ambulatory at which time the femoral artery is an option. Infants usually tolerate loss of a unilateral carotid artery, but adults are at greater risk of hemispheric stroke complicating carotid artery cannulation and ligation. Like other neonates treated with CPB^[36-39], the majority of critically ill neonates treated with ECMO survive with subtle cognitive deficits, but approximately 10%-15% of

survivors manifest more severe neurologic complications and central nervous system complications also increase mortality risk^[40-47].

CHANGES AND ADVANCEMENTS IN TECHNOLOGY IN ECMO FOR RESPIRATORY FAILURE

As care for patients with respiratory failure evolved during last 30 years, technological advances in ECMO have also changed to enhance safety, accessibility and facilitate its use, contributing to decreased morbidity and improved survival of patients requiring ECMO support^[48].

Major advances in ECMO deployment paralleled advances in conventional CPB including cannulas, pumps, oxygenator bubble detectors and heparin bonded circuits which decrease platelet activation, circuit clotting and prolong the circuit life. There is an overall tendency to use smaller circuit size decreasing priming volume, and exposure to foreign material and blood products.

CANNULAE

Double lumen venous cannulae were initially developed for use in neonates and small infants for veno-venous (VV) support, while multiple single lumen venous cannulas were used for VV support in toddlers, older children, adolescent and adults with respiratory failure. Newer double lumen cannulas with better flow profiles and less blood recirculation have increased ease of VV use in older children.

VV double lumen catheter provides drainage of SVC and IVC and more directed "arterial flow" towards tricuspid valve but require echocardiography or fluoroscopy for initial placement^[49,50]. Insertion of these cannulas can be done percutaneously, theoretically decrease risk of infection and bleeding. In adult patients, use of these cannulas is associated with less sedation use and active rehabilitation of patients during ECMO support^[51,52]. Finally manufacture of double lumen catheters for older patients made this technique possible for all size patients^[53,54]. However rigorous evaluation of these catheters compared to VV ECMO accomplished with use of multiple venous catheters is needed. Although the catheters appear to decrease reperfusion and provide adequate flow, reported complications include right heart perforation during insertion^[55].

PUMPS

The majority of programs traditionally used roller-head (semi-occlusive) pumps, but use of smaller, low-friction centrifugal pump has increased over last several years. These pumps have potential advantages compared to roller-head pumps where circuit flow is dependent on gravity drainage and a reservoir or "bladder" is required. These mechanical features increase turbulent flow, and tubing

rupture can occur so longer circuit tubing is needed to “walk the raceway”. Thanks to magnetic drives centrifugal pumps enable use of shorter tubing and smaller priming volume. Hemolysis and renal injury appear to be more common with centrifugal pumps especially in neonates. However, hemolysis can occur with both pump types^[56-59].

OXYGENATORS

Initial silicon oxygenators had very large surface areas, which were more difficult to prime and debubble and furthermore their use was associated with a large inflammatory response. Polypropylene, hollow fiber devices were developed and appeared to elicit less inflammation but have a tendency to leak plasma, which decreased oxygenator life span. Some ECMO programs used the hollow fiber devices for rapid deployment and reserved the silicon oxygenators for replacement after ECMO initiation. The newest polymethyl pentene, nonporous hollow fiber oxygenators, are now widely used, provide very efficient gas exchange, with low resistance to flow and use smaller priming volumes^[59-61].

CIRCUIT CONFIGURATION AND ANTICOAGULATION

Attention to flow monitoring and pressure changes across the circuit prompted modification to decrease clotting and hemolysis. Removal of the bridge blood prime during ECMO initiation potentially could lower risk of embolic events during trials off when the circuit flow is decreased and the bridge “flushed” periodically. Heparin coated tubing often decreases requirement for anticoagulation use during the initial hours after ECMO initiation, which can be especially important for patients with bleeding complications and requiring surgical procedures.

Anticoagulation strategies to prevent circuit clotting vary widely between institutions. Currently no consensus exists regarding the best way to manage anticoagulation and blood product administration for patients supported on ECMO^[62-64]. All centers use unfractionated heparin as the primary anticoagulant, while few centers reported use of alternative anticoagulation agents (direct thrombin inhibitors: Argatroban and Lepirudin or Bivalirudin) when heparin-induced thrombocytopenia is suspected.

Likewise practice varies regarding anticoagulation monitoring. ACT remains the predominant diagnostic test utilized to monitor and adjust anticoagulation, but more specific tests including anti-factor Xa level, antithrombin III (AT III) as well as thromboelastograms are used with increasing frequency at many centers. No studies have demonstrated advantages of one test over another either in complications or cost of monitoring.

VENO VENOUS ECMO VS VENO ARTERIAL

Recognition that profound respiratory failure frequently

could be supported with VV ECMO (Table 1), a mode where deoxygenated blood from the patient and oxygenated blood from the ECMO circuit mix in the venous circulation and any venous clots are “filtered” by the patient’s native lungs. Thus for this approach to succeed in pediatric patients, native cardiac output must be adequate and in order to limit VILI, medical providers must accept relative hypoxia in some patients as a treatment goal (saturation 75%-85%).

VV ECMO can be accomplished using two separate venous catheters or a double lumen catheter. However, recirculation of blood can complicate both blood saturation monitoring and limits effective blood flow. As described above, double lumen catheter improvements decreases recirculation and improved patient arterial oxygenation when optimally positioned.

While extracorporeal support for patients with severe respiratory failure is implemented as a life saving and lung protective measure, it also carries significant risks of complications. Most commonly described and feared are neurological complications: intracranial hemorrhage, thromboembolic or ischemic strokes and seizures as they can have a profound impact on the patient’s overall outcome^[42-47]. These complications are related to mode of support, with VV ECMO thought to be safer from thromboembolic stand point. Also sparing of the carotid artery, which remains the most common arterial cannulation site in children with respiratory failure, could contribute to less neurological injury.

In a single center report comparing neonates who survived ECMO, infants treated with VV had significantly lower risk evidence of embolic brain lesions compared to those supported with VA when patients were routinely imaged with MRI^[43]. Similarly analysis of ELSO data for pediatric patients with respiratory failure compared to patients found lower rates of central nervous system radiological injury and seizures for children treated with VV compared to VA, however, reports to ELSO, review clinical data and ascertainment of these complications likely vary by reporting center and asymptomatic patients are not routinely evaluated^[65]. These findings are also similar to reports of patients supported with VA ECMO to treated failed CPR in adults^[66] and children^[67-69].

Surveillance of brain function among pediatric patients supported on ECMO varies. Although most centers routinely follow serial cranial ultrasound studies in infants with an open fontanel, imaging of the brain among older patients is often reserved for patients with new neurological deficits. Thus avoidance of prolonged neuromuscular blockage and minimal sedation when possible enhances neurologic monitoring for frequent patient assessment. However assessment of sedated patients is often difficult, and a quarter of pediatric patients with intracranial pathology detected by CT did not have clinical evidence of neurological compromise^[70].

Rates of other commonly reported complications during ECMO support including renal failure; bleeding and infection differ by support mode. Development of acute kidney injury (AKI) and fluid overload are common

Table 1 Extracorporeal membrane oxygenation limitations and advantages comparing veno venous to veno arterial support

| Factors | Veno venous | Veno arterial |
|-------------------------|---|--|
| Systemic emboli | Lower rate unless intra cardiac shunt present | Increased rate of stroke and seizures with carotid cannulation, risk increases with patient age Limb ischemia with femoral arterial cannulation |
| Cardiopulmonary support | Does not provide direct hemodynamic support Lower systemic oxygenation Increased rate of hypertension during ECMO Usually requires some degree of pulmonary gas exchange and lung recruitment Indirect support with more oxygenated blood provided to pulmonary circulation | Provides full hemodynamic support High systemic oxygenation Non pulsatile flow More commonly used with severe air leak |
| Organ injury | Less acute kidney injury- preserved pulsatile blood flow Less central nervous system injury risk | More acute kidney injury More central nervous system injury risk |
| Monitoring | Mixed venous oxygen saturation less reliable due to recirculation | Reliable mixed venous saturation measurements |
| Bleeding | Increased cannula site bleeding | More bleeding with multiple site cannulation and femoral arterial cannulation compared to carotid |
| Infection | Less risk with percutaneous and single cannula use | Greater rates of infection |
| Rehabilitation | Less sedation use if adequate oxygen delivery possible Mobilization of patients more feasible with single catheter neck catheter | |

ECMO: Extracorporeal membrane oxygenation.

among patients supported on ECMO and especially renal failure is seen more commonly during VA support^[3]. It is impossible to assess how much ECMO support contributes to renal failure distinct from injury related to pre-ECMO events. Overzealous fluid removal with diuretics or continuous renal replacement therapy (CRRT), lack of pulsatile flow with VA support and hemolysis all may contribute to development of renal insufficiency^[71-75]. A recent report by Wolf *et al*^[76] of patients with congenital heart disease supported on ECMO, highlighted that early implementation of CRRT and too aggressive fluid removal may lead to intravascular volume depletion, aggravate AKI and worsen outcome.

As with other modes of mechanical support, ECMO also carries risk of acquired infection during the bypass run. In 2010 the ELSO international summary data reported the incidence of culture-proven bacterial infection increased with age: 6.1 % in neonates, 18.7% in children and 20.5% in adults and was associated with increased mortality^[77,78]. Duration of catheter use, ECMO to support CPR, VA mode were all associated with increased infection risk^[79,80].

Bleeding on ECMO is the most frequently described complication resulting from necessity of continuous anti-coagulation to prevent circuit clotting and thromboembolic events. Surgical cannulation site and other procedural incisions are the most commonly reported bleeding sites. Rollins *et al*^[63] evaluated bleeding from surgical cannula site among pediatric patients receiving ECMO for respiratory failure and reported hemorrhage rates were significantly greater for VV (19%) than VA (15%) but among arterial cannula site rates of hemorrhage were greater in the femoral artery (28%) compared to carotid artery (15%).

Trials off VV support are simplified compared to VA because the oxygenator can be “isolated” from the

patient at full flow by simply removing the gas source. Trials off VA support increase risk of clot development and emboli due to both stasis with lower pump flows, changes in blood volume relative to heparin dosing and flushing the bridge, which leads to turbulent flow. Finally, among patients treated with VA ECMO for respiratory failure, infants, children and adults have higher mortality compared to patients supported with VV^[3,48]; however, this observation is likely confounded at least in part by severity of illness as high need for vasoactive medications and cardiopulmonary arrest immediately preceding initiation of ECMO are viewed by many critical care physicians as a contraindication for VV ECMO use.

OUTCOME/MORTALITY

Because the ELSO registry and other administrative data sets do not systematically collect information regarding disability, hospital mortality is most commonly reported. Among patients treated with ECMO mortality varies by pulmonary diagnosis, underlying condition, other non-pulmonary organ dysfunction as well as patient age^[48,81], but has remained relatively unchanged overall (43%) over the past several decades. Although survival among patients without concurrent non-pulmonary disease has improved, ECMO has increasingly been reserved for medically complex patients with acute other organ failure and/or underlying chronic diseases (Table 2). This is logical as ECMO continues to be a “rescue” therapy and mortality from acute respiratory failure in children has declined concurrent with recognition of successful strategies to decrease VILI as well as other improvements in critical care^[82-84]. Indirect evidence that “gentle” ventilation has been embraced by the pediatric critical care community is provided by the most recent ELSO registry analysis, in which the duration of pre-ECMO mechanical

Table 2 Factors associated with hospital mortality among pediatric patients receiving extracorporeal membrane oxygenation for respiratory failure

| Factors | Increased survival | Increased death |
|---|---|---|
| Age | Younger | Age > 10 yr |
| Pulmonary process | Asthma Viral pneumonia/bronchiolitis Aspiration pneumonia | Pertussis Sepsis Opportunistic infections |
| Organ dysfunction | | Renal failure/dialysis Liver injury Immune impairment/deficiency |
| Severity of ventilator associated lung injury prior to ECMO | | Cardiac arrest prior to ECMO Severe acidosis High mean airway pressure Duration ventilation > 14 d |
| Mode | VV | VA |
| Complications during ECMO | | Infection Stroke Cardiac arrest Organ failure |

VV: Veno venous; VA: Veno arterial; ECMO: Extracorporeal membrane oxygenation.

ventilation was no longer associated with lower survival until ECMO deployment occurred at 2 wk or more after initiation of mechanical ventilation^[48,85].

ECMO use and prognosis in pediatric patients with intractable respiratory failure differs from use in newborns in several obvious (*e.g.*, range of patient size, age, survival) and less obvious ways (reversibility of disease process). Like neonates, use of VV ECMO is increasing but remains less common than VA support. Recent advances in availability of double lumen catheters that decrease recirculation for use in patients of all sizes may continue to enhance use of VV; however, VV cannulation is technically more difficult and associated with increased cannulation site bleeding and flow issues^[65]. VV support should be the default choice for pediatric respiratory failure because central nervous system injury is less common, and recent ELSO analysis did not find increased mortality from a “failed” trial of VV requiring conversion to VA support. Among pediatric patients who require VA, firm recommendations cannot be made regarding arterial site. Although carotid cannulation is avoided in adults due to concern for hemispheric stroke, insufficient data are available in older children to make firm recommendations when children requiring VA support should transition to femoral artery use rather than carotid^[65]. When using the femoral artery for VA ECMO, a bypass graft or reperfusion catheter to maintain adequate limb perfusion is often required.

Other factors associated with increased survival among pediatric ECMO patients with respiratory failure include: young age, obstructive lung diseases compared to restrictive processes (*e.g.*, asthma or bronchiolitis *vs* acute lung injury), and primary lung injury compared to secondary lung injury (*e.g.*, pneumonia *vs* sepsis)^[48,86,87]. Risk of mortality increases for potential ECMO patients with acute respiratory failure if they have either pre-

existing chronic non-pulmonary organ failure or develop additional acute organ failure before or after institution of ECMO. Patients who can tolerate net fluid loss while receiving ECMO support have lower risk of death^[88], while development of renal failure during ECMO has repeatedly been associated with increased mortality^[71-75]. It remains unclear if early fluid removal on ECMO improves outcome. Recently Selewski *et al.*^[75] examined the association between fluid overload and outcomes in pediatric ECMO patients receiving continuous renal replacement therapy (CRRT). Among patients treated with ECMO, 28% received concurrent CRRT and survival was significantly lower (34% *vs* 58%) compared to those not treated with CRRT. However, it is likely that those receiving CRRT had greater severity of illness and greater risk of death.

As expected patients with underlying immune disorders or an active malignancy have lower survival compared to patients with intact immune function^[48]. Although profound immunosuppression was once considered an absolute contraindication, now decisions regarding whether a child is an ECMO candidate include nuisances such as the anticipated duration of neutropenia, other organ failure and ultimate cancer prognosis. Although numbers of patients treated with ECMO after hematopoietic stem cell transplantation are few, some cases have survived to hospital discharge; however, long term cancer survival was not reported.

Complications occurring after institution of ECMO that reflect either inadequate cardiorespiratory support or end organ failure arising from pre-ECMO injury have consistently been associated with increased risk of mortality^[48,87]. Thus care to avoid complications during ECMO may increase survival. Although most pediatric patients with respiratory failure are able to be liberated from ECMO within 3 wk, survival decreases with pro-

longed duration; however, no studies have enumerated factors that clearly predict death and typically support is continued till either complications ensue causing multiple organ dysfunction or pulmonary status improves and the patient can be supported without ECMO. Survival among patients treated with ECMO for longer than 3 wk decreases to 38%.

CARE OF PEDIATRIC RESPIRATORY FAILURE ECMO PATIENTS

Many management aspects of respiratory failure for patients treated with ECMO are not based on medical evidence specific to ECMO care, but mirrors care recommended for similar patients treated without ECMO. However, ECMO does affect management. For instance some medications bind to or interact with the ECMO circuit (*e.g.*, fentanyl) or clearance may be altered by addition of dialysis (*e.g.*, barbiturates) so critical care teams should include expertise from a pharmacologist. Certainly patients must be able to cooperate with care without risk of unplanned medical appliance dislodgement. Some pediatric age patients require high levels of sedation; however, when possible neuromuscular blocking agents (NMBA) should be avoided and sedation minimized to allow spontaneous coughing, optimize respiratory secretion clearance and decrease respiratory and peripheral muscle de-conditioning. In addition, reduced use of deep sedation and NMBA will allow better assessment of patient neurological status^[62,89]. As with survivors of any critical illness, ECMO survivors may be left with significant psychological and functional disabilities^[90]. Recently more attention is paid to early recognition of possible neurological injury which should lead to early implementation of rehabilitation. Although implementation of physical therapy (PT) for patients while still on ECMO is very challenging due to increased risk of acute decompensation, medical device dislodgement, some authors suggest use of simple PT interventions to avoid motor and cardio-respiratory deconditioning^[91]. Reports from multiple centers show that cooperative patients can assist with mobility including pulmonary rehabilitation while on ECMO without high risk of appliance movement and that prone positioning is routinely possible in pediatric patients^[91-94]. However, it is unclear which components of rehabilitation are essential to maintain and improve functional outcomes (*e.g.*, passive limb range of motion, splinting, active limb exercises/strengthening, ambulation) are not known. If tolerated by the patient, rehabilitation should be continued through post-ECMO hospitalization period and following hospital discharge^[94].

No studies have evaluated optimal nutrition goals, but many critical care providers consider enteral feeds preferable to intravenous nutrition. Our center routinely uses trans pyloric feeding tubes rather than nasogastric to decrease risk for aspiration of formula. The optimal transfusion threshold during ECMO also remains unclear. Especially for patients treated with VV ECMO,

providers must weigh potential benefits from increased oxygen deliver and potential harm from increased fluid overload. Recent trends in both adult and pediatric critical care medicine have found similar patient outcomes with lower red blood cell administration thresholds^[95,96]. Many providers now accept lower transfusion thresholds (hgb > 10 g/dL) for ECMO pediatric patients with normal arterial saturations but maintain higher thresholds for desaturated patients. Trending mixed venous desaturation is an additional measure to aid transfusion decisions. If the mixed venous saturation increases after a transfusion then a higher hemoglobin concentration may provide physiologic benefit. However, ECMO patients who tolerate fluid loss either using diuretics or hemoconcentration have higher rates of survival^[88,97].

The mechanical ventilator strategy for respiratory ECMO should limit VILI^[98-100]. Maintaining lung recruitment is ideal unless severe air-leak syndrome has developed, our practice is to reduce positive end expiratory pressure till the leak is minimized. Otherwise, PEEP is maintained and a low stretch ventilation strategy initiated as the circuit removal of carbon dioxide is efficient. No studies have compared conventional to high frequency oscillation ventilation in ECMO patients but patient care and avoidance of NMBA is easier to achieve during conventional ventilation.

Other care should be directed to decrease complications. Because they are intensively monitored ECMO patients have increased risk of catheter associated blood stream infections^[101] and other nosocomial infections. Development of other organ failure substantially increases mortality. ECMO should be removed as soon as pulmonary compliance and gas exchange have improved and the patient can be maintained on non-toxic ventilator settings.

CONCLUSION

ECMO continues to be used as a rescue therapy for increasingly complex pediatric patients with respiratory failure. VV ECMO should be the used as the default mode due to lower complication rates and many aspects of ideal care remain unstudied. Linkage of the ELSO dataset with other databases or collaborative research networks will be required to address this knowledge deficit as most centers treat only a few pediatric respiratory failure patients each year.

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Neurologic complications and neurodevelopmental outcome with extracorporeal life support

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Abstract

Extracorporeal life support is used to support patients of all ages with refractory cardiac and/or respiratory failure. Extracorporeal membrane oxygenation (ECMO) has been used to rescue patients whose predicted mortality would have otherwise been high. It is associated with acute central nervous system (CNS) complications and with long-term neurologic morbidity. Many patients treated with ECMO have acute neurologic complications, including seizures, hemorrhage, infarction, and brain death. Various pre-ECMO and ECMO factors have been found to be associated with neurologic injury, including acidosis, renal failure, cardiopulmonary resuscitation, and modality of ECMO used. The risk of neurologic complication appears to vary by age of the patient, with neonates appearing to have the highest risk of acute central nervous system complications. Acute CNS injuries are associated with increased risk of death in a patient who has received ECMO support. ECMO is increasingly used during cardiopulmonary resuscitation when return of spontaneous circulation is not achieved rapidly and outcomes may be good in select populations. Economic analyses have shown that neonatal and adult respiratory ECMO are cost effective. There have been several intriguing reports of active physical rehabilitation of patients during

ECMO support that is well tolerated and may improve recovery. Although there is evidence that some patients supported with ECMO appear to have very good outcomes, there is limited understanding of the long-term impact of ECMO on quality of life and long-term cognitive and physical functioning for many groups, especially the cardiac and pediatric populations. This deserves further study.

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Key words: Respiratory failure; Cardiopulmonary resuscitation; Pediatrics; Extracorporeal life support; Congenital heart disease; Stroke

Core tip: Extracorporeal life support is used to support patients of all ages with refractory cardiac and/or respiratory failure. It is associated with acute central nervous system complications and with long-term neurologic morbidity. Many patients treated with extracorporeal membrane oxygenation (ECMO) have acute neurologic complications, including seizures, hemorrhage, infarction, and brain death. In this review paper, we review the incidence of and factors associated with neurologic complications associated with the use of ECMO and the associated long term neurologic outcomes of patients treated with ECMO.

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INTRODUCTION

Extracorporeal life support (ECLS) is used to provide pulmonary, cardiac, or cardiopulmonary support in neonate, pediatric, and adult patients refractory to con-

ventional management. Deployment of ELCS may be planned, urgent/emergent, or associated with cardiopulmonary resuscitation (ECPR). Various cannulation strategies exist with the dominant differentiating factor being veno-venous (VV) vs veno-arterial (VA) circuits. Survival has improved since extracorporeal membrane oxygenation (ECMO) was first utilized in the 1970s and indications and populations supported have expanded as techniques and strategies of deployment have evolved.

Patients supported by ECLS are at risk of neurologic injury from pre-ECLS factors including hypoxia, acidosis, hypotension and low cardiac output, infection, and organ failure, and from ECLS factors including hemorrhage, infarction, seizures, disrupted cerebral circulation, and development of new organ failure. Functional outcome after critical care, including ECLS support, is difficult to assess on a systematic basis, as follow up studies are limited and not standardized. Although children and adults are treated with ECMO, nearly 50% of treated patients are neonates^[1] and assessing their long-term outcomes requires both time and an appropriate comparison population to account for severity of illness and social factors^[2,3]. Neurodevelopmental and longitudinal outcomes after ECLS are most important to assess but are largely limited to neonatal and limited adult studies. More information is available on the incidence and risk factors for acute neurologic complications associated with ECLS.

The Extracorporeal Life Support Organization (ELSO) collects utilization, mortality, and complication data from 200 centers internationally on all technologies used to support cardiopulmonary function. Acute neurologic complications (seizures, infarction, hemorrhage, and brain death) are reported but functional outcome or disability is not. Administrative databases such as the Pediatric Health Information System or the Kids Inpatient Database also collect complication diagnoses but do not collect functional outcome specifically. Most reports of functional outcome after ECMO support are from single centers or multiple centers over a small time period^[4-9].

ANATOMY AND PHYSIOLOGY OF NEUROLOGIC INJURY ASSOCIATED WITH ECLS

Neurologic injury associated with ECLS ranges from subtle neurocognitive defects to devastating intracranial hemorrhage to brain death. Injury may be sustained prior to ECLS support, during ECLS support, or after ECLS support has been discontinued. Neurologic complications reported to ELSO include hemorrhage and infarction documented by ultrasound and or computed tomography, clinical seizures, EEG documented seizures, and brain death (Table 1). The incidence of complications may be underreported due to the difficulty of obtaining reliable imaging in critically ill patients during extracorporeal support, and many patients who sustain

neurologic injury likely have increased risk of death and may die without imaging^[10-12].

Hemorrhage is generally poorly tolerated due to the anti-coagulation that is needed during ECLS support. Most common hemorrhagic injuries include intraventricular, intracerebral, and subdural hemorrhages. Risk factors for intraventricular hemorrhage have been most clearly demonstrated in neonatal patients^[13]. Intracerebral hemorrhages are thought to be at significant risk of extension due to anti-coagulation but there is little published information on the natural history of intracranial pathology during ECMO^[14].

Infarctions may be small and related to micro emboli of clot or air, or may be large and related to large embolic clots. The incidence of image documented infarction is roughly similar to that of hemorrhage. Clinical seizures occur in 5%-10% of neonatal and pediatric patients, and 1%-2% of adult patients^[1]. The difference between the adult and pediatric incidence of seizures may be related to trends in VV versus VA cannulation techniques^[12] or may be due to relative sparing of cerebral vessels given that adults are more likely to be cannulated through femoral vessels or may be due to increase likelihood of infants to seizures due to developmental vulnerability^[15].

Hypoxic ischemic damage due to poor cardiac output or acidosis prior to, during, or after mechanical support is difficult to quantify and makes outcome studies difficult to interpret in the absence of appropriate control groups.

HISTORICAL TRENDS

ECMO was developed in the 1970's and although the first reported case was an adult, the first series of neonates^[16,17] reported success whereas the first series of adults reported dismal survival (9%)^[18]. It became clear that ECMO was efficacious for patients with reversible disease and that prematurity or other risk factors for bleeding posed a significant risk. The importance of early recognition of intraventricular hemorrhage in neonates became evident. It appears that after the first week of life premature infants have reduced risk of intracranial hemorrhage^[19].

Neonatal respiratory ECMO volume peaked in the early 1990s and has remained relatively stable since the early 2000's. Overall survival has diminished likely reflecting advances in standard therapies and application of ECMO to more diverse and ill patients. Neonates with congenital diaphragmatic hernia continue to be a high-risk group with high mortality among respiratory patients. The majority of neonatal respiratory ECMO support is VA. Pediatric respiratory ECMO has increased substantially in the past 3 decades with a peak in 2009 coincident with the H1N1 influenza pandemic. About half of pediatric respiratory ECMO support is VA but there is increasing utilization of VV support modes. Adult ECMO was rarely performed until late in

Table 1 Survival and cumulative incidence of neurologic complications by age and indication for extracorporeal membrane oxygenation (Extracorporeal Life Support Organization 2013)

| | Cumulative survival to discharge or transfer | 2012 survival to discharge or transfer | Clinical seizures | Central nervous system hemorrhage |
|-------------|--|--|-------------------|-----------------------------------|
| Neonatal | | | | |
| Respiratory | 75% | 69% | 9.20% | 7.10% |
| Cardiac | 40% | 45% | 7.20% | 11.10% |
| ECPR | 39% | | | |
| Pediatric | | | | |
| Respiratory | 56% | 58% | 5.70% | 6.00% |
| Cardiac | 49% | 55% | 6.80% | 4.90% |
| ECPR | 41% | | | |
| Adult | | | | |
| Respiratory | 55% | 57% | 1.10% | 4.00% |
| Cardiac | 39% | 39% | 2.00% | 2.00% |
| ECPR | 28% | | | |

ECPR: Extracorporeal membrane oxygenation support initiated during cardiopulmonary resuscitation.

the 2000s and has also increased substantially in 2009, with further increases since. The significant majority of adult ECMO support is VV.

ECMO support for cardiac indications in all age groups has increased steadily since the early 1990s^[1]. ECPR was first described in 1992^[20] and its application has expanded substantially in the past several years though indications remain controversial.

NEUROLOGIC COMPLICATIONS AND NEURODEVELOPMENTAL OUTCOME BY AGE GROUP

Neonatal

Neonates have the highest rate of neurologic complications when examining the ELSO reports by patient age. Cumulative ELSO data on neonates who undergo ECMO for respiratory support report a 9.2% incidence of clinical seizures and a 7.1% incidence of intracranial hemorrhage^[1]. Neonates who are undergoing support for cardiac indications have a 7.2% incidence of seizures and an 11.1% incidence of hemorrhage. An initial assessment of risk factors for intracranial hemorrhage included lower gestational age, sepsis, acidosis, coagulopathy, and inotropic support^[13]. Gestational age less than 34 wk has repeatedly been associated with unacceptably high rates of intracranial hemorrhage^[13,17]. In a recent analysis of the ELSO registry^[21], for those neonatal patients supported with ECMO from 2005-2010, a 20% incidence of neurologic complications was noted. Risk factors for neurologic complications included birth weight less than three kg, gestational age less than 34 wk, need for CPR, acidosis, and use of VA ECMO support.

Studies of long-term neurodevelopmental outcomes of infants who undergo ECMO support suggest that impairment is similar to that of comparable conventionally treated infants. Single institutions series have noted impairment or disability in 20%-50% of surviving infants^[4,22,23]. Factors that may influence the determination of disability include differences in socioeconomic status

of those who complete follow-up^[4], time from ECMO support to evaluation^[22], and institutional selection criteria. Long-term outcome studies highlight the changing neurologic function over time, with some initial disabilities likely resolving, and new more subtle learning and language deficits emerging. The 1996 United Kingdom collaborative randomized trial of neonatal ECMO versus conventional management^[24] demonstrated similar proportions of survival without disability at seven years of age, and overall severe disability is less common than that in earlier reports. Sensorineural hearing loss is increasingly recognized as an important consequence of ECMO^[23,25]. Sensorineural hearing loss has been found to be associated with pre-ECLS seizures^[26].

In neonates treated with ECMO, those with seizures were found to have lower IQ at preschool age than those without seizures^[27]. In another small group of neonatal ECMO patients, seizures were found to be a risk factor for the subsequent development of cerebral palsy or developmental delay^[28].

An understanding of baseline characteristics of patients undergoing ECMO including ECPR is critical to any evaluation of outcome. Patients who receive ECMO support have generally had periods of serious illness including underlying congenital heart disease or hypoxemia which may play an important role in modifying outcome. Long-term neurodevelopmental outcomes of children who undergo cardiopulmonary bypass for congenital heart disease reveal a range of outcomes including mild cognitive and psychomotor delays^[29,30] as well as speech and language abnormalities^[31] in a substantial proportion of survivors. Newborns with congenital heart disease have brain abnormalities including white matter injury prior to cardiac surgery^[32].

Pediatric

Pediatric ECMO patients represent a population of patients that are substantially more varied than the neonatal group. Cumulative ELSO data on pediatric patients who undergo ECMO for respiratory support report a 5.7% incidence of clinical seizures and a 6% incidence

of intracranial hemorrhage. Pediatric cardiac ECMO patients have a slightly greater incidence (6.8%) of clinical seizures and a 4.9% incidence of hemorrhage^[1]. Acute neurologic complications including CNS hemorrhage or infarct, and EEG-determined or clinically determined seizures are associated with reduced hospital survival^[1,14]. Similar to neonates, risk factors for severe CNS complications in pediatric patients include metabolic acidosis, inotrope or vasopressor requirement, renal failure, cardiopulmonary resuscitation, or left ventricular assist device prior to initiation of ECMO^[33].

There is little data on long-term neurodevelopmental outcomes in the extremely heterogeneous pediatric ECMO population^[7]. Zabrocki *et al.*^[34] demonstrated that over a 15-year period from 1993-2007 the survival of pediatric patients supported for respiratory indications did not change, but ECMO was offered to increasingly medically complex patients, which could easily confound assessments of disability after ECMO.

Adult

Adults comprise the smallest, though growing, population of ECMO patients. Cumulative ELSO data on adult patients who undergo ECMO for respiratory support report a 1.1% incidence of clinical seizures and a 4% incidence of intracranial hemorrhage. Adults supported for cardiac indications have a 2% incidence of seizures and a 2% incidence of intracranial hemorrhage^[1]. The lower incidence of severe CNS complications may be due to patient factors, selection factors, or technical factors. Adult patients are almost exclusively supported with VV ECMO and this has been shown to lower the rate of neurologic complications in pediatric patients^[12] although this association may not remain consistent in adults^[35]. When adult patients are supported with VA ECMO, cannulation of the cervical vessels is avoided, which may decrease the incidence of neurologic complications.

As for pediatric patients there is relatively little long-term functional outcome data for adult patients. The CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory Failure) trial, demonstrated no difference in severe disability of any measure of health care quality between patients randomized to the consideration for ECMO group versus the control group^[36].

Cardiac and ECPR outcome

The use of ECMO to support low cardiac output, failure to wean from bypass, or cardiac arrest has been steadily increasing for the past 20 years and during that time the use of ECPR has emerged as an important strategy. Although somewhat variable year to year, overall survival of ECMO for cardiac indications has not shown definitive trends over time and cumulative ELSO survival now averages 39% in adults, 49% in pediatric patients, and 39% in neonates. ECPR survival is slightly lower at 28% in adults, 41% in children, and 39% in neonates^[1]. ECPR survival does not appear to have changed significantly over time^[37,38].

The incidence of major neurologic morbidity in cardiac patients as reported to ELSO is highest in neonates, with 7.2% suffering seizures, 3.5% infarction, and 11.1% intracranial hemorrhage. Children have slightly lower incidence of seizures and hemorrhage and a slightly higher incidence of infarction. Adults have the lowest incidence of major neurologic morbidity with 2% suffering seizures, 3.7% infarction, and 2% hemorrhage. In all age groups those patients who suffer major neurologic complications have a lower hospital survival^[1].

Several single institution studies have reported neurologic outcomes after cardiac ECMO^[5,6,39-42]. Evaluations included chart review, telephone interviews, and neurodevelopmental testing but no studies that performed detailed neurologic and neurodevelopmental testing included control groups of normal infants or of infants who had similar cardiac defects or illnesses. Hospital survival was similar to that reported by ELSO and all series had patients who died following discharge and who were lost to follow-up. Time to evaluation was extremely variable ranging from months to years within individual cohorts. Those studies that performed detailed neurodevelopmental assessments^[6,42] found 50% incidence of moderate to severe cognitive delay and 12%-25% incidence of neuromotor delay among long term survivors. Predictors of poor cognitive outcome included time to normalization of lactate, highest inotrope score, and chromosomal abnormality. As previously discussed, pre-morbid characteristics of cardiac patients undergoing ECMO support are critical to assessment of outcomes.

Significant neurologic complications during ECPR are more prevalent than during other support strategies, with a 12% incidence of seizures, 11.8% incidence of radiologic evidence of infarct or hemorrhage, and 11% incidence of brain death in one evaluation of the ELSO database^[37]. Infarction or hemorrhage but not seizures were more common in nonsurvivors than survivors. Further evaluation of this data revealed that risk factors for major neurologic complication included acidosis, non-cardiac disease, pulmonary hemorrhage, need for dialysis, and CPR while on ECMO^[11]. In this analysis, there was a trend towards less neurologic injury over time.

Limited long-term neurologic and neurodevelopmental outcome after ECPR data are available from several single institution series^[38,43-48]. In these series survival to hospital discharge ranges from 33%-74%, with most ranging from 33%-41%. Some studies reported neurologic outcome based on chart review and some assigned Pediatric Cerebral Performance Category (PCPC) and Pediatric Outcome Performance Category (POPC) scores. None reported detailed neurodevelopmental evaluations^[49] but the PCPC and POPC scores have been rigorously validated^[50]. An early series^[43] reported no change from baseline POPC or PCPC in 50% of patients, and several authors^[38,46,48] reported post ECPR PCPC scores of 1-2 (normal or mild cerebral disability) in 3/4 of patients. A recent analysis of the National

Registry of Cardiopulmonary Resuscitation confirms favorable [PCPC 1-3 (normal, mild cerebral disability or moderate cerebral disability)] neurologic outcomes in at least 64% and up to 95% of ECPR survivors^[51]. This is similar to an analysis of the National Registry of Cardiopulmonary Resuscitation database, which showed the outcome of pediatric survivors of in hospital cardiac arrest, where the overall hospital survival was lower than that usually reported for ECPR (27%) but 65% of surviving patients had good neurologic outcome^[52].

The effect of duration of CPR on outcome, either survival or neurodevelopmental outcome is difficult to determine. Several studies report no correlation between duration of CPR and survival^[38,43,44,51] and several report remarkable grossly normal survival after prolonged (> 60 min of CPR) in a few patients^[43,46,51], yet this is not a universal finding^[47]. Cardiac disease as the indication for ECPR appears to improve the odds of survival^[51]. In general the term ECPR is reserved for those patients who do not achieve return of spontaneous circulation (ROSC) prior to cannulation. When evaluating these studies it is important to consider that the decisions to perform ECPR vary considerably between institutions and are not standardized. The development of rapid deployment teams, which could cannulate during CPR or after ROSC may lead to improved outcomes^[53]. As with any form of ECMO support the premise of reversible disease as a prerequisite for ECMO support must be kept in mind.

QUALITY OF LIFE ASSESSMENT

Increasingly quality of life and functional and school related outcomes are appreciated as important indicators of the efficacy of critical care. Several reports have described relatively subtle cognitive, physical, and school related problems in survivors of pediatric critical care. A recent report showed that pediatric survivors of critical illness had verbal, spatial, and memory problems, attention and problem solving difficulty, and school performance following paediatric intensive care unit (PICU) admission^[54]. A different study evaluated health care related quality of life and adaptive behavior functioning and found it to be significantly reduced in survivors of urgent PICU admission^[55]. In this study prolonged ECMO support was one factor associated with reduced quality of life.

Looking at the issue of quality of life differently, a study that looked at patients with prolonged ICU stays (> 28 d) found that the majority of children (57%) had a normal quality of life, with 22.9% having impaired quality of life and 20% having poor quality of life^[56]. In a single institution cohort of cardiac ECMO survivors physical health related quality of life was lower than that of the general population but similar to those with complex congenital heart disease. Psychosocial quality of life as reported by parents and by older surviving patients was similar to that of the general population^[8].

There have been relatively few analyses of the cost-effectiveness of ECMO but there have been some positive reports. The United Kingdom Collaborative ECMO Trial was a randomized, controlled trial of neonatal respiratory ECMO. Over 7-year follow-up of enrolled subjects they found an incremental cost per disability-free life year gained to be below the nationally acceptable threshold^[24]. Similarly the CESAR trial found referral to an ECMO center to be cost effective when evaluated in terms of quality of life year expense^[36]. In a single institution evaluation of ECPR for patients with congenital heart disease, ECMO was found to be within acceptable cost efficacy^[57].

TECHNICAL ISSUES INFLUENCING NEUROLOGIC OUTCOME

Along with evolving indications for ECMO, the support and monitoring technology has changed dramatically over the past 30 years. Most recently newer dual lumen VV cannulas for respiratory support have been introduced and centrifugal pumps are increasingly being used to support pediatric patients. There have been advances in anticoagulation strategies as well as the development of more biocompatible circuits and oxygenators. Near infrared spectroscopy monitoring is increasingly being used during ECMO support. With the exception of a VV cannulation strategy none of these technologies has yet been shown to improve neurologic outcome^[34].

REHABILITATION

An intriguing development in the care of the ECMO patient is the concept of active rehabilitation during ECMO support. Critical illness of any sort leads to deconditioning due to immobility and this is especially problematic with highly invasive support technologies. If patients can be exercised and kept mobile during mechanical support they may be more able to progress quickly once liberated from invasive support. There have been several small series of patients who received active physical or occupational therapy, advancing to ambulation, while undergoing ECMO support^[58-60]. Thus far this strategy has been limited to older patients supported for respiratory indications, almost exclusively with single dual lumen catheters.

CONCLUSION

Neurologic outcomes after ECMO support vary by patient age, type of support, indications for support, and underlying diagnosis. There are not widely accepted standards for initiation of ECMO outside of the neonatal respiratory population so severity of illness and underlying conditions among patients supported by ECMO may vary widely between institutions. Acute severe neurologic complications are more prevalent in neonates and children than adults. The long-term impact of ECMO sup-

port on development, school performance, and quality of life is poorly defined and needs further study. Where it has been evaluated, ECMO appears to be cost effective.

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Molecular targeting therapy using bevacizumab for peritoneal metastasis from gastric cancer

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Author contributions: Aoyagi K was responsible for writing and revising the full text original article in response to an invitation from an editorial office member of the *WJCCM*; Kouhuji K instructed the research and clinical work; Miyagi M established the high potential peritoneal dissemination cell line MKN-45P; Kizaki J cultured the two cell lines and measured the concentration of various cytokines; Isobe T performed the *in vivo* study on the peritoneal dissemination model using nude mice; Hashimoto K performed the pathological study on the intra-abdominal tumor of nude mice; and Professor Shirouzu K, Chair of the Department of Surgery, provided useful critique and advice for our research.

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of peritoneal metastasis.

RESULTS: The concentrations of interleukin-6 (IL-6), IL-8, VEGF and matrix metalloproteinase-2 protein in the culture supernatant were each significantly higher than each of those for MKN-45. In the *in vivo* study, the volume of ascites and the mitotic index were significantly lower in the therapy group than in the non-therapy group. The survival curve of the therapy group was significantly higher than that of the non-therapy group. These results suggested that VEGF was correlated with peritoneal metastasis from gastric cancer.

CONCLUSION: Findings suggested that bevacizumab for inhibiting VEGF could suppress peritoneal dissemination from gastric cancer.

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Key words: Gastric cancer; Peritoneal metastasis; Vascular endothelial growth factor; MKN-45P; Bevacizumab

Abstract

AIM: To clarify the significance of vascular endothelial growth factor (VEGF) in peritoneal metastasis from gastric cancer, using the gastric cancer cell line MKN-45 compared with the high potential peritoneal dissemination gastric cancer cell line MKN-45P.

METHODS: The supernatant of culture medium of MKN-45 cells or MKN-45P cells was collected and the concentrations were measured of various cytokines, matrix metalloproteinases, growth factor and angiogenic factors, including VEGF. We performed an initial pilot study to explore whether bevacizumab, a humanized monoclonal antibody against VEGF, had any suppressive effect on the peritoneal dissemination from gastric cancer in an experimental nude mouse model

Aoyagi K, Kouhuji K, Miyagi M, Kizaki J, Isobe T, Hashimoto K, Shirouzu K. Molecular targeting therapy using bevacizumab for peritoneal metastasis from gastric cancer. *World J Crit Care Med* 2013; 2(4): 48-55 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v2/i4/48.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v2.i4.48>

INTRODUCTION

Peritoneal metastasis is the most common form of recurrence from gastric cancer and is associated with a poor prognosis. Therefore, the management of any dissemination in the peritoneal cavity is important in the treatment of gastric cancer. However, there is as yet no effective treatment against peritoneal metastasis from gastric cancer. The development of peritoneal metastasis

is a multistep process, beginning with the detachment of cancer cells from the primary tumor, their attachment to peritoneal mesothelial cells, retraction of the mesothelial cells, and exposure of the basement membrane. After attachment to the basement membrane, the cancer cells degrade in the extracellular matrix and then proliferate^[1-3]. Finally, the cancer cells induce angiogenesis and lymphangiogenesis. Many cytokines, growth factors, matrix metalloproteinases and angiogenic factors play important roles in these steps. Tumor growth requires new vessel formation and this is driven predominantly by vascular endothelial growth factor (VEGF), the most potent angiogenic molecule known and the principle target for antiangiogenic therapy. VEGF levels in malignant ascites are remarkably elevated^[4]. VEGF has been reported to enhance vascular permeability and angiogenesis in the abdominal wall and contributes to the establishment of peritoneal dissemination with malignant ascites^[4,5]. In ovarian cancer, three pathological events are thought to cause malignant ascites: obstruction of the lymphatic vessels by tumor cells inhibiting lymphatic drainage from the peritoneal cavity; hyperpermeability of microvessels lining the peritoneal cavity; and angiogenesis^[6]. In gastric cancer, there was a tendency for the tumor/normal ratio of VEGF mRNA to be correlated with distant metastasis^[7] and positive expression of tissue VEGF, circulating VEGF, VEGF-C and VEGF-D were each associated with poor prognosis in resected gastric cancer^[8]. We have previously reported that tissue VEGF was a useful indicator of peritoneal recurrence of gastric cancer^[9]. The aim of the present study was to clarify the significance of VEGF in peritoneal metastasis from gastric cancer. We compared cytokines, matrix metalloproteinases (MMPs) and VEGF in the gastric cancer cell line MKN-45 and in the high potential peritoneal dissemination gastric cancer cell line MKN-45P, using an enzyme-linked immunosorbent assay (ELISA) method. Furthermore, we investigated whether administration of VEGF antibody could prevent peritoneal metastasis from gastric cancer. Bevacizumab is a humanized monoclonal antibody against VEGF and was the first commercially available angiogenesis inhibitor. We investigated whether bevacizumab had a suppressive effect on peritoneal dissemination from gastric cancer, experimentally, using a mouse peritoneal metastasis model.

MATERIALS AND METHODS

Cell lines

We used the high potential peritoneal dissemination cell line MKN-45P, established from the human gastric cancer cell line MKN-45 (derived from a poorly differentiated adenocarcinoma in a 62 year old woman; Health Science Research Resources Bank, Tokyo, Japan) in our institute, as described previously^[10]. Briefly, nude mice (BALB/c nu/nu) were subcutaneously inoculated with MKN-45 cells and the subcutaneous nodules were removed and injected into other nude mice intraperito-

neally. The cancer cells from the peritoneal nodules were injected into the abdominal cavity of other mice. The process was continued through to a seventh generation. The resulting high potential peritoneal dissemination cell line was named MKN-45P. MKN-45 and MKN-45P cells were each maintained in RPMI-1640 medium (Nihon Seiyaku Co., Komaki, Aichi, Japan) supplemented with 10% heat inactivated fetal bovine serum (FBS) (Gibco Uxbridge, Middlesex, United Kingdom), 2 mmol/L-glutamine and penicillin-streptomycin (50 IU/mL and 50 µg/mL, respectively) at 37.0 °C in humidified air with 5% CO₂.

Measurement of cytokines in conditioned medium

For measurement of cytokines in conditioned medium, the MKN-45 cells (1×10^6 cells/10 mL) or MKN-45P cells (1×10^6 cells/10 mL) were placed in 100 mm tissue culture dishes (IWAKI Co., Funabashi, Chiba, Japan) and cultured for 72 h in medium containing 10% FBS at 37.0 °C in humidified air with 5% CO₂. The number of cells in each cell line was evaluated visually at 12, 24, 48 and 72 h (values: mean of three fields). The supernatant was then collected and the concentrations of interleukin-1β (IL-1β), IL-6, IL-8, IL-10, hepatocyte growth factor (HGF), transforming growth factor-β1 (TGF-β1), VEGF, MMP-2, MMP-9 and tissue inhibitor of metalloproteinases-1 (TIMP-1) proteins were each measured using the ELISA method (IL-1β, IL-8 and IL-10: Bio Source Europe S. A., Nivelles, Belgium; IL-6: Fujirebio Inc., Tokyo, Japan; HGF: Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan; TGF-β1 and VEGF: RD System Inc., Minneapolis, MN, United States; MMP-2, MMP-9 and TIMP-1: Daiichi Fine Chemical Co. Ltd., Takaoka, Toyama, Japan). Each cytokine was measured in 5 samples and the means of these were compared between the MKN-45 cells and the MKN-45P cells.

Animals

4 wk old athymic male BALB/c nu/nu nude mice, each weighing 18 g, were obtained from CLEA (Tokyo, Japan). The mice were housed in cages under specific pathogen-free conditions and provided with sterilized food and water ad libitum.

Drugs

The humanized murine monoclonal antibody against human VEGF (bevacizumab, Avastin) was purchased from Genetech (San Francisco, CA, United States).

Experimental design

The experimental group consisted of 5 wk old male mice ($n = 10$). We determined a working concentration of bevacizumab according to Wildiers *et al.*^[11]. On day 0, we injected 1×10^7 MKN-45P cells into the abdominal cavity of each mouse, followed by a single intraperitoneal (ip) injection of 200 µg bevacizumab in 1 mL saline on day 0 and day 4. On day 21, five mice were sacrificed under ether anesthesia; these were weighed and then we

Table 1 Comparison of cytokines between MKN-45 and MKN-45P

| | IL-1 β (pg/mL) | IL-6 (pg/mL) | IL-8 (pg/mL) | VEGF (pg/mL) | MMP-2 (ng/mL) | TIMP-1 (ng/mL) |
|---------|----------------------|---------------|-------------------|--------------------|---------------|----------------|
| MKN-45 | 0.9 \pm 0.7 | 1.2 \pm 0.7 | 381.9 \pm 147.1 | 1335.0 \pm 624.3 | 0.3 \pm 0.1 | 2.7 \pm 1.8 |
| MKN-45P | 0.4 \pm 0.2 | 2.9 \pm 0.6 | 891.4 \pm 210.2 | 3806.0 \pm 229.8 | 0.7 \pm 0.5 | 6.0 \pm 4.0 |
| P value | 0.109 | 0.045 | 0.011 | 0.013 | 0.021 | 0.126 |

IL: Interleukin; VEGF: Vascular endothelial growth factor; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase.

calculated the mean number of tumor nodules in a 1 cm² area in three fields on the mesentery and calculated the volume of ascites. We also extracted retroperitoneal tissues for histological examination. Another five mice were monitored until they died and the survival rate was calculated using the Kaplan-Meier method. A matching number of control mice were given 1 mL of drug-free saline.

Histology

After extraction, the retroperitoneal tissues were fixed for 12 h in 10% neutral buffered formaldehyde, then cut every 5 mm horizontally and embedded in paraffin. Paraffin sections were stained with hematoxylin-eosin (HE) and examined using light microscopy. We counted the frequency of hydronephrosis on the retroperitoneal tissues. The mitotic index was defined as the mean number of mitotic figures in a 400 times magnified field from ten arbitrary microscopic fields.

Immunohistochemistry

VEGF was analyzed using immunohistochemical staining and the avidin-biotin-peroxidase complex technique (Vectastain ABC Kit; Vector, Burlingame, CA, United States). Briefly, 3 μ m thick sections of the formalin-fixed paraffin-embedded tissue specimens were deparaffinized and dehydrated. The sections were washed with phosphate-buffered saline (PBS), treated with 0.3% hydrogen peroxide in methanol for 30 min to block endogenous peroxidase, and then incubated with primary antibody in a humidified chamber at 4 °C overnight. As the primary antibody, rabbit polyclonal antibody A-20 was used (Santa Cruz Biotechnology, Santa Cruz, CA, United States) for VEGF, diluted at 1:200. Sections were washed three times with PBS, then incubated with biotinylated horse anti-rabbit immunoglobulin G antibody for 30 min, washed again three times with PBS, and then incubated with avidin-biotinylated peroxidase complex for 30 min. After three additional washings with PBS, staining was developed by incubating the sections in 3-amino-9-ethylcarbazole (Vector) for 5 min. The sections were then counterstained with hematoxylin and mounted. The cell types showing positive staining for VEGF were defined morphologically by H and E staining, using serial sections. VEGF expression was classified as one of three categories using a method modified from the literature that was previously used on gastric tissue^[9], depending on the percentage of tumor cells stained: category 1 being less than 30% of cells stained; category 2 being from

30% to 49% stained; and category 3 being 50% or more cells stained.

Ethics

This study was approved by Kurume University Institutional Animal Care and Use Committee of Ethics.

Statistical analysis

Student's *t*-test and the χ^2 test were used to analyze the data for any significant difference and any difference was considered statistically significant when the *P* value was less than 0.05. The cumulative survival rate was calculated using the Kaplan-Meier method. The significance of any difference between the survival curves was determined using the log-rank test and any difference was considered significant at the 5% level.

RESULTS

Measurement of cytokines in condition medium

The number of MKN-45 or MKN-45P cells was counted at 24, 48 and 72 h. There was no difference in the number of cancer cells between the two cell lines. The concentrations of cytokines in conditioned media from MKN-45 and from MKN-45P are shown in Table 1. The concentrations of IL-6, IL-8, VEGF and MMP-2 protein in the culture supernatants from MKN-45P were each significantly higher than each of those from MKN-45 (*P* = 0.045, *P* = 0.011, *P* = 0.013 and *P* = 0.021, respectively) (Table 1).

Peritoneal dissemination model

Peritoneal dissemination with bloody ascites was recognized in all five mice using the MKN-45P cell line (Figure 1A). Numerous nodules were seen on the mesentery (Figure 1B). We confirmed histologically that the nodule in the peritoneum was composed of cancer cells. All five mice in the non-therapy group were cachectic; however, there was no significant difference in body weight (*P* = 0.591) and no difference in the number of peritoneal nodules (*P* = 0.783) between the therapy and non-therapy group. The volume of ascites in the therapy group was significantly less than that in the non-therapy group (*P* = 0.042). No side-effects of bevacizumab were evident, such as bleeding, bowel perforation or thrombosis (Table 2).

Histopathological findings

In the therapy group, two right kidneys (40%) and one

Table 2 Number of tumor nodules, volume of ascites, body weight, frequency of hydronephrosis and mitotic index in the mice treated with bevacizumab and the untreated mice

| Treatment | n | Tumor nodules | Ascites (mL) | Body weight (g) | Hydronephrosis | | Mitosis index |
|-------------|---|---------------------------|--------------------------|---------------------------|----------------|-------------|-------------------------|
| | | | | | Right kidney | Left kidney | |
| Non-therapy | 5 | 16.64 ± 5.06 ¹ | 0.60 ± 0.51 ² | 12.21 ± 0.51 ³ | 4 (80) | 2 (40) | 21.0 ± 5.7 ^b |
| Therapy | 5 | 17.66 ± 3.45 | 0.04 ± 0.03 | 12.41 ± 0.61 | 2 (40) | 1 (20) | 9.6 ± 2.1 |

¹P = 0.783; ²P = 0.042; ³P = 0.591; ^bP < 0.01 *vs* therapy group.

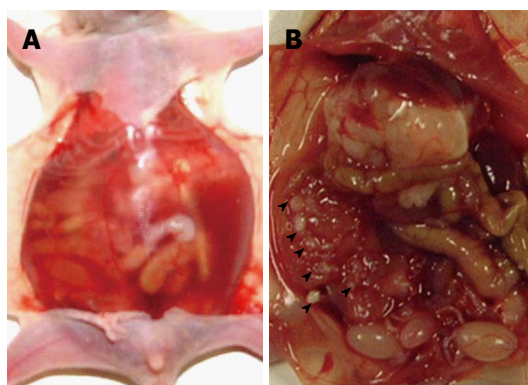


Figure 1 Peritoneal dissemination model. A: Bloody ascites was recognized in the peritoneal cavity of the peritoneal dissemination model, using the MKN-45P cell line; B: Numerous tumor nodules (arrowheads) were recognized on the mesentery.

left kidney (20%) showed hydronephrosis. In the non-therapy group, four right kidneys (80%) and two left kidneys (40%) showed hydronephrosis. The frequency of hydronephrosis in the therapy group was lower than that in the non-therapy group (Table 2). In the therapy group, the grade of hydronephrosis was mild and only a small amount of tissue was recognized in the retroperitoneum. In contrast, in the non-therapy group, the grade of hydronephrosis was severe and a large amount of tumor tissue was recognized in the retroperitoneum (Figure 2). High magnification examination of the tumor tissue revealed a lower number of mitoses in the therapy group than in the control group (Figure 3).

Immunohistochemical findings

Immunoreactivity for VEGF was mainly identified as supranuclear staining or diffuse staining in the cytoplasm of the cancer cells (Figure 4). Based on the percentage of positive tumor staining, all of the five mice in the therapy group were in category 2, whereas all of the five mice in the non-therapy group were in category 3 (Figure 4).

Mitotic index

The mitotic index was 9.6 ± 2.1 in the therapy group and this was significantly lower than that of 21.0 ± 5.7 in the non-therapy group ($P < 0.01$) (Table 2).

Survival curves

We investigated the findings for any correlation between survival and bevacizumab treatment. The median

survival of the treated mice was 30.8 d and that of the untreated mice was 26.6 d. The survival of the therapy group was significantly longer than that of the non-therapy group ($P = 0.005$) (Figure 5).

DISCUSSION

Research in the field of tumor angiogenesis has provided a foundation for radical development in the management and treatment of human cancers. VEGF is the most sensitive angiogenic factor and is expressed in cancer cells. Several clinical trials have confirmed that targeting the vascular VEGF/VEGF receptor pathway can show some clinical benefit. VEGF was initially described as a vascular permeability factor by Senger *et al.*^[12] in 1983 and was later cloned and found to be homologous to VEGF by Ferrara *et al.*^[13]. VEGF has been reported to enhance the permeability of tumor vessels^[14,15], to induce serine protease or metalloproteases^[14,15], to inhibit apoptosis in endothelial cells^[16,17], and to inhibit the maturation of dendritic cells^[18]. Since then, several randomized trials have shown a clinical benefit by various VEGF-targeted agents in patients with metastatic colorectal cancer, advanced non small cell lung cancer, renal cell carcinoma, hepatocellular carcinoma and metastatic breast cancer^[19]. VEGF-targeted therapy has thus become an important treatment option for several human malignancies.

Peritoneal metastasis in gastric cancer takes place through a multistep process involving the detachment of cancer cells from the primary tumor, their attachment to the distant peritoneum, invasion into the subperitoneal space, proliferation and angiogenesis^[1-3]. Angiogenesis is a key step in the various stages of human cancer development and dissemination. Previous reports have indicated that the presence of angiogenic factors is an essential event in the development of peritoneal metastasis^[20-22].

In gastric cancer, there is a tendency for the tumor/normal ratio of VEGF mRNA to be correlated with distant metastasis^[7]. Positive expression of tissue VEGF, circulating VEGF, VEGF-C and VEGF-D were each associated with poor prognosis in resected gastric cancer^[8]. We have previously reported that tissue VEGF was a useful indicator of peritoneal recurrence from gastric cancer^[9]. In our immunohistochemical study on clinical specimens, the VEGF score of patients with peritoneal recurrence was significantly higher than that of patients without peritoneal recurrence and the VEGF score was

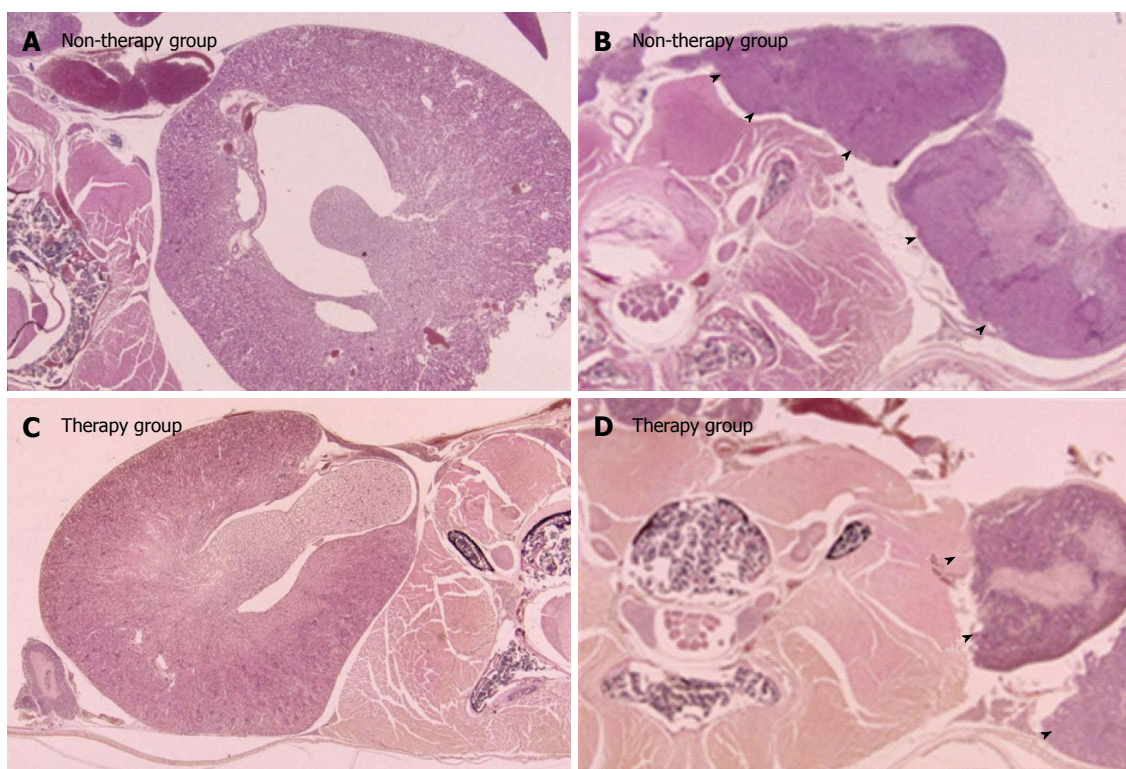


Figure 2 Macroscopic and histological findings of the retroperitoneal tissue. A: Hydronephrosis in the left kidney in the non-therapy group (HE, × 40); B: A large amount of tumor tissues (arrowheads) was recognized on the retroperitoneum in the non-therapy group (HE, × 40); C: Mild hydronephrosis in the right kidney in the therapy group (HE, × 40); D: A small amount of tumor tissues (arrowheads) was recognized on the retroperitoneum in the therapy group (HE, × 40). HE staining, with low magnification, on the cut surface of retroperitoneal tissues in the non-therapy group and the therapy group.

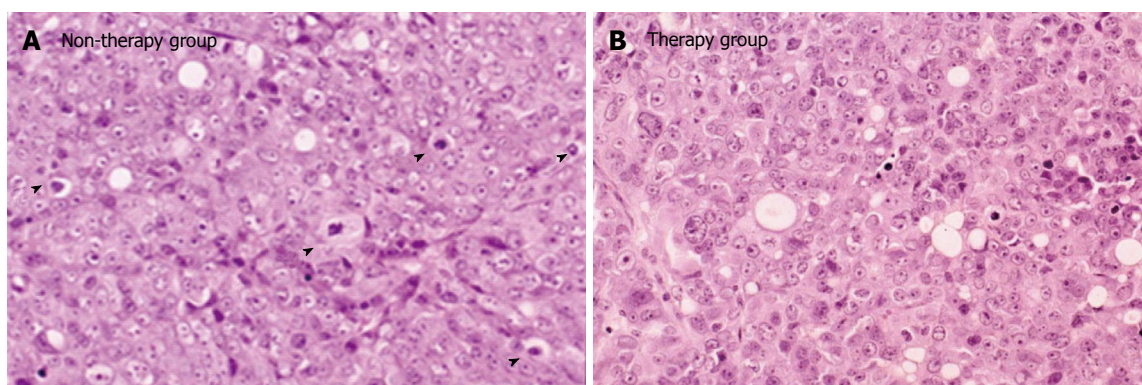


Figure 3 High magnification of tumor tissue. High magnification revealed tumor tissue in both the non-therapy group (A) and in the therapy (B) group. The number of mitoses (arrowheads) in the non-therapy group was larger than that in the therapy group (HE, × 400).

a significant parameter of peritoneal recurrence, suggesting that VEGF was correlated with peritoneal metastasis from gastric cancer and that VEGF was a useful indicator of peritoneal recurrence^[9].

The present study reveals that the concentrations of IL-6, IL-8, VEGF and MMP-2 protein in the culture supernatant of MKN-45P are each significantly higher than each of those of MKN-45. IL-6 has been reported as a prognostic factor in gastric carcinoma and is significantly correlated with the incidence of lymph node metastasis and liver metastasis^[23]. IL-8 has been reported as a prognostic factor in gastric carcinoma and

is significantly correlated with the depth of invasion and vessel infiltration^[24]. IL-6 and IL-8 are each related to the accomplishment of peritoneal dissemination by induction of angiogenesis^[25,26].

Degradation of the extracellular matrix is considered to be a prerequisite for peritoneal metastasis and MMPs are thought to play an important role in this process^[27,28]. There are many reports that highly invasive cancer cells with a high potential for metastasis stimulate the production of MMPs^[27] and that MMP-2 is significantly correlated with depth of invasion, lymph node metastasis and distant metastasis from gastric cancer^[29].

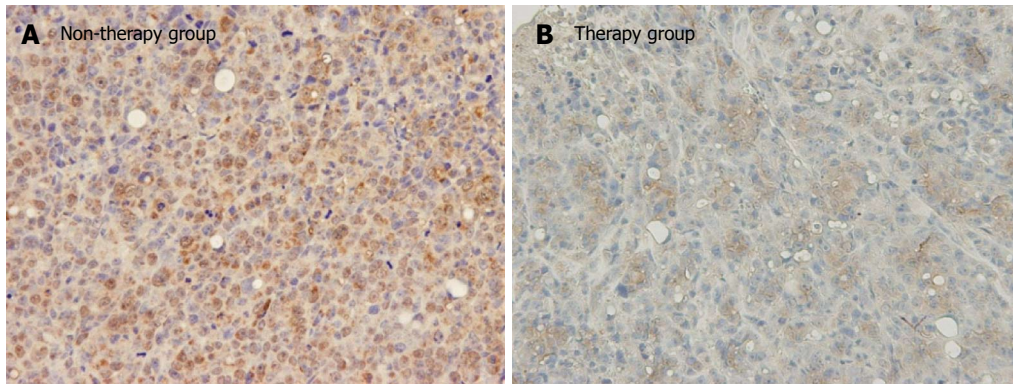


Figure 4 Immunohistochemical staining of tumor tissue. Immunoreactivity for vascular endothelial growth factor (VEGF) was mainly identified as supranuclear staining or diffused staining in the cytoplasm of cancer cells. A: All 5 mice in the non-therapy group according to the percentage of positive tumor staining were in category 3, with 50% or more cells stained (VEGF, $\times 200$); B: All 5 mice in the therapy group were in category 2, with 30 to 49% stained (VEGF, $\times 200$).

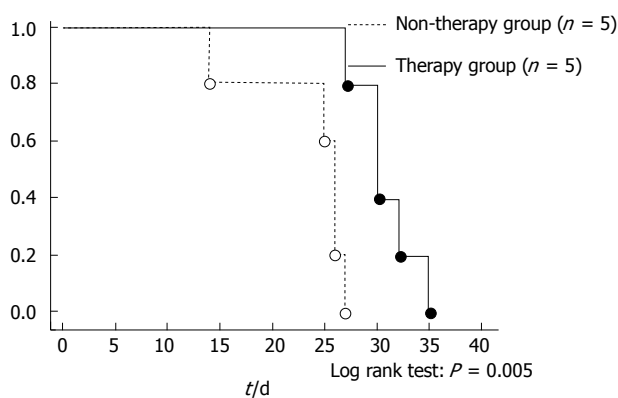


Figure 5 Survival curves. Survival curves of the bevacizumab-treated ($n = 5$), and untreated mice ($n = 5$). The mean survival duration of the treated mice was 30.8 d and of the untreated mice was 23.6 d ($P = 0.005$).

These studies have provided clear evidence that VEGF is an essential element in the development of peritoneal metastasis. Accordingly, we investigated whether VEGF antibody might prevent peritoneal metastasis from gastric cancer.

Bevacizumab is a monoclonal antibody against VEGF that inhibits tumor growth by blocking angiogenesis. Cancer cells transferred with VEGF have been found to have an increased potential for the development of tumorigenesis in a xenograft model^[21]. According to several reports, antiangiogenic agents can decrease tumor vessel permeability and prevent tumor growth^[11,30,31]. Jain *et al.*^[31] have reported that antiangiogenic therapy normalized tumor vessels and reduced interstitial fluid pressure, which finally decreased malignant ascites. In the present study, all the mice in the non-therapy group were cachexic. However, there was no significant difference in body weight between the therapy group and the non-therapy group because the volume of ascites in the therapy group was significantly less than that in the non-therapy group. These findings suggested that bevacizumab suppressed cell proliferative activity by inhibiting angiogenesis of VEGF, thus contributing to the smaller amount of tumor tissue and the low incidence of hydronephro-

sis in the therapy group. Although the number of peritoneal nodules did not differ significantly between the two groups, the nodules on the mesentery in the treated group appeared to have been smaller but these were too small to be measured or weighed. The tumors on the retroperitoneum in the non-therapy group were larger than those in the therapy group and large tumors need new blood vessels for their growth. On immunohistochemical staining, the percentage of tumor cells stained for VEGF in the therapy group was lower than that in the non-therapy group. The mitotic index in the therapy group was also significantly lower than that in the non-therapy group. These results suggested that bevacizumab might suppress the vascular permeability effect and the cell proliferative activity by inhibiting angiogenesis of VEGF and thereby prolonging survival in the mice in the therapy group.

The findings from the present study indicate that the addition of bevacizumab to standard treatment might prolong the survival of gastric cancer patients, especially those with peritoneal metastasis. In conclusion, combination of bevacizumab with anticancer drugs may suppress peritoneal dissemination from gastric cancer.

The results from the present study show that VEGF was correlated with peritoneal metastasis from gastric cancer. Accordingly, using bevacizumab to inhibit VEGF may suppress peritoneal dissemination from gastric cancer. Therefore, combination of bevacizumab with anticancer drugs might suppress peritoneal dissemination from gastric cancer.

COMMENTS

Background

The therapy for peritoneal metastasis is the most important treatment to improve the prognosis of advanced gastric cancer. However, there is yet no effective treatment against peritoneal metastasis from gastric cancer. The relationship between vascular endothelial growth factor (VEGF) and peritoneal metastasis has been reported. Therefore, the authors investigated whether bevacizumab, a humanized monoclonal antibody against VEGF, had a suppressive effect on peritoneal dissemination from gastric cancer, experimentally, using a mouse peritoneal metastasis model.

Research frontiers

The research hot spot is suppression of peritoneal metastasis and prolonging the survival of peritoneal metastasis by bevacizumab.

Innovations and breakthroughs

The authors proved that bevacizumab reduced the volume of ascites and decreased the proliferative activity of cancer cells on the peritoneum macroscopically and microscopically. So, this research proved the suppressive effect of bevacizumab for peritoneal metastasis from gastric cancer more clearly than other similar articles. Moreover, hydronephrosis is one of the most popular events of peritoneal metastasis from gastric cancer clinically. In this research, the authors focused on the hydronephrosis and proved the suppressive effect of bevacizumab for hydronephrosis to reduce the tumor volume on the retroperitoneum.

Applications

The results show that using bevacizumab to inhibit the VEGF may suppress peritoneal dissemination from gastric cancer. Therefore, bevacizumab could be used in preventing peritoneal recurrence and the combination of bevacizumab with anticancer drugs may suppress peritoneal dissemination from gastric cancer.

Peer review

The authors think that the design of this study is good and they analyze the effect of molecular targeting therapy for VEGF against peritoneal metastasis from gastric cancer. The results are interesting and suggest that bevacizumab could be used in preventing peritoneal recurrence. The combination of bevacizumab with anticancer drugs may suppress peritoneal dissemination from gastric cancer.

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Pyruvate-fortified resuscitation stabilizes cardiac electrical activity and energy metabolism during hypovolemia

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Abstract

AIM: To test the hypothesis that fluid resuscitation with Ringer's solution enriched with pyruvate (PR), a physiological antioxidant and energy substrate, affords protection of myocardial metabolism and electrophysiological performance superior to lactated Ringer's (LR) during hypovolemia and hindlimb ischemia-reperfusion.

METHODS: Male domestic goats (25-30 kg) were exsanguinated to a mean arterial pressure of 48 ± 1 mmHg. Right hindlimb ischemia was imposed for 90 min by applying a tourniquet and femoral crossclamp. LR or PR, infused *iv*, delivered 0.05 mmol/kg per minute L-lactate or pyruvate, respectively, from 30 min hindlimb ischemia until 30 min post-ischemia. Time controls (TC) underwent neither hemorrhage, hindlimb ischemia nor resuscitation. Goats were sacrificed and left ventricular myocardium biopsied at 90 min fluid resuscitation ($n = 6$ per group) or 3.5 h later ($n = 9$ LR, 10 PR, 8 TC).

RESULTS: Myocardial 8-isoprostane content, phosphocreatine phosphorylation potential, creatine kinase activity, and heart rate-adjusted QT interval (QTc) variability were evaluated at 90 min resuscitation and 3.5 h post-resuscitation. PR sharply lowered pro-arrhythmic QTc variability *vs* LR ($P < 0.05$); this effect persisted 3.5 h post-resuscitation. PR lowered myocardial 8-isoprostane content, a product of oxidative stress, by 39 and 37% during and 3.5 h after resuscitation, respectively, *vs* LR. Creatine kinase activity fell 42% post-LR *vs* TC ($P < 0.05$), but was stable post-PR ($P < 0.02$ *vs* post-LR). PR doubled phosphocreatine phosphorylation potential, a measure of ATP free energy state, *vs* TC and LR ($P < 0.05$); this energetic enhancement persisted 3.5 h post-resuscitation.

CONCLUSION: By augmenting myocardial energy state and protecting creatine kinase activity, pyruvate-enriched resuscitation stabilized cardiac electrical function during central hypovolemia and hindlimb ischemia-reperfusion.

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Key words: Creatine kinase; Electrocardiogram; Hypovolemia; 8-Isoprostane; Phosphocreatine; Reactive oxygen species; Ringer's lactate

Core tip: In goats subjected to exsanguination-induced hypovolemia and tourniquet-imposed hindlimb ischemia-reperfusion, intravenous resuscitation with Ringer's lactate produced marked electrocardiographic instability, lipid peroxidation and inactivation of the critical creatine kinase system, which supplies energy for membrane ion transport. In comparison with lactated Ringer's, resuscitation enriched with the natural antioxidant and energy substrate pyruvate stabilized cardiac rhythm, prevented lipid peroxidation, preserved creatine kinase activity and augmented myocardial energy reserves. Importantly, these favorable effects persisted for at least 3.5 h after terminating pyruvate-enriched resuscitation. Thus, pyruvate-enriched resuscitation prevented creatine kinase inactivation by oxidative stress, thereby preventing cardiac rhythm disturbances after central hypovolemia.

Gurji HA, White DW, Hoxha B, Sun J, Olivencia-Yurvati AH, Mallet RT. Pyruvate-fortified resuscitation stabilizes cardiac electrical activity and energy metabolism during hypovolemia. *World J Crit Care Med* 2013; 2(4): 56-64 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v2/i4/56.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v2.i4.56>

INTRODUCTION

Central hypovolemia and systemic hypotension can compromise myocardial perfusion, thereby depleting cellular energy reserves and generating cytotoxic reactive oxygen species (ROS). Interventions to stabilize blood pressure after hemorrhage include fluid resuscitation to expand intravascular volume and application of tourniquets to slow bleeding from wounded extremities^[1]. Tourniquets impose ischemia on the distal tissue; reintroduction of oxygenated blood upon tourniquet removal triggers massive production of ROS which provoke systemic inflammation^[2,3].

In myocardium, ROS can destabilize electrophysiological function by decreasing mitochondrial membrane potential^[4], disrupting ATP production^[5,6] and increasing K⁺ flux through sarcolemmal ATP-sensitive potassium (K_{ATP}) channels^[4,5]. Creatine kinase (CK), which catalyzes high energy phosphate shuttling from the mitochondria to the cytosol, can be reversibly inactivated by ROS^[6-8], potentially producing a pro-arrhythmic state^[7]. Dzeja *et al*^[9] proposed that CK inactivation by ROS causes ADP accumulation that opens K_{ATP} channels, thereby shortening cardiac action potentials and provoking arrhythmias. CK was shown to be physically associated with the SUR2A subunit of the sarcolemmal K_{ATP} channel^[10], raising the possibility that changes in CK activity may directly modulate K_{ATP} channel current. Thus, CK inactivation by ROS may contribute to cardiac electrical instability.

Ringer's lactate ranks among the mainstay fluids for resuscitation of trauma victims^[11]. A non-antioxidant, lactate does not protect myocardium from oxidative

stress^[12-14]. In contrast, pyruvate is a potent physiological antioxidant^[7,13,15,16]. Accordingly, fluid resuscitation with pyruvate-enriched Ringer's solution could dampen ROS formation in the myocardium, protecting CK and ameliorating cardiac electrical instability during hypovolemia and tourniquet application and release.

This study tested the hypothesis that substituting pyruvate resuscitation for lactate can suppress myocardial ROS formation, preserve CK activity and ATP metabolism and, thus, maintain cardiac electrical stability in goats subjected to hemorrhage and hindlimb ischemia-reperfusion. We also examined whether these beneficial effects would persist at least 3.5 h after completing pyruvate-enriched resuscitation. This study revealed that pyruvate-enhanced Ringer's resuscitation effectively and persistently suppressed ROS formation in the myocardium, prevented loss of CK activity, augmented energy reserves, and stabilized cardiac electrical rhythm more effectively than lactated Ringer's.

MATERIALS AND METHODS

Animal experimentation was approved by the Institutional Animal Care and Use Committee of the University of North Texas Health Science Center and conducted in accordance with the Guide to the Care and Use of Laboratory Animals (NIH publication 85-23, revised 1996) and the Position of the American Heart Association on Research Animal Use. Forty-five male Boer goats, 25-30 kg, were randomly assigned to time control (TC), lactate Ringer's (LR) resuscitation, or pyruvate Ringer's (PR) resuscitation.

Surgical preparation

Goats were anesthetized by *iv* injection of ketamine (5 mg/kg) and midazolam (0.2 mg/kg), intubated, and mechanically ventilated with 1%-2% isoflurane supplemented with 100% O₂. The right carotid artery, jugular vein, and femoral vein were isolated and cannulated with saline-filled polyurethane catheters. A pressure transducer (Argon Medical Devices; Athens, TX) was connected to the arterial catheter to monitor blood pressure and heart rate. Blood O₂ saturation was continuously monitored by pulse oximetry. Anticoagulant heparin (650 U/kg) was injected *iv* to prevent thrombosis within the catheters. Needle electrodes were applied to the forelimbs and left hindlimb. Standard lead 2 electrocardiogram was captured with a National Instruments analog-to-digital acquisition board sampling at 500 Hz and stored on a Dell laptop running Windaq (Dataq, Akron, OH) acquisition software.

Hemorrhage, hindlimb ischemia, and fluid resuscitation

Mean arterial pressure was lowered to 48 ± 1 mmHg by controlled blood withdrawal (20 mL/min) from the jugular vein (total withdrawal 220 ± 13 mL, *i.e.*, 8.5 ± 0.6 mL/kg). The target mean arterial pressure was chosen to impose moderately severe hypotension while avoiding irreversible hemodynamic collapse. Next, the right femoral

artery was occluded with an atraumatic vasoclamp and a veterinary tourniquet was applied to the right hindlimb proximal to the femoral cutdown to impose hindlimb ischemia. The tourniquet was placed and tightened until the locking mechanism could no longer be advanced. 30 min later, resuscitation was administered for 90 min by jugular venous infusion (10 mL/min) of freshly prepared Ringer's solution containing the sodium salts of pyruvate or the natural lactate stereoisomer, *L*-lactate (Sigma, St. Louis MO)^[17] at concentrations (110-150 mmol/L) adjusted to deliver 0.05 mmol pyruvate or lactate/kg per minute. At 60 min of resuscitation, the vasoclamp and tourniquet were released to reperfuse the hindlimb. Time control (TC) goats were surgically prepared and instrumented, but were not subjected to hemorrhage, resuscitation, or hindlimb ischemia. Left ventricular myocardium was biopsied at 90 min fluid resuscitation ($n = 6$ per group), or 3.5 h after resuscitation, *i.e.*, 4 h after hindlimb reperfusion ($n = 9$ LR, 10 PR). In TC experiments, myocardium was harvested at times corresponding to 90 min resuscitation ($n = 6$) and 3.5 h post-resuscitation ($n = 8$).

QTc interval variability

Variability of the QT interval provides a measure of pro-arrhythmic electrical instability^[18,19]. The QT interval was the time from the initial deflection from the isoelectric PR segment to the point at which voltage returned to the isoelectric TP segment. No U waves were detected in the electrocardiograms. The Bazett equation^[20] was used to adjust QT intervals for variations in heart rate, yielding corrected QT (QTc) intervals. A minimum of 20 consecutive cardiac cycles per timepoint were analyzed; the standard deviation of the QTc values represented QTc interval variability^[21].

Myocardial metabolites and enzymes

Left ventricular myocardium was snap-frozen *in situ* with liquid N₂-precooled Wollenberger tongs, quickly excised, immersed in liquid N₂ and stored at -80 °C. These biopsies were pulverized under liquid N₂, and then phosphocreatine (PCr), creatine (Cr), inorganic phosphate (Pi), ATP, pyruvate, lactate and citrate were extracted in 0.3 mol/L HClO₄^[22,23] and measured by spectrophotometry^[24-30]. Intracellular free ADP concentration ([ADP]) was estimated from the CK equilibrium^[31], where $[ADP] = \{[ATP] [Cr]\} / \{[PCr] K_{CK} / [H^+]\}$. The equilibrium constant for CK was taken to equal 5.18×10^{-10} mol/L at a cytosolic free Mg²⁺ concentration of 0.6 mmol/L which was estimated from indicator metabolite analyses in guinea-pig myocardium^[32]. Intracellular [H⁺] was assumed to equal 63×10^{-10} mol/L, based on measurements in *in situ* canine left ventricular myocardium^[33]. Phosphocreatine phosphorylation potential, $[PCr] / \{[Cr] [Pi]\}$, provided a measure of the free energy state of ATP in the myocardium^[22,23]. The intracellular space estimates used to calculate the phosphorylation potential were calculated as $1 - [(dry\ mass/wet\ mass) + extracellular\ volume]$, where extracellular volume was taken as 0.2

mL/g wet mass based on measurements in *in situ* canine myocardium^[22].

Proteins in frozen myocardium were extracted in phosphate buffer^[34]. Protein concentrations in the extracts were measured colorimetrically^[35] with a Coomassie Plus Bradford kit (Pierce, Rockford, IL). CK and lactate dehydrogenase (LDH) activities were spectrophotometrically assayed^[36,37] and expressed as IU/mg protein.

Isolation and analysis of creatine kinase MB isoform

Left ventricular protein extracts, 6 µg per sample, were electrophoretically separated in a gel composed of 30 mL 1.5% agarose in 30 mM barbital buffer (pH 8.6) at 70 V for 4 h at 4 °C. Next, gels were incubated at 37 °C in a reaction buffer containing 100 mmol/L Tris-HCl (pH 7.4), 5 mmol/L MgCl₂, 5 mmol/L glucose, 1 mmol/L ADP, 15 mmol/L PCr, 3 mmol/L AMP, 10 mmol/L N-acetylcysteine, 0.3 mmol/L NADP⁺, 10 µg/mL glucose-6-phosphate dehydrogenase, and 10 µg/mL hexokinase for 20 min. Lastly, gels were imaged in ultraviolet light in an Alpha Innotech Fluorchem Imaging system. Band densitometry was performed with AlphaEase Fluorchem. Activities of the CK_{MB} isoform in the LR and PR long protocols were identified from the position of standard CK_{MB} and normalized to the long protocol mean TC value.

Myocardial 8-isoprostane

A product of phospholipid oxidation by ROS, 8-isoprostane provided a stable marker of oxidative stress^[38]. 8-isoprostane was extracted from frozen myocardium and assayed at 412 nm in a 96 well plate reader (BioTek KCJunior, Winooski, VT) using an ELISA kit (Cayman Chemical, Ann Arbor, MI). 8-isoprostane contents in the LR, PR and long protocol TC groups were normalized to the short protocol TC values.

Statistical analysis

Presented values are mean \pm SD. QTc variability was analyzed using a two-factor (treatment, time) ANOVA with repeated measures. All other variables were analyzed by single-factor (treatment) ANOVA. When ANOVA detected statistically significant effects, Student-Newman-Keuls *post hoc* tests were applied to identify the specific between-group differences. Statistical analyses were performed using SigmaStat v10. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Effects of pyruvate- vs lactate-enriched fluid resuscitation on systemic arterial pressure

Controlled exsanguination of the goats lowered mean arterial pressure from 100 to 48-50 mmHg (Figure 1). Intravenous LR resuscitation, initiated 30 min after exsanguination and imposition of hindlimb ischemia, restored mean arterial pressure to that of time control goats. PR resuscitation was more effective than LR; at 90 min re-

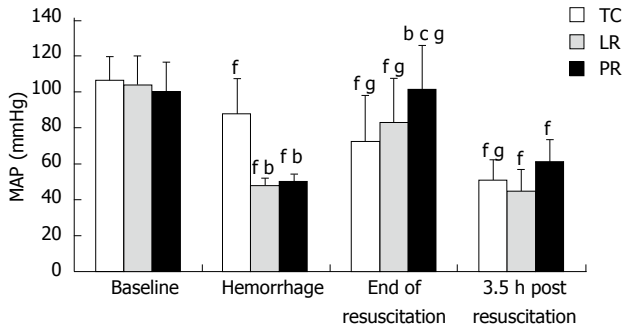


Figure 1 Systemic arterial pressure during hemorrhage, resuscitation and recovery. Values are mean \pm SD from 8 time control (TC), 9 lactate Ringer's (LR), and 10 pyruvate Ringer's (PR) experiments. ^a $P < 0.01$ vs TC; ^c $P < 0.05$ vs LR; ^f $P < 0.01$ vs baseline of same group; ^g $P < 0.05$ vs pre-resuscitation hemorrhage of same group.

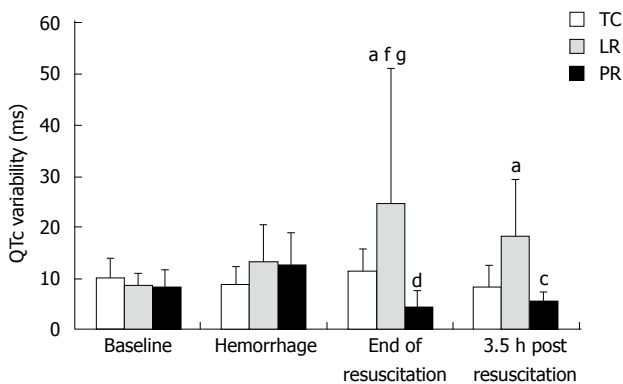


Figure 2 QTc variability during fluid resuscitation and recovery. Values are mean \pm SD from 8 time control (TC), 9 lactate Ringer's (LR), and 10 pyruvate Ringer's (PR) experiments. ^a $P < 0.05$ vs TC; ^c $P < 0.05$, ^d $P < 0.01$ vs LR; ^f $P < 0.01$ vs baseline of same group; ^g $P < 0.05$ vs pre-resuscitation hemorrhage of same group.

suscitation, mean arterial pressure in the PR-resuscitated goats was appreciably higher than that of LR ($P < 0.05$) and TC ($P < 0.05$) goats. Mean arterial pressure fell after resuscitation. At 3.5 h post-resuscitation, the difference in mean arterial pressure in PR *vs* LR goats persisted but was no longer statistically significant ($P = 0.084$).

Cardiac electrical instability

Increased variability of the heart rate adjusted ventricular depolarization-repolarization period, *i.e.* QTc interval, indicates cardiac electrical instability^[39]. QTc variability sharply increased during LR resuscitation (Figure 2) to twice the TC value ($P < 0.05$). In contrast, PR lowered QTc variability to 18% of the respective LR value ($P < 0.01$). QTc variability was still elevated 3.5 h after LR resuscitation *vs* TC ($P < 0.05$) but remained suppressed post-PR *vs* post-LR ($P < 0.05$). Hence, PR stabilizes cardiac electrical function both during and for 3.5 h after its administration.

Myocardial pyruvate, lactate and citrate

In the cytosol, LDH maintains an equilibrium between pyruvate and lactate^[13]; in the mitochondria, pyruvate

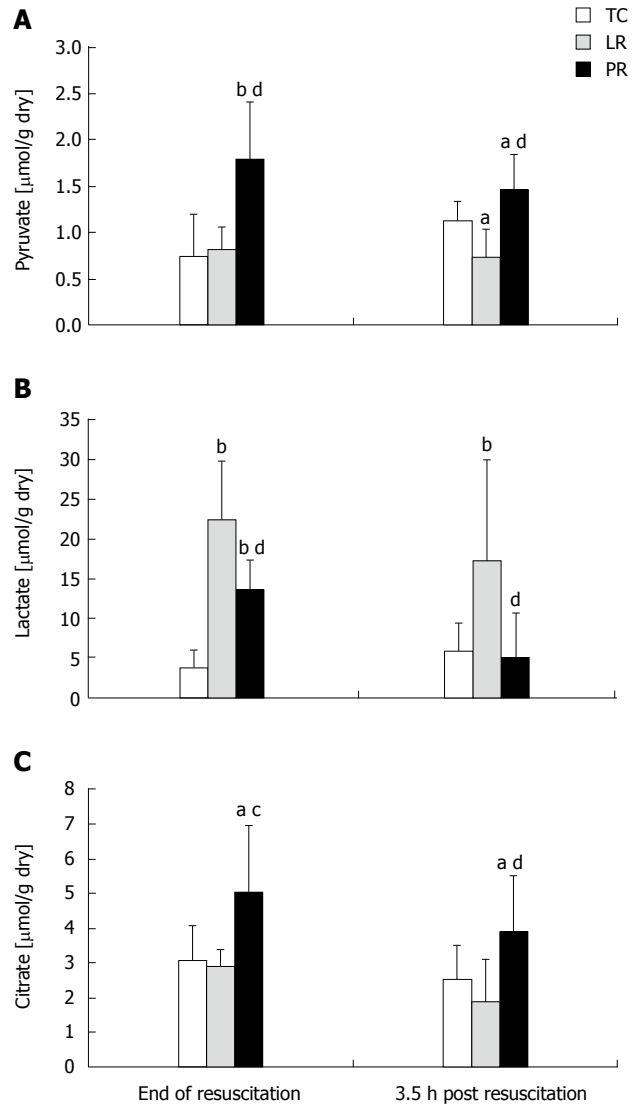


Figure 3 Myocardial pyruvate (A), lactate (B) and citrate (C) contents. Values (mean \pm SD) are from left ventricular myocardium biopsied at 90 min resuscitation ($n = 6$ per group) or at 3.5 h post resuscitation [8 time control (TC), 9 lactate Ringer's (LR), and 10 pyruvate Ringer's (PR)]. ^a $P < 0.05$, ^b $P < 0.01$ vs TC; ^c $P < 0.05$, ^d $P < 0.01$ vs LR.

carboxylation generates oxaloacetate and, thus, Krebs cycle intermediates including citrate^[15,16]. To assess pyruvate metabolism, pyruvate, lactate, and citrate were measured in left ventricular myocardium at 90 min resuscitation and 3.5 h post-resuscitation, *i.e.*, 30 min and 4 h hindlimb reperfusion. As expected, pyruvate content (Figure 3A) was higher during PR *vs* both LR resuscitation ($P < 0.01$) and the corresponding TC value ($P < 0.01$). Notably, pyruvate content remained elevated for 3.5 h after PR resuscitation. Lactate contents (Figure 3B) were increased by LR and, to a lesser extent, PR ($P < 0.01$ *vs* TC); the latter result indicated conversion of pyruvate to lactate in PR-resuscitated myocardium. Lactate content remained elevated 3.5 h after LR resuscitation ($P < 0.01$ *vs* TC) but subsided post-PR ($P < 0.01$ *vs* LR). Myocardial citrate content (Figure 3C) paralleled pyruvate content. Thus, PR resuscitation increased citrate content by 62% and 77% *vs* TC and LR, respectively ($P < 0.05$).

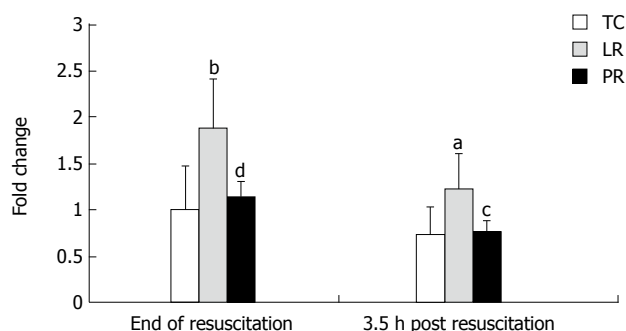


Figure 4 Myocardial 8-isoprostane content. Values (mean \pm SD) are normalized to the 'end of resuscitation' time control (TC) values [8 time control (TC), 9 lactate Ringer's (LR), and 10 pyruvate Ringer's (PR)]. ^a $P < 0.05$, ^b $P < 0.01$ vs TC; ^c $P < 0.05$, ^d $P < 0.01$ vs lactate Ringer's (LR).

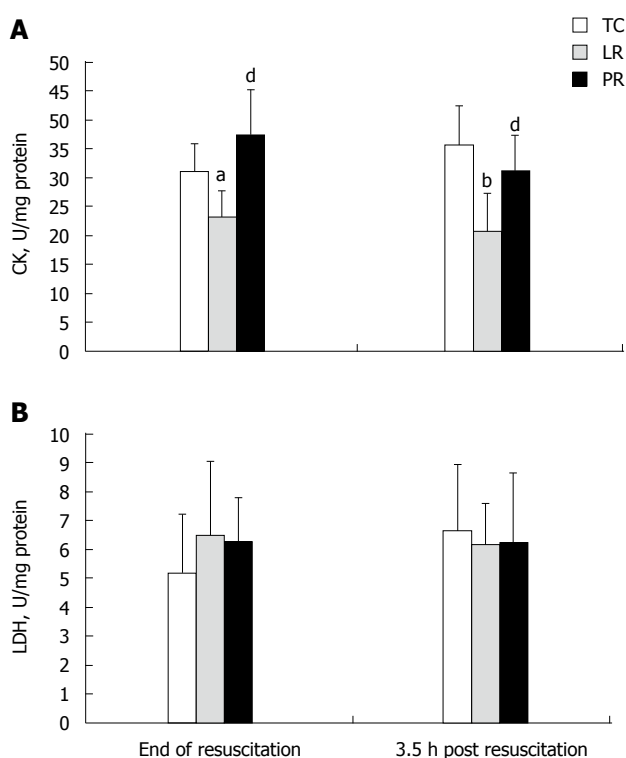


Figure 5 Myocardial creatine kinase (A) and lactate dehydrogenase (B) activities. Enzyme activities were measured in 8 time control (TC), 9 lactate Ringer's (LR) and 10 pyruvate Ringer's (PR) experiments. ^a $P < 0.05$, ^b $P < 0.01$ vs TC; ^c $P < 0.01$ vs LR. CK: Creatine kinase; LDH: Lactate dehydrogenase.

Citrate content fell by 22% during the 3.5 h after PR resuscitation, but remained well above the respective post-LR ($P < 0.01$) and TC ($P < 0.05$) contents.

8-Isoprostane

Oxidative stress is potentially arrhythmogenic^[4,40]. The lipid peroxide 8-isoprostane is a marker of oxidative stress and antioxidant deficiency^[7,38]. The combination of hemorrhage, LR resuscitation and hindlimb ischemia-reperfusion imposed oxidative stress on the myocardium: 8-isoprostane content, measured 30 min after hindlimb reperfusion, increased 88% ($P < 0.01$) vs TC (Figure 4). In contrast, PR resuscitation suppressed ox-

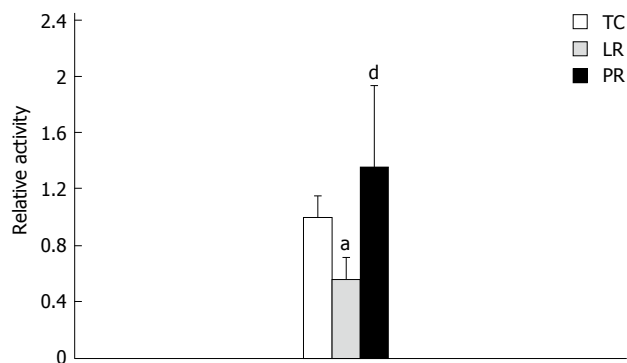


Figure 6 Myocardial creatine kinase MB isoenzyme activities. Creatine kinase-MB activities, measured in 8 time control (TC), 9 lactate Ringer's (LR) and 10 pyruvate Ringer's (PR) experiments, are expressed relative to the TC value. ^a $P < 0.05$ vs TC; ^d $P < 0.01$ vs LR.

idative stress: 8-isoprostane content in the PR group was 39% below the LR value ($P < 0.01$), and did not differ from TC (Figure 4). This pattern persisted until 4 h of hindlimb reperfusion: 8-isoprostane content in the post-LR myocardium was 65% above the TC value ($P < 0.05$), but in the post-PR myocardium, 8-isoprostane content was 37% below post-LR content ($P < 0.05$) and similar to that of TC. Thus, the combination of hemorrhage, LR resuscitation, and hindlimb ischemia-reperfusion imposed oxidative stress in left ventricular myocardium which was prevented by PR resuscitation.

Creatine kinase activity

CK plays a pivotal role in myocardial energy metabolism by shuttling high energy phosphates from the mitochondria to the myofilaments and membrane ion pumps^[41]. Myocardial CK activity fell 25% ($P < 0.05$) during LR resuscitation vs TC (Figure 5A), but PR resuscitation preserved CK activity ($P < 0.01$ vs LR). These treatment effects persisted for 3.5 h after resuscitation: CK activity post-LR was 42% below the respective TC value ($P < 0.001$), but remained robust 3.5 h after PR resuscitation ($P < 0.01$ vs LR). Examination of CK_{MB} isoenzyme activity (Figure 6) revealed that LR resuscitation was unable to protect the cardiac specific isoenzyme from inactivation, but PR resuscitation preserved CK_{MB} activity ($P < 0.001$ vs LR). Activities of LDH, which is released from damaged cardiomyocytes^[42], did not differ among the treatments, and remained stable throughout the protocol (Figure 5B). Thus, loss of CK activity after LR resuscitation probably was not due to CK leakage from damaged cardiomyocytes.

Myocardial energy metabolites

The combination of hemorrhage, hindlimb ischemia-reperfusion, and LR resuscitation slightly depleted myocardial ATP (Figure 7A) at 3.5 h post-resuscitation ($P < 0.05$ vs TC). PR resuscitation not only stabilized but even increased ATP content ($P < 0.01$ vs LR and $P < 0.05$ vs TC). At 3.5 h post-PR, ATP content remained 20% above the post-LR value ($P < 0.05$; Figure 7A). Resus-

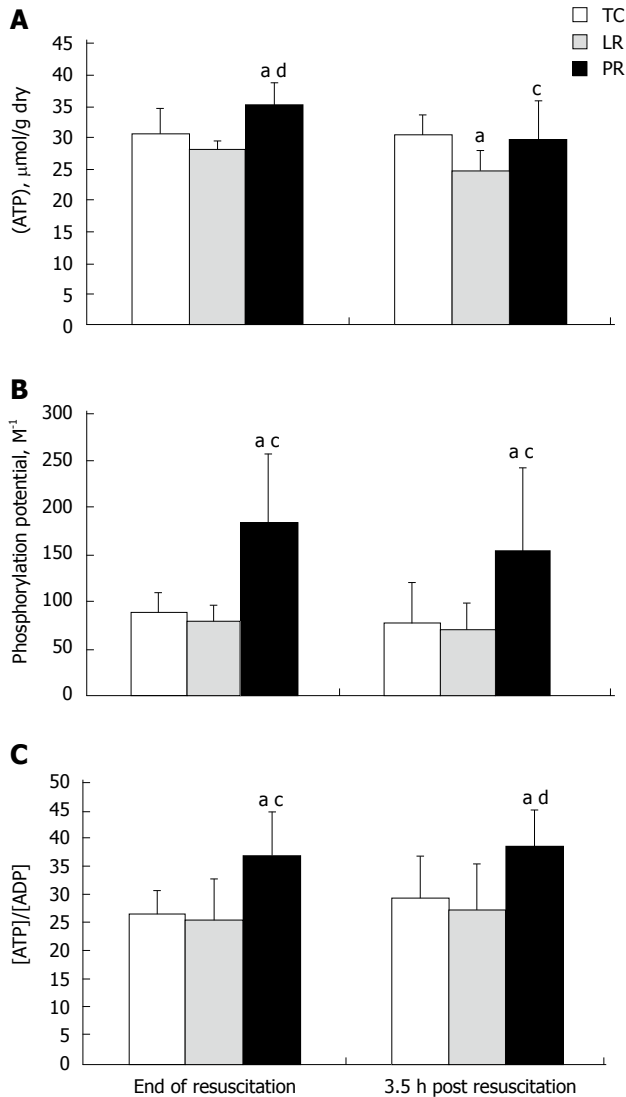


Figure 7 Myocardial ATP content (A), phosphorylation potential (B) and ATP/ADP ratio (C). Metabolites were measured in the same biopsies [8 time control (TC), 9 lactate Ringer's (LR), and 10 pyruvate Ringer's (PR)]. ^a $P < 0.05$ vs TC; ^c $P < 0.05$, ^d $P < 0.01$ vs LR.

citation with PR sharply increased myocardial phosphocreatine phosphorylation potential, *i.e.* $[PCr]/\{[Cr][P_i]\}$, *vs* LR-resuscitated and TC myocardium ($P < 0.05$), an effect that persisted 3.5 h after resuscitation (Figure 7B). Another measure of myocardial energetics, the ATP/free ADP concentration ratio (Figure 7C) defines the poise of the cytosolic free adenylate system^[31]. PR resuscitation increased ATP/ADP ratio by 30%-40% ($P < 0.05$) *vs* LR-resuscitated and TC myocardium. Enhancement of ATP/ADP, like $[PCr]/\{[Cr][P_i]\}$, persisted 3.5 h after PR resuscitation. Thus, PR resuscitation stabilized myocardial energetics more effectively than LR; importantly, these favorable effects persisted for 3.5 h after pyruvate administration.

DISCUSSION

This study tested the hypothesis that resuscitation with a

pyruvate-fortified Ringer's solution during hypovolemia and hindlimb ischemia-reperfusion would stabilize cardiac electrical function and preserve creatine kinase activity in the face of oxidative stress, and maintain myocardial energy reserves in a manner superior to Ringer's lactate. In addition, we proposed that these beneficial effects would be evident not only during pyruvate administration, but also would persist another 3.5 h. Compared to LR, PR resuscitation stabilized cardiac electrical activity, suppressed lipid peroxidation, prevented CK inactivation, preserved ATP content and augmented myocardial phosphorylation potential and $[ATP]/[ADP]$ ratio. Importantly, these myriad favorable effects of PR persisted at least 3.5 h after its administration. PR also restored arterial pressure more effectively than LR, although this effect was no longer statistically significant 3.5 h post-resuscitation.

Pyruvate provides antioxidative protection against ROS

The combination of hemorrhage, systemic hypotension, hindlimb ischemia-reperfusion and LR resuscitation imposed oxidative stress on the myocardium. By chemically modifying cellular components, ROS can impair cellular metabolism and compromise function^[6,16,43]. A natural antioxidant, pyruvate dampened myocardial ROS formation both during and for 3.5 h after its administration. LR resuscitation was comparatively ineffective at suppressing ROS. Previous studies of pyruvate-enriched resuscitative fluids for treatment of hemorrhagic shock also have documented pyruvate's antioxidant capabilities^[12,13,44]. Pyruvate detoxifies ROS in direct, non-enzymatic reactions^[15,45]. In addition, pyruvate carboxylation generates Krebs cycle intermediates, producing citrate which, by inhibiting phosphofructokinase, diverts glucose-6-phosphate into the hexose-monophosphate pathway, the source of NADPH to maintain the endogenous antioxidant glutathione^[15].

Pyruvate protects creatine kinase

Studies of myocardial ischemia-reperfusion have implicated ROS in the inhibition of metabolic enzymes and have shown that pyruvate preserves these enzymes in parallel with enhanced glutathione redox state^[8,46]. Sharma *et al.*^[8] demonstrated that ROS inactivated key glycolytic and Krebs cycle enzymes in canine myocardium during cardiac arrest, but pyruvate infusion restored these enzyme activities. Cardioplegia-arrested swine myocardium reperfused for 3 min with whole blood had lower glutathione redox state and activities of CK and other enzymes than myocardium reperfused with pyruvate-enriched blood^[7]. In the present study, PR protected myocardial CK activity more effectively than LR, and this effect persisted 3.5 h after PR administration. Creatine kinase is physically associated with SUR2A subunits of sarcolemmal K_{ATP} channels^[10]. CK inactivation could open these channels and promote potassium efflux, thereby shortening the action potential and favoring proarrhythmic afterdepolarizations. Thus, preservation

of CK by PR may have helped to stabilize action potential duration and cardiac electrical function. Loss of the cytosolic enzyme LDH indicates sarcolemmal rupture. Because LDH activity was stable, the loss of myocardial CK activity in LR-resuscitated goats likely was not due to sarcolemmal rupture but rather inactivation by ROS. In that case, PR preservation of CK activity could be ascribed specifically to pyruvate's antioxidant properties.

Pyruvate stabilizes cardiac electrical function: role of ATP: ADP ratio

Victims of hemorrhage are at risk of developing cardiac electrical instability^[47] which can be monitored by assessing QTc variability^[18,48-50]. ROS have been implicated in the pathogenesis of arrhythmias, and it has been suggested that the antioxidative properties of certain medications could suppress ROS-mediated arrhythmogenesis^[40]. Several studies have identified K⁺ channels that are sensitive to oxyradical attack^[4,51]. Zhang *et al.*^[52] elegantly demonstrated that ROS could dampen the delayed rectifier and HERG K⁺ channel activities, thereby prolonging the action potential. Inactivation of the transient outward K⁺ channel by hydrogen peroxide^[53,54] could prolong the QT interval and action potential duration. However, S-nitrosylation of cardiac ion channels can either attenuate or prolong the action potential^[52]. Thus, the temporal variability of repolarization produced by oxyradical attack on various cardiac ion channels can place the myocardium in a proarrhythmic state. Pyruvate supplementation can prevent ST segment elevation in myocardial ischemia-reperfusion^[55,56], but pyruvate's influence on cardiac repolarization has not been reported. In this study, pyruvate-enriched resuscitation prevented the increased instability of repolarization produced by lactated Ringer's resuscitation following hypovolemia and hindlimb ischemia-reperfusion. Importantly, this anti-arrhythmic protection persisted at least 3.5 h after pyruvate administration.

Resuscitation with PR augmented ATP content and PCr phosphorylation potential *vs.* LR, both during and 3.5 h after resuscitation. These favorable energetic effects are likely due, in large part, to pyruvate's antioxidative properties as a ROS scavenger and stabilizer of glutathione redox state^[16], thereby protecting metabolic enzymes, combined with its energy-yielding capabilities as a readily oxidized fuel. Indeed, pyruvate- but not lactate-enriched perfusion bolstered PCr phosphorylation potential of post-ischemic guinea-pig myocardium^[57]. Studies of the energy-generating properties of pyruvate have focused on responses during pyruvate supplementation^[6,16]. This study is the first to demonstrate that pyruvate's enhancement of myocardial energy state persists at least 3.5 h after pyruvate administration.

The dynamic balance between ATP and ADP modulates the gating properties of the sarcolemmal K_{ATP} channel, a sensor of cellular energy state^[58]. Zhou *et al.*^[5] demonstrated that a decrease in ATP/ADP ratio opened K_{ATP} channels and shortened action potentials; restoring

ATP/ADP inactivated the channels. Crawford *et al.*^[10] demonstrated that ATP dampened K_{ATP} channel activity, but its conversion to ADP activated the channel. Accordingly, increased myocardial ATP/ADP ratio may have contributed importantly to PR-induced stabilization of cardiac electrical activity. This study provides the first *in vivo* evidence that pyruvate administration can minimize the cardiac electrophysiological consequences of hemorrhagic shock and tourniquet-imposed ischemia-reperfusion of extremities.

Limitations

This project aimed to decipher the mechanism linking pyruvate-enriched resuscitation to cardiac electrical stabilization. *In vitro* experiments are required to define the contributions of the K_{ATP} channel and possibly other membrane ion channels and pumps to the heart's electrophysiological responses to PR *vs.* LR. CK is present in various subcellular locations within cardiomyocytes, including the mitochondrial inter-membrane space^[41], adjacent to the myofilaments^[41] and in association with membrane ion pumps and K_{ATP} channels^[9,10]. Although total CK activity was assessed in this study, the enzyme could not be measured at its different subcellular locations, so the specific impact of LR *vs.* PR resuscitation on K_{ATP}-associated CK is undefined. The cardiac effects of PR *vs.* LR resuscitation beyond the first 4 h recovery, pyruvate-enrichment of other resuscitative media, including colloidal fluids, and the efficacy of esterified pyruvate derivatives, *e.g.*, ethyl pyruvate^[59,60] have not been examined in this model of hemorrhagic shock.

This study revealed several beneficial effects of pyruvate-enriched crystalloid resuscitation during central hypovolemia and hindlimb ischemia-reperfusion. Pyruvate-enriched Ringer's effectively scavenged ROS, protecting CK and augmenting myocardial energy state during and 3.5 h after PR resuscitation. These actions may have contributed to the observed pyruvate stabilization of cardiac electrical function. Fluid resuscitation is an important therapeutic strategy for central hypovolemia. These findings support development of resuscitative fluids enriched with pyruvate or its derivatives, *e.g.*, ethyl pyruvate, to improve treatment and outcomes in combat casualties and civilian trauma victims.

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COMMENTS

Background

Central hypovolemia and systemic hypotension can compromise myocardial

perfusion, thereby depleting cellular energy reserves and generating cytotoxic reactive oxygen species (ROS). Creatine kinase (CK), which catalyzes high energy phosphate shuttling from the mitochondria to the cytosol, can be reversibly inactivated by ROS^[6-8], potentially producing a pro-arrhythmic state^[7].

Research frontiers

Ringer's lactate ranks among the mainstay fluids for resuscitation of trauma victims. A non-antioxidant, lactate does not protect myocardium from oxidative stress. In contrast, pyruvate is a potent physiological antioxidant. Accordingly, fluid resuscitation with pyruvate-enriched Ringer's solution could dampen ROS formation in the myocardium, protecting CK and ameliorating cardiac electrical instability during hypovolemia and tourniquet application and release.

Innovations and breakthroughs

This study tested the hypothesis that substituting pyruvate resuscitation for lactate can suppress myocardial ROS formation, preserve CK activity and ATP metabolism and, thus, maintain cardiac electrical stability in goats subjected to hemorrhage and hindlimb ischemia-reperfusion.

Applications

This study revealed several beneficial effects of pyruvate-enriched crystalloid resuscitation during central hypovolemia and hindlimb ischemia-reperfusion. Pyruvate-enriched Ringer's effectively scavenged ROS, protecting CK and augmenting myocardial energy state during and 3.5 h after pyruvate Ringer's resuscitation.

Peer review

This was a well written manuscript and suitable for publication. The hypothesis is one of constant debate in the clinical literature and I think their experiment was well performed in a good/appropriate animal model. Their methods and results appear well supported.

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