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EDITORIAL

Deep sternal wound infection after cardiac surgery: Evidences and controversies

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Abstract

Despite many advances in prevention and perioperative care, deep sternal wound infection (DSWI) remains a pressing concern in cardiac surgery, with a still relevant incidence and with a considerable impact on in-hospital mortality and also on mid- and long-term survival. The permanent high impact of this complication is partially related to the increasing proportion of patients at high-risk for infection, as well as to the many patient and surgical risk factors involved in the pathogenesis of DSWI. The prophylactic antibiotic therapy is one of the most important tools in the prevention of DSWI. However, the choice of antibiotic, the dose, the duration, the adequate levels in serum and tissue, and the timing of antimicrobial prophylaxis are still controversial. The treatment of DSWI ranges from surgical revision with primary closure to surgical revision with open dressings or closed irrigation, from reconstruction with soft tissue flaps to negative pressure wound therapy (NPWT). However, to date, there have been no accepted recommendations regarding the best management of DSWI. Emerging evidence in the literature has validated the efficacy and safety of NPWT either as a single-line therapy, or as a "bridge" prior to final surgical closure. In conclusion, the careful control of patient and surgical risk factors - when possible, the proper antimicrobial prophylaxis, and the choice of validated techniques of treatment could contribute to keep DSWIs at a minimal rate.

Key words: Risk factors; Sternotomy; Wound healing; Wound infection; Postoperative care

Core tip: Intensivists and cardiothoracic surgeons are commonly worried about surgical site infections due to increasing length of stay, costs, and mortality. In particular, deep sternal wound infection (DSWI) is a worrying complication after cardiac surgery, with a still relevant incidence. Unfortunately, DWSI appearance is related to a wide number of both patient and surgical factors. This review may be useful for guiding

physicians to the knowledge of main risk factors and the choice of the appropriate management of DWSIs with the aim of reducing the rate of this potentially devastating complication in cardiac surgery patients.

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INTRODUCTION

Deep sternal wound infection (DSWI) is one of the most complex and potentially devastating complications following median sternotomy in cardiac surgery with a significant impact on both patient prognosis and hospital budgets[1-5]. Despite many advances in prevention, it still remains significant and ranges between 0.5% and 6.8%[6-10], with in-hospital mortality rates between 7% and 35%[2,3,7,9,11-13]. Moreover, mid- and long-term survival is significantly reduced in patients that have experienced DSWI. By the end of the first year, Filsoufi *et al*[6] found a 15% absolute survival difference between patients without DSWI and those who had developed this complication. In a 10-year follow-up study after coronary artery bypass grafting, the adjusted survival rate was 39% for patients who developed DSWI compared with 70% in patients who did not[14]. Excess costs arise primarily owing to additional antibiotic treatments and surgical procedures, as well as increased hospital length of stay[13,15].

The management of DSWI has progressed through long-lasting clinical experience. Commonly adopted strategies of treatment include surgical revision with primary closure, surgical revision with open dressings or closed irrigation, reconstruction with soft tissue flaps, and application of negative pressure wound therapy (NPWT)[16-18]. However, at the moment, there has been no general consensus regarding the appropriate management of DSWI.

DEFINITION

According to Centers for Disease Control and Prevention (CDC) guidelines, the definition of a DSWI requires positive culture results of surgical sites or drainage from the mediastinal area or evidence of infection during surgical re-exploration or fever, sternal instability, and positive blood culture results[19].

RISK FACTORS

Patient and surgical factors contribute to the risk of DSWI after cardiothoracic surgery. Patient factors include age[20-22], female sex[20,22,23], obesity[2,4,20,21,24-28], diabetes mellitus or hyperglycemia during the perioperative period[2,20,21,24,26-29], smoking tobacco[2,4,28-30], recent treatment with antibiotics[31], *Staphylococcus aureus* nasal carriage[32,33], skin infection anywhere on the body[31], chronic obstructive pulmonary disease[25,27], heart failure[2,34], kidney dysfunction[27,34], peripheral vascular disease[2,26], and emergent or urgent surgery[28,35].

The reason for the increased risk of DSWI in obese patients can be related to the poor perfusion of subcutaneous adipose layers with low levels of prophylactic antibiotics in this tissue. Gummert *et al*[24] found a 1.5-times increased adjusted risk of DSWI after cardiac surgery in patients with body mass index > 30 kg/m^2. Filsoufi *et al*[6] reported that obesity was associated with a more than 2-fold increased risk of DSWI.

Convincing evidence has emerged that the control of blood glucose levels during surgery and the immediate postoperative period with frequent monitoring and protocols for continuous intravenous administration insulin can decrease DSWI rate[36,37]. Researchers at the Mayo Clinic concluded that a 20 mg/dL (1.11 mmol/L) increase in the mean intraoperative blood glucose level correlated with an increase of more than 30% in adverse outcomes[38]. A large prospective study of diabetic patients undergoing cardiac surgery demonstrated that hyperglycemia was an independent risk factor for death, length of hospital stay, and infection rates, and found that a continuous insulin infusion reduced these risks[39].

Smoking tobacco can impair the tissue microcirculation and increase the risk of DSWI. Møller *et al*[40] showed that preoperative cessation of smoking 6-8 wk prior to operation significantly reduced the infection rate in a prospective randomized trial in orthopedic prosthesis surgery. Actually, the CDC guidelines recommend smoking cessation at least 30 d prior to surgery[19].

The patient's carriage of *Staphylococcus aureus* on skin and nares has been identified as an important risk factor for DSWI[32,33]. The Society of Thoracic Surgeons practice guidelines upon antimicrobial prophylaxis recommend routine 5-d mupirocin 2% nasal administration for all patients undergoing cardiac surgery in the absence of a documented negative testing for staphylococcal colonization[41]. However, concerns still remain about the extensive use of mupirocin because of lack of efficacy, risk of widespread high-level resistance, and costs[42-44]. A systematic review of the literature and meta-analysis by Kallen *et al*[45] demonstrated a 45% reduction in surgical site infections (SSIs) caused by *Staphylococcus aureus* with the use of preoperative mupirocin among cardiac surgery patients known to be colonized with *Staphylococcus aureus*. Of note, the only prospective, randomized, and double-blinded trial of mupirocin in cardiac surgery patients did not show benefit: No patients with poststernotomy mediastinitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) had identical isolates in preoperative and surgical-site cultures[46].

Surgical risk factors include prolonged duration of aortic cross clamp, cardiopulmonary bypass perfusion or overall surgery[22,26], use of internal mammary artery (IMA) grafts-especially bilaterally-[2,24,25,27,30], inadvertent paramedian sternotomy[47], use of bone wax, extensive use of electrocauterization[27], surgical procedures requiring prosthesis implant, use of intra-aortic balloon pump or ventricular assist device[23,27], postoperative bleeding[10], blood transfusions, re-exploration for bleeding[6,23,24,48,49], re-operation, postoperative respiratory failure with prolonged mechanical ventilation[2,6], and prolonged stay in intensive care unit (ICU)[4,24,26].

Controversial opinions still remain on the IMA harvest technique. The skeletonization harvest technique is already known to severely reduce the incidence of DSWI - particularly in diabetic and obese patients - because of the better preservation of collateral sternal blood flow and internal thoracic veins[50]. However, many cardiothoracic surgeons are reluctant to application this technique as it can easily lead to graft conduit damage[51]. Evidences also suggest the need for dosing adjustment following IMA harvesting as this significantly diminishes antibiotic penetration into the presternal tissue[52].

Level of concern has varied regarding to the risk of DSWI due to use of bone wax. Animal studies showed an increased risk of *Staphylococcus aureus* infections[53]; however, a prospective, randomized trial of 400 patients found no detrimental effects[54].

Finally, adherence to basic principles of care contributes to reduce the risk of DSWI. These mainly include reduced preoperative hospital stay, increased perioperative oxygenation, preoperative showering using antiseptic solution, hair removal over the operating site using scissors or a depilatory cream instead of shaving, and scrubbing of the operation site with a proper antiseptic solution and letting it dry[6,19,31,55]. Chlorhexidine-, alcohol- or povidone-iodine-based solutions can be used; indeed, the CDC guidelines do not recommend one antiseptic solution over the others[19].

PATHOGENS

Recent reports focused on a growing number of DSWIs caused by methicillin-resistant Gram-positive pathogens[56]. *Staphylococcus epidermidis* is one of the most common agents in poststernotomy mediastinitis when foreign materials such as prosthetic heart valve are implanted; moreover, approximately 75% of the *Staphylococcus epidermidis* strains are methicillin-resistant[57]. The other major pathogen in poststernotomy mediastinitis is *Staphylococcus aureus*. The latter microorganism has been increasingly associated with colonization of the patients' nares. National Nosocomial Infections Surveillance System reports that the rate of MRSA has risen from 30% in 1989 to 60% in 2005 in ICU patients with nosocomial infections and MRSA was the causative microorganism in a third of the patients with DSWI[58].

ANTIMICROBIAL PROPHYLAXIS

The advantages of proper antimicrobial prophylaxis in patients undergoing cardiac surgery have been clearly demonstrated[19,59,60]. However, the choice of antibiotic, the dose, the duration, the adequate levels in serum and tissue, and the timing of antimicrobial prophylaxis are still controversial[11,41,61].

The Society of Thoracic Surgeons Practice Guidelines on antimicrobial prophylaxis in cardiac surgery recommended that a cephalosporin should be given within 60 min from the skin incision and be continued for 24-72 h[41,61]. First generation (cefazolin), second generation (cefamandole and cefuroxime), and third generation (cefotaxime) cephalosporins have been shown to be effective in reducing SSIs in cardiac surgery; however, the superiority of one class over another has not been proven[62-64].

The frequent identification of MRSA as the cause of DSWI has brought the attention on vancomycin as the prophylactic drug of choice[10]. Engelman *et al*[41] stated that vancomycin is reserved mainly for patients with a history of type Ⅰ allergic reaction to β-lactam agents or in the setting of the institutional presence of a "high incidence" of MRSA (class ⅡB recommendation, level of evidence C). Vancomycin should be given with any of the following doses: 1000 mg, 1500 mg, or 15 mg/kg over 1 h, with completion within 1 h of the skin incision[41]. The reason for the 1-h infusion is related to the risk of histamine-release phenomenon characterized by extensive erythematous rash that involves the upper chest and face ("red man syndrome") that can be triggered by a rapid infusion of vancomycin[41,61]. Moreover, studies in the literature showed that the incidence of infection is decreased when the preoperative dose is administered within 1 h before surgical incision[11,65]. Regarding the duration, postoperative prophylactic antibiotics are given for 48 h or less (class ⅡA recommendation, level of evidence B)[61].

A meta-analysis comparing cephalosporins with glycopeptides as antimicrobial prophylaxis regimens found a higher frequency of postoperative SSIs and a trend toward an increased risk of Gram-positive SSI in the glycopeptide group but a lower frequency of SSIs caused by resistant gram-positive pathogens[66].

The relationship between timing of prophylactic antimicrobial administration and risk of infection is an additional field of debate. The 2011 American College of Cardiology/American Heart Association guidelines for cardiac surgery recommend that "Antibiotic prophylaxis should be initiated 30 to 60 min before surgery"[9]. Key studies have demonstrated that antimicrobial prophylaxis administered too late or too early reduces the efficacy of the antimicrobial prophylaxis and increases the risk of infection[10,11,65,67]; conversely, other reports do not clearly demonstrated the superiority of the 1-h window[68-70].

Ideally, short courses of antimicrobial prophylaxis are preferred over longer courses to reduce costs, drug

toxicity, infection with *Clostridium difficile*, and the appearance of resistant pathogens[11,19,61,65,71]. However, the use of cardiopulmonary bypass, the hypothermia, the length of operation, the high mortality and costs of DSWI suggest to prolonging the antimicrobial prophylaxis in cardiac surgery. A 2011 systematic review and meta-analysis of the literature significantly favored longer-term antimicrobial prophylaxis of more than 24 h in these patients[72]. Similarly, Lador *et al*[73] showed that shorter duration of prophylaxis ($\leqslant$ 24 h) was associated with a higher rate of DSWI, surgical intervention for any kind of SSI, and endocarditis; whereas, no difference between 48 h *vs* longer durations was found for all outcomes.

There is absolutely no data for continuing antimicrobial prophylaxis until chest drains are removed[61]. Some studies highlighted the importance of weight-based antibiotic dosing in obese patients and the need for repeated doses during prolonged procedures (more than two half-lives of the drug) or in case of excessive blood loss during the procedure[11,74]. Other investigators reported that a cefazolin bolus followed by continuous infusion improved pharmacokinetic and pharmacodynamic values, including concentrations in the cardiac muscle[75].

MANAGEMENT

Debridement with primary closure has been the treatment of choice for a long time and, until now, it can be considered for infection localized to a small part of the sternum with little or no purulent drainage. Debridement is usually associated with the advancement of the pectoralis muscles and can be done in a single phase procedure or in a delayed closure with multiple open dressing changes followed by sternal re-wiring[17,76-78]. The latter treatment allows improved accuracy in assessing the extent of the sternal infection and reduces the risk of recurrent infection but carries on major disadvantages: Thoracic instability, prolonged immobilization, and mechanical ventilation with increased risk of complications such as thrombosis, muscular weakness, and pneumonia[17,76-79]. Concerns still remain about the need for obtaining negative cultures at the time of closure. Two recent studies found that the presence of positive tissue cultures did not affect the rate of recurrent infections[80,81].

An important step forward in the treatment of DSWI occurred with the introduction of continuous irrigation using closed chest catheter following revision. Further developments were achieved with antibiotic irrigation but several studies have reported high rates of failure and mortality[82-84].

The unsatisfactory results of these different approaches increased interest in plastic procedures as alternative treatments[6,79,84]. Bilateral pectoralis muscle flaps, as either advancement or turnover flaps, are the most usual plastic procedures in the dealing of DSWI[16,85]. This surgical management has a quite low mortality rate but carries a series of disadvantages, including additional surgical trauma and late flap-related morbidity such as muscular weakness, pain, and hernias[86]. An alternative plastic procedure to pectoralis muscle flaps is the use of omentum that promotes significant angiogenesis, immunologic function, and antimicrobial activity supporting tissue-generation promotion with great capacity to occupy dead space[6,87,88]. Usually, the use of omentum is considered in the case of complex wounds or when the defect is extremely wide with significant sternal loss. Specifically, a definite preference has been expressed for the use of omentum when the primary causative pathogen is particularly resistant, such as MRSA[80,89] and Candida[90] or when the patients suffering from diabetes mellitus[91].

However, complications occurred in up to 18% of patients treated with this approach[16,92].

Several recent studies, meta-analyses, and systematic reviews have validated the efficacy of NPWT in DSWI either as a single-line therapy, or as a "bridge" prior to final surgical closure[93-97]. This wound-healing technique is based on the application of continuous or intermittent negative pressure to a wound, which results in arteriolar dilatation and, subsequently, determines wound perfusion and granulation tissue proliferation[57,85,93]. *In vitro* and clinical studies designed to determine the effect of NPWT lent convincing evidence of efficacy and safety in term of decrease of edema, exudation, and microbial colonization as well as reduction of inflammatory cytokine release[57,85,98-100].

In case of diagnosis of DSWI, an early application of NPWT was associated to a faster healing and an increased likelihood of survival[18,97,101,102]. Moreover, several studies demonstrated shorter treatment duration and length of hospital stay, as well as lower costs in patients treated with NPWT[96,98,100,103]. NPWT was also successfully applied in the case of MRSA mediastinitis and as a temporizing treatment prior to secondary closure in mediastinitis due to Candida[90,104,105].

Conversely, other authors suggested that prolonged application of NPWT can result in chronic infection due to a shift in bacterial species and to an increased growth of some of them, such as *Staphylococcus aureus*[99,106]. Different studies have focused on factors that can predict failure of NPWT. Gdalevitch *et al*[107] found that positive blood cultures, wound depth of $\geqslant$ 4 cm, and high degree of bony exposure and sternal instability are significant predictors of NPWT failure. Pericleous *et al*[108] highlighted also the importance of lung emphysema, corticosteroids, and advanced age. Finally, Gustafsson *et al*[109] stressed bacteremia or elevated plasma C-reactive protein levels as the most sensitive predictors of failure.

The positive effects of NPWT on complicated surgical wounds have triggered the interest in using NPWT also after closure of clean and sutured wounds to prevent SSIs in patients at high risk of developing DSWI[110]. The surgical incision management system (Prevena™ Incision Management System, Kinetic Concepts Inc., San Antonio, TX, United States) consists of a single-use NPWT that delivers negative pressure of 75-125 mmHg (10-16.7

KPa); this system holds the incision edges together, reduces lateral tension and edema, stimulates perfusion, and protects the surgical site from external infectious sources[110]. Grauhan *et al*[111] showed significant reduction of SSIs in obese patients (body mass index > 30 kg/m^2) with median sternotomy compared with patients treated with standard wound dressings. In general, retrospective studies and randomized controlled trials provided a substantial body of evidence that the use of this prophylactic wound dressing technique may reduce the incidence of wound infections[112-114].

CONCLUSION

Despite several progresses in prevention and perioperative care, DSWI is still a permanent concern in cardiac surgery because of its significant rate and relevant impact on length of hospital stay, costs, and mortality. The incidence of this complication is in part due to the increased number of patients at high-risk for infection because of advanced age and rate of relevant comorbidities in the population undergoing cardiac surgery. A rigorous attention to the details of preoperative, intraoperative, and postoperative management could contribute to keep DSWIs at a minimal rate.

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EDITORIAL

Why there is a need to discuss pulmonary hypertension other than pulmonary arterial hypertension?

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Abstract

Pulmonary hypertension (PH) is a condition characterized by the elevation of the mean pulmonary artery pressure above 25 mmHg and the pulmonary vascular resistance above 3 wood units. Pulmonary arterial hypertension (PAH) is an uncommon condition with severe morbidity and mortality, needing early recognition and appropriate and specific treatment. PH is frequently associated with hypoxemia, mainly chronic obstructive pulmonary disease and DPLD and/or left heart diseases (LHD), mainly heart failure with reduced or preserved ejection fraction. Although in the majority of patients with PH the cause is not PAH, a significant number of published studies are still in regard to group Ⅰ PH, leading to a logical assumption that PH due to other causes is not such an important issue. So, is there a reason to discuss PH other than PAH? Chronic lung diseases, mainly chronic obstructive lung disease and DPLD, are associated with a high incidence of PH which is linked to exercise limitations and a worse prognosis. Although pathophysiological studies suggest that specific PAH therapy may benefit such patients, the results presented from small studies in regard to the safety and effectiveness of the specific PAH therapy are discouraging. PH is a common complication of left heart disease and is related to disease severity, especially in patients with reduced ejection fraction. There are two types of PH related to LHD based on diastolic pressure difference (DPD, defined as diastolic pulmonary artery pressure - mean PAWP): Isolated post-capillary PH, defined as PAWP > 15 mmHg and DPD < 7 mmHg, and combined post-capillary PH and pre-capillary PH, defined as PAWP > 15 mmHg and DPD ⩾ 7 mmHg. The potential use of PAH therapies in patients with PH related to left heart disease is based on a logical pathobiological rationale. In patients with heart failure, endothelial dysfunction has been proposed as a cause of PH and hence as a target for treatment, supported by the presence of increased endothelin-1 activity and impaired nitric oxide-dependent vasodilation. Unfortunately, so far, there is no evidence supporting the use of specific PAH therapies in patients with PH related to left heart disease. In conclusion, the presence of PH in patients with conditions other than PAH contributes to the severity of the disease, affecting the outcome and quality of life. The disappointing results regarding the effectiveness of specific PAH therapies in patients with

chronic lung diseases and LHD underline the need for seeking new underlying mechanisms and thus novel therapies targeting PH due to left heart disease and/or lung diseases.

Key words: Pulmonary hypertension; Pulmonary arterial hypertension; Chronic obstructive pulmonary disease; Heart failure; Treatment

Core tip: Pulmonary arterial hypertension (PAH) is a rare disease that concerns a small population of patients. Recently, there has been a significant number of research, publications and novel therapies concerning PAH. However, pulmonary hypertension (PH), that concerns a much larger population of patients with common diseases such as lung and left heart diseases (LHD), is generally overlooked despite the fact that it significantly affects the prognosis of these patients. This editorial underlines the need for further research in regard to the pathogenesis and novel therapies for PH related to lung and LHD.

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TEXT

Pulmonary hypertension (PH) is a condition characterized by the elevation of mean pulmonary artery pressure (mPAP) above 25 mmHg and pulmonary vascular resistance (PVR) above 3 wood units[1]. Pulmonary arterial hypertension (PAH), *i.e.*, group Ⅰ according to the latest international guidelines[2], is a rather uncommon condition requiring specific treatment. In the majority of patients with PH, elevated pressures in pulmonary circulation are due to hypoxemia, mainly chronic obstructive pulmonary disease (COPD) and diffuse parenchymal lung diseases (DPLD including idiopathic pulmonary fibrosis and sarcoidosis), and/or due to left heart diseases (LHD), mainly heart failure with reduced or preserved ejection fraction. Furthermore, a small proportion of PH is due to chronic thromboembolic disease and other conditions. Definitions of the above mentioned subgroups of patients with PH are shown in Table 1.

Group Ⅰ PH, *i.e.*, PAH, is either familial, idiopathic or is associated with various well specified diseases[1]. In recent years, a large number of studies have shed light on the underlying pathophysiologic mechanisms for the development of PAH, eventually leading to targeted therapies that improved the morbidity and survival of these patients. Currently, there are three known pathways that play a part in cell proliferation and vasoconstriction in the pulmonary arteries of patients with PAH[3]. Treatments for PAH are aimed at these pathways[4]. The first one is the prostacyclin pathway. Prostacyclin is a potent vasodilator and drugs called epoprostanoids, *i.e.*, epoprostenol, treprostinil and iloprost, targeting this pathway, aim to increase the level of prostacylin in the body. The second pathway is the endothelin pathway. Endothelin is a known potent vasoconstrictor. The class of drugs that targets this pathway is called endothelin receptor antagonist, *i.e.*, bosentan, macitentan and ambrisentan. These drugs block the A and B endothelin receptors in the blood vessels from responding to endothelin. Finally, the third pathway is the nitric oxide pathway. Nitric oxide is a potent vasodilator. There are two classes of medications that target this pathway. Phosphodiesterase type 5 is a molecule in the body that interrupts the production of nitric oxide. The drugs that target this pathway are called phosphodiesterase type 5 inhibitors. Soluble guanylate cyclase stimulators work by stimulating an enzyme inside the cells called soluble guanylate cyclace. By increasing the activity of this enzyme, there is an increase in the production of cyclic GMP, which in turn leads to relaxation of the pulmonary arteries and improvements in PH. Currently, two phosphodiesterase type 5 inhibitors, sildenafil and tadalafil, and one soluble guanylate cyclase stimulator, riociguat, have been approved[4].

The majority of published studies concern PAH, thus leading to a logical assumption that PH due to other causes is not such an important issue. This is also enforced by the fact that published guidelines regarding PH groups Ⅱ, Ⅲ and Ⅳ cover only 26 out of 126 pages. So, is there a reason to discuss PH other than PAH?

COPD and DPLD, including idiopathic pulmonary fibrosis and sarcoidosis, are associated with a high incidence of PH, which is linked to exercise limitations and a worse prognosis[5]. Data showed that the prevalence of PH in COPD patients depends on the severity of the disease and the definition of PH. Accumulating data suggests that in approximately 90% of patients with severe disease, mPAP was more than 20 mmHg, with most ranging between 20 and 35 mmHg while 3% to 5% of the patients demonstrated "severe PH", *i.e.*, mPAP > 35 to 40 mmHg[6]. The "severe PH group" includes only a minority of chronic lung disease patients suspected of having significant vascular abnormalities (remodelling) accompanying the parenchymal disease[7]. For COPD, this corresponds to approximately 1% of the entire population[6].

Chronic hypoxia and fibroproliferation in DPLD lead to the remodelling of both the pulmonary arterial vascular wall and the pulmonary parenchyma due to common pathophysiological ways, while new data indicate that pathogenetic concepts that primarily relate to idiopathic pulmonary fibrosis may also take place in other forms of pulmonary fibrosis, including connective tissue diseases

Table 1 The definitions of pulmonary hypertension groups Ⅰ, Ⅱ, Ⅲ, Ⅳ[1,7,22]

Group	Definition
Group Ⅰ: Pulmonary arterial hypertension	Is defined as: Mean pulmonary artery pressure ⩾ 25 mmHg at rest, and end-expiratory pulmonary artery wedge pressure ⩽ 15 mmHg, and pulmonary vascular resistance > 3 Wood units
Group Ⅱ: PH due to left heart disease	Is defined as: mPAP ⩾ 25 mmHg, and PAWP > 15 mmHg, and normal or reduced CO
Group Ⅲ: PH due to chronic lung disease and/or hypoxia	Patients with confirmed COPD or DPLD, without chronic thromboembolic disease or left heart disease, who meet at least two of the following criteria: mPAP > 35 mmHg mPAP ⩾ 25 mmHg AND cardiac index < 2 lt/min per square pulmonary vascular resistance > 6 Wood units
Group Ⅳ: Chronic thromboembolic pulmonary hypertension	CTEPH is defined as pre-capillary PH as assessed by right heart catheterization (mean PAP ⩾ 25 mmHg, PCWP ⩽ 15 mmHg) in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least three months of effective anticoagulation

PH: Pulmonary hypertension; CO: Cardiac output; COPD: Chronic obstructive pulmonary disease; DPLD: Diffuse parenchymal lung diseases; PAP: Pulmonary artery pressure.

and granulomatous diseases such as sarcoidosis[8]. This leads to a rationale for evaluating the safety and effectiveness of the specific PAH therapy in such patients[5]. Data from such trials are discouraging. In COPD, pulmonary vasodilation without deterioration of gas exchange is more challenging than in lung fibrosis caused by the presence of low ventilation/perfusion ratio areas. Inhaled prostanoids may acutely reduce mPAP and PVR while largely maintaining gas exchange in COPD patients with PH[9].

However, long-term clinical trials have not been reported. In COPD patients with mild PH, bosentan, a nonselective endothelin-1 receptor antagonist, caused deterioration of gas exchange with a lack of improvement in peak oxygen uptake, exercise capacity and quality of life in a small randomized controlled trial[10]. On the other hand, another small trial reported an improvement in exercise capacity upon treatment of COPD patients with PH with bosentan[11].

Robust data on the effect of endothelin receptors antagonists on pulmonary hemodynamics and exercise tolerance in COPD patients are lacking[5].

PH is a common complication of LHD[12]. The presence of PH is often considered as a symptom of the underlying condition and often related to disease severity, especially in patients with reduced ejection fraction of the left ventricle[13]. The current hemodynamic definition of PH related to LHD combines a mPAP ⩾ 25 mmHg, a pulmonary artery wedge pressure (PAWP) > 15 mmHg and a normal or reduced cardiac output. There are also two types of PH related to LHD based on the diastolic pressure difference (DPD, defined as diastolic PAP - mean PAWP): Isolated post-capillary PH, defined as PAWP > 15 mmHg and DPD < 7 mmHg, and combined post-capillary PH and pre-capillary PH defined as PAWP > 15 mmHg and DPD ⩾ 7 mmHg[13].

The potential use of PAH therapies in patients with PH related to LHD is based on a logical pathobiological rationale, while in patients with heart failure, endothelial dysfunction has been proposed as a cause of PH and hence as a target for treatment, supported by the presence of increased endothelin-1 activity and impaired nitric oxide-dependent vasodilation[14]. Unfortunately, so far, there is no evidence supporting the use of specific PAH therapies in patients with PH related to LHD[13]. It must be pointed out that there are fundamental differences in the pathophysiologic pathways between patients with heart failure with reduced and preserved ejection fraction. These differences suggest that more pathophysiologically targeted drugs and therapies are needed for each case[15].

Therefore, it is anticipated that PAH therapies might have a different effect in patients with heart failure and preserved ejection fraction compared with other forms of heart failure. Data on the use of PAH therapies in the context of heart failure and reduced or preserved ejection fraction with or without PH are scarce; with sildenafil and riociguat the most studied medications in this setting[16-18].

Finally, specific PAH therapies may have a place in the treatment of acute PH. In one of our studies, we showed that the postoperative co-administration of inhaled nitric oxide and oral sildenafil, a phosphodiesterase-5 inhibitor, in patients with out-of-proportion PH undergoing cardiac surgery is safe and results in an additive favourable effect on pulmonary arterial pressure and PVR, without systemic hypotension and ventilation/perfusion mismatch[19].

Finally, left heart disease is a well-known but often underdiagnosed co-morbidity of COPD[20,21]. The presence of left heart disease in COPD patients may additionally contribute to the pathogenesis and severity of PH and thus the cause of moderate to severe PH in patients with COPD may be the result of multiple causal factors. Data regarding the incidence of HF in COPD patients are accumulating, but there is little known about the contribution of each condition to the presence and severity of PH in such patients.

In conclusion, the presence of PH in patients with conditions other than PAH contributes to the severity of the disease affecting the outcome and quality of life. Although these conditions affect a large proportion of patients with common diseases such as LHD and COPD/DPLD, there is a lack of data, pathophysiologic studies, and multicentre randomised trials addressing a target therapy for PH in such populations. The disappointing results for the effectiveness of specific PAH therapies in such populations underline the need to seek new

underlying mechanisms and thus novel therapies targeting PH due to LHD and/or lung diseases.

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MINIREVIEWS

Recruitment maneuvers in acute respiratory distress syndrome: The safe way is the best way

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Abstract

Acute respiratory distress syndrome (ARDS) represents a serious problem in critically ill patients and is associated with in-hospital mortality rates of 33%-52%. Recruitment maneuvers (RMs) are a simple, low-cost, feasible intervention that can be performed at the bedside in patients with ARDS. RMs are characterized by the application of airway pressure to increase transpulmonary pressure transiently. Once non-aerated lung units are reopened, improvements are observed in respiratory system mechanics, alveolar reaeration on computed tomography, and improvements in gas exchange (functional recruitment). However, the reopening process could lead to vascular compression, which can be associated with overinflation, and gas exchange may not improve as expected (anatomical recruitment). The purpose of this review was to discuss the effects of different RM strategies - sustained inflation, intermittent sighs, and stepwise increases of positive end-expiratory pressure (PEEP) and/or airway inspiratory pressure - on the following parameters: hemodynamics, oxygenation, barotrauma episodes, and lung recruitability through physiological variables and imaging techniques. RMs and PEEP titration are interdependent events for the success of ventilatory management. PEEP should be adjusted on the basis of respiratory system mechanics and oxygenation. Recent systematic reviews and meta-analyses suggest that RMs are associated with lower mortality in patients with ARDS. However, the optimal RM method (*i.e.*, that providing the best balance of benefit and harm) and

the effects of RMs on clinical outcome are still under discussion, and further evidence is needed.

Key words: Recruitment maneuvers; Acute respiratory distress syndrome; Positive end-expiratory pressure; Transpulmonary pressure; Lung ultrasonography

Core tip: Experimental and clinical studies show that stepwise recruitment maneuvers (RMs) improve oxygenation and lung aeration and are associated with less hemodynamic instability and inflammatory impact on lung tissue compared to traditional abrupt maneuvers. Patients with severe acute respiratory distress syndrome, characterized by increased edema and atelectasis, are good candidates for RMs. Patients whose oxygenation improves with increased pressure are at lower risk of death. Post-recruitment positive end-expiratory pressure (PEEP) titration is critical to maintaining stabilization of alveolar units and avoiding derecruitment. The use of individualized PEEP based on lung compliance might move clinical management forward.

Santos RS, Silva PL, Pelosi P, Rocco PRM. Recruitment maneuvers in acute respiratory distress syndrome: The safe way is the best way. *World J Crit Care Med* 2015; 4(4): 278-286 Available from: URL: http://www.wjgnet.com/2220-3141/full/v4/i4/278.htm DOI: http://dx.doi.org/10.5492/wjccm.v4.i4.278

INTRODUCTION

The acute respiratory distress syndrome (ARDS) is clinically characterized by severe hypoxemia, reduced lung compliance, and bilateral radiographic infiltrates[1]. Protective mechanical ventilation strategies, which are characterized by protective tidal volumes [V_T = 6 mL/kg, predicted body weight (PBW)] and end-inspiratory (plateau) airway pressures lower than 28 cm H_2O, have been associated with improved survival in randomized clinical trials[2,3]. However, the use of protective V_T alone seems to be not enough to maintain homogeneous distribution of ventilation across different alveolar units[4]. In this line, V_T titrated to 6 mL/kg (PBW) may result in repetitive opening and closing of such units, which may result in atelectrauma unless sufficient positive end-expiratory pressure (PEEP) is applied. On the other hand, overdistension and disruption of alveolar units may develop if high PEEP values are used[5].

General anesthesia and neuromuscular blockade may potentiate the generation of atelectatic areas[6]. In a normal homeostatic condition, the sigh reflex maintains lung compliance and decreases atelectasis[7]. However, during mechanical ventilation, there is no sigh reflex. One possibly way to maintain oxygenation, functional residual capacity, and respiratory system elastance is the application of recruitment maneuvers (RMs), which have become a component of lung-protective ventilation strategies[8,9]. A recent systematic review suggested that, when included in ventilatory strategies, RMs reduced mortality by 6% in patients with moderate to severe ARDS[10]. Since this is only a slight improvement in mortality and no major differences in length of intensive care unit or hospital stay were observed, subsequent studies raised concerns regarding the beneficial effects and the safety of RMs.

This review sought to discuss: (1) the physiologic effects of RMs; (2) describe different types of RMs and their safety; (3) techniques of positive end-expiratory pressure titration; and (4) the future perspectives of RMs in the presence of protective ventilation strategies.

PHYSIOLOGICAL EFFECTS OF RMS

A RM is a dynamic, transient increase in transpulmonary pressure (difference between airway pressure and pleural pressure) which is directly proportional to the reopening of lung units. Its success and/or adverse events can be predicted by the magnitude of transpulmonary pressure, balancing the increase in aerated lung areas and the reduction of mechanical stress between the edge of collapsed and aerated areas[11]. Traditionally, RMs usually improve lung mechanics and oxygenation, but whether these are the only positives consequences of RM use remains unknown. Thus far, no randomized clinical trial has aimed to show whether the presence or absence of RM among the constituent elements of a protective ventilator strategy bundle makes a difference. A randomized clinical trial designed to answer this question with sufficient statistical power, the alveolar recruitment for ARDS trial, is ongoing. Nevertheless, important, physiologically based studies have attempted to answer key questions. In a prospective study of 16 mechanically ventilated patients with ARDS by Di Marco *et al*[12] divided participants into responders and non-responders based on an increase in diffusing capacity for carbon monoxide associated with a higher PEEP. Increasing PEEP from 5 to 15 cm H_2O has been demonstrated to yield increased lung volume (anatomical recruitment) in half of patients, while in other patients, higher PEEP results in improvement of lung volume and perfusion (functional recruitment). In other words, opening of alveolar units does not necessarily entail restoration of lung perfusion in that specific region. In cases of functional recruitment, an increment in PaO_2/FiO_2 can be expected (Figure 1).

The viscoelastance and time-dependent force required to open collapsed areas is a function of both transpulmonary pressure and time[13], known as the pressure-time product. In an attempt to evaluate optimal RM duration and hemodynamic changes, Arnal *et al*[14] conducted a prospective clinical trial of 12 recruited patients with ARDS. The authors found that most recruitment occurs in the first few seconds of a sustained inflation, suggesting that time is less important as a determinant of RM success. Instead, time plays a critical

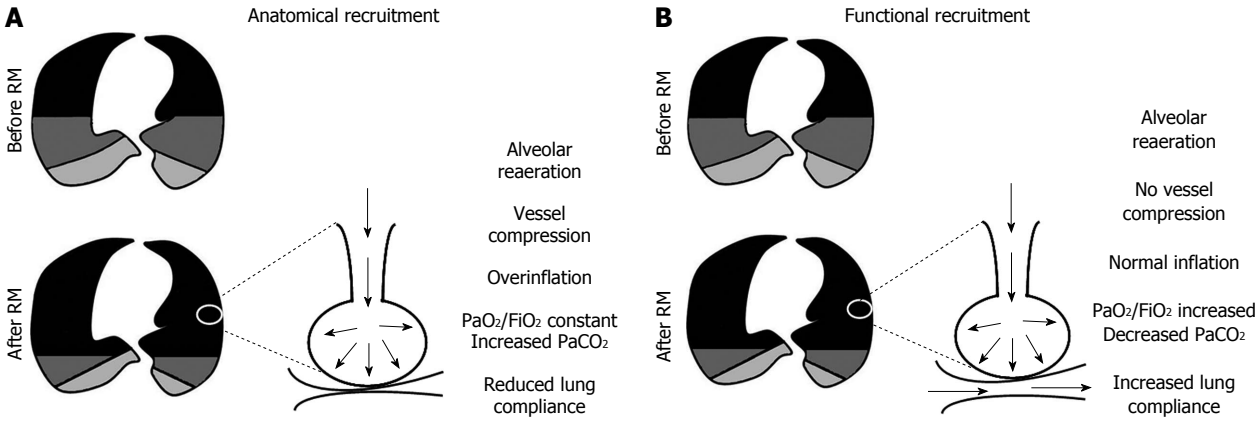

Figure 1 Schematic representation of lung morphology before and after application of recruitment maneuvers. A: Anatomical recruitment. Alveolar reopening is not accompanied by reperfusion and PaO_2/FiO_2 remains unchanged; B: Functional recruitment. Reperfusion is a landmark of functional recruitment and, after application of a recruitment maneuver, an increment in PaO_2/FiO_2 ratio is expected. RM: Recruitment maneuver.

role in hemodynamic alterations, which generally occur with a longer duration of inflation.

RMs are largely related to reversal of atelectasis in the context of ARDS. Moreover, their beneficial effects have also been described in patients under general anesthesia, during postoperative ventilation, and in other conditions related to hypoxemia, including heart failure[7,15].

TYPES OF RMS

Tables 1 and 2 summarize clinical and experimental studies comparing different RM methods according to Population, Intervention, Comparison, Outcome criteria. Sigh was the first reported RM, applied interposed with monotonous ventilation to mimic physiological breathing as it occurs in healthy subjects[16]. This RM consists of high V_T in controlled mode or high PEEP up to a specific plateau pressure level, for a selected number of cycles. In this line, Pelosi *et al*[17], in an observational study, ventilated 10 ARDS patients for 1 h with a lung-protective strategy consisting of three consecutive sighs/minute at 45 cm H_2O plateau pressure. These patients exhibited improvement in oxygenation, lung elastance, and functional residual capacity compared to patients who did not receive sighs. Despite the beneficial effects of this maneuver, high sigh frequency (up to 180/h) was associated with hyperinflation and expression of type Ⅲ procollagen mRNA in lung tissue in experimental models[18]. Lower sigh frequency can protect the lung[18], mainly when combined with pressure-support ventilation[19].

The most widely described RM is sustained inflation, in which airway pressure is abruptly raised for a given time interval. A common sustained inflation is 40 cm H_2O for 40 s[20-22]. More recently, RMs with a stepwise increase in airway pressure and/or PEEP (stepwise RM) have been proposed to provide slowly increasing transpulmonary pressure instead of the rapid increase used in sustained inflation, in experimental[8,23,24] and clinical studies[25-27]. Both sustained inflation (fast RM) and stepwise RM (slow RM) have been reported to improve oxygenation and lung function and minimize atelectasis in experimental[8,24,28] and clinical scenarios[20,25]. Since stepwise RMs recruit lung units as effectively as sustained inflation with a lower mean airway pressure, they may lead to less hemodynamic compromise and hyperinflation. In this context, sustained inflation has also been associated with risk of hypotension[29], barotrauma[29], and has even been reported to be ineffective in improving oxygenation and reducing intrapulmonary shunting[30]. In an observational study and randomized controlled trial, respectively, stepwise RM improved lung compliance, shunt fraction, and oxygen saturation[25] and was associated with less release of inflammatory mediators[24] compared to a ventilator strategy that did not incorporate RMs. However, stepwise RMs may have a heterogeneous impact on respiratory mechanics and cause adverse hemodynamic effects in an observational clinical study[26]. In experimental endotoxin-induced mild ARDS, stepwise RM, compared to sustained inflation, was associated with reduced type Ⅱ epithelial cell damage and decreased expression of markers associated with fibrosis and endothelial cell damage, depending on ARDS etiology[8].

Despite extensive research into the applications of RMs, definitive guidelines for these maneuvers have not been established. As a step toward standardization, a trial with high methodological quality is being conducted to assess the 28-d survival of ARDS patients subjected to maximum stepwise alveolar recruitment followed by ventilation with PEEP titrated according to best compliance[31]. This multicenter study may represent a valuable contribution to the treatment of patients with ARDS[31].

Assisted ventilation may be associated with homogeneous lung recruitment. In the presence of lung recruitment, end-expiratory lung volume increases, thus reducing strain, while lung elastance decreases, resulting in lower inspiratory transpulmonary pressure and stress[32]. However, in the absence of lung recruitment, transpulmonary pressure might be higher than during controlled mechanical ventilation and thus,

Table 1 Recruitment maneuver methods and outcomes reported in the literature about clinical studies

Ref.	Population	Design	Interventions	Comparison	Outcome
Pelosi *et al*[17]	Patients with pulmonary and extrapulmonary ARDS	Observational study	3 sighs/min at Pplat 45 cm H_2O, V_T to maintain Pplat ⩽ 35 cm H_2O. PEEP level to keep the lung open	(1) 1 h of ventilator strategy; (2) 2 h of ventilator strategy; and (3) 1 h of ventilator strategy with three consecutive sighs/min at Plat 45 cm H_2O	Sigh during protective ventilation improved lung recruitment
Borges *et al*[44]	Patients with early ARDS	Observational study	Stepwise maximum-recruitment strategy with sequential increments in Paw, in 5-cm H_2O steps, until the detection of PaO_2 + $PaCO_2$ = 400 mmHg	No comparisons	Stepwise maximum recruitment reverted hypoxemia and fully recruited the lungs
Meade *et al*[29]	Patients with ARDS (PaO_2/FiO_2 ⩽ 250 mmHg)	Randomized controlled trial	Low V_T, Pplat ⩽ 30 cm H_2O or ⩾ 40 cm H_2O, and lower or higher PEEP levels according to PEEP/FiO_2 table	(1) Ventilator strategy with Pplat ⩽ 30 cm H_2O, and conventional PEEP levels; (2) "open lung" approach with Pplat ⩽ 40 cm H_2O, RM, and higher PEEP levels	"Open-lung" approach improved oxygenation associated with lower use of rescue therapies
Hodgson *et al*[25]	Patients with early ARDS	Observational study	Staircase RM, Paw set to 15 cm H_2O above the PEEP, which was increased in a stepwise manner to 20, 30 and then 40 cm H_2O every 2 min, followed by PEEP titration	No comparisons	80% of early ARDS patients responded to staircase RM
Hodgson *et al*[27]	Patients with ARDS	Randomized controlled trial	Control ventilation strategy compared to staircase recruitment maneuver	(1) Control group: PCV, Pplat < 30 cm H_2O, V_T < 6 mL/kg. FiO_2 adjusted to SaO_2: 90% to 92%; and (2) Staircase RM: Paw adjusted to 15 cm H_2O above PEEP level, which was increased in a stepwise manner to 20, 30 and 40 cm H_2O every 2 min, and then reduced in steps of 2.5 from 25 to 15 cm H_2O every 3 min until a decrease in SaO_2 ⩾ 1%	Staircase RM improved plasma cytokines, oxygenation and lung function over 7 d
Morán *et al*[26]	Patients with early ARDS	Observational study	Stepwise RM started from plateau pressure/PEEP of 40/25 cm H_2O, 5 cm H_2O of PEEP was sequentially increased until PaO_2/FiO_2 of 350 mmHg or plateau pressure/PEEP of 60/40 cm H_2O	No comparisons	Stepwise RM improved oxygenation but caused hemodynamic instability and transient hypoxemia

Summary of the results of clinical and experimental studies comparing different recruitment maneuver (RM) methods, according to population, intervention, comparison, outcome criteria. ARDS: Acute respiratory distress syndrome; FiO_2: Inspiratory oxygen fraction; PaO_2: Arterial oxygen partial pressure; $PaCO_2$: Arterial carbon dioxide partial pressure; PCV: Pressure-controlled ventilation; PEEP: Positive end-expiratory pressure; Pplat: Plateau pressure; SaO_2: Arterial oxygen saturation; V_T: Tidal volume.

assisted ventilation may lead to deleterious effects[33,34]. Additionally, spontaneous breathing during assisted mechanical ventilation may exacerbate lung injury by increasing patient-ventilator asynchrony and rapid shallow breathing[35]. Furthermore, negative pleural pressures may increase intrathoracic blood volume, worsening pulmonary edema and lung damage[36]. In short, we suggest that assisted mechanical ventilation can be applied for mild and moderate ARDS.

It is well established that prone positioning improves oxygenation in patients who require mechanical ventilatory support for management of ARDS[37]. Guérin *et al*[38] recently showed that early application of prolonged prone positioning significantly reduces mortality in patients with severe ARDS. Pronation acts as a RM, increasing transpulmonary pressure in dorsal regions and reducing alveolar instability and hyperinflation. In this line, Galiatsou *et al*[39] assessed lung computed tomography findings in ARDS patients in the supine and prone positions after RM application. The authors found that prone position had an additive effect on oxygenation and recruitment of dependent lung regions, and was associated with a reduction in ventral overinflation areas. These findings were confirmed by Cornejo *et al*[40] who evaluated the interaction of lung recruitability, high PEEP values, and prone positioning. Reductions in atelectasis and/or overdistension were observed in patients in both categories (low and high recruitability) at both low and high PEEP in the prone position. Furthermore, in a subgroup of patients with high recruitability, prone positioning added to the effect of high PEEP on atelectrauma, and prevented its effects on tidal overinflation.

SAFETY OF RMS

RMs are being increasingly used in clinical practice, and even if full re-expansion is expected, negative effects can occur, especially on hemodynamics. The type of RM seems to be a crucial predictor of hemodynamic adverse effects. In a prospective clinical trial, Iannuzzi *et al*[41] evaluated hemodynamic changes in 40 patients with ARDS randomized to receive RMs with sustained inflation or pressure-controlled ventilation (PCV) adjusted to generate the same pressure-time product. PCV-RM,

Table 2 Recruitment maneuver methods and outcomes reported in the literature about experimental studies

Ref.	Population	Design	Interventions	Comparison	Outcome
Rzezinski *et al*[23]	Animals with mild extrapulmonary lung injury	Randomized experimental study	Prolonged RM stepwise increase in PIP of 15-20-25 cm H_2O above a PEEP of 15 cm H_2O (maximal PIP = 40 cm H_2O)	(1) Animals ventilated with V_T = 6 mL/kg and PEEP = 5 cm H_2O with no RMs; (2) Sustained inflation (40 cm H_2O for 40 s); or (3) Stepwise increase in Paw of 15, 20, 25 cm H_2O above a PEEP of 15 cm H_2O (maximal PIP = 40 cm H_2O), with interposed periods of Paw = 10 cm H_2O above a PEEP = 15 cm H_2O	Prolonged RM improved lung function, with less damage to alveolar epithelium, resulting in reduced pulmonary injury
Steimback *et al*[18]	Animals with extrapulmonary lung injury	Randomized experimental study	Sigh with different PIP and frequencies	(1) Animals ventilated with V_T = 6 mL/kg and PEEP = 5 cm H_2O with no RMs; (2) Sustained inflation (40 cm H_2O for 40 s); (3) RM (180 sighs/h) and PIP (40 cm H_2O) (S180/40); (4) RM (10 sighs/h) and PIP (40 cm H_2O) (S10/40); and (5) RM (10 sighs/h) and PIP (20 cm H_2O) (S10/20)	The reduction in sigh frequency led to a protective effect on the lung and distal organs
Silva *et al*[8]	Animals with pulmonary and extrapulmonary lung injury	Randomized experimental study	Stepwise RM (5 cm H_2O/step, 8.5 s at each step during 51 s); Stepwise RM (5 cm H_2O/step, 5 s at each step during 30 s)	(1) Sustained inflation (30 cm H_2O for 30 s; (2) Stepwise PIP increase 30 cm H_2O over 51 s (STEP-51); and (3) Stepwise PIP increase over 30 s with maximum PIP sustained for a further 30 s (STEP-30/30)	Stepwise RM prevented fibrogenesis and endothelial cell damage

Summary of the results of clinical and experimental studies comparing different recruitment maneuver (RM) methods, according to population, intervention, comparison, outcome criteria. PEEP: Positive end-expiratory pressure; PIP: Peak inspiratory pressure; V_T: Tidal volume.

compared to sustained inflation, resulted in greater oxygenation and less hemodynamic impairment as reflected by lower central venous and pulmonary artery pressures, lower right ventricle workload, and higher cardiac output. In addition, the post-RM level of PEEP and lung recruitability should be taken into account to avoid complications related to high intrathoracic pressure during RMs[42,43].

Desaturation and barotrauma are less common complications of RMs. Hodgson *et al*[25], demonstrated that although 8 of 20 patients desaturated and exhibited transient circulatory depression during application of RMs, they had improved shunt fraction, oxygenation, and respiratory system compliance 60 min after maneuver application followed by PEEP titration. In a randomized controlled trial by Meade *et al*[29], five patients with ARDS developed ventilator asynchrony, three experienced discomfort during the RM, two had hypotension, and four developed barotrauma. However, some issues should be taken into account, such as the sedation protocol allowing spontaneous cycles during the application of a sustained maneuver for 40 s. In addition, the level of PEEP was returned to the same value as before RM application. On the other hand, in a previous observational study, Borges *et al*[44] demonstrated that two of 26 patients developed barotrauma; one case occurred 24 h and the other 12 h after application of the RM. Despite the preceding reports, recent data confirm that RMs are not associated with an increased risk of barotrauma[10,45].

Lung recruitability could provide valuable information before RM application to prevent possible deleterious effects. Oxygenation and respiratory system elastance are often used to evaluate response to RMs. Gattinoni *et al*[42] aimed to establish an estimation of lung recruitability in patients with ARDS based on three physiological variables: Oxygenation, respiratory system compliance, and alveolar dead space in patients exposed to a progressive increase in PEEP. However, these variables had low sensitivity and specificity to predict higher lung recruitability. Static lung compliance (the difference between respiratory system compliance and chest wall compliance) reflects transpulmonary pressure as well as lung recruitment, and could be used instead of respiratory system compliance to measure lung recruitability[46]. Esophageal pressure monitoring permits measurement of lung compliance, but its implementation in the intensive care unit setting is still a challenge. In research settings, computed tomography can be used to assess recruitment, as well as to individualize ventilation strategies in order to keep the lungs open[45,47,48]. Additionally, the use of lung ultrasonography (LUS) can be a useful imaging tool to assess lung aeration in critically ill patients[49,50]. In this context, studies have shown the utility of LUS in the detection and quantification of lung recruitment *via* a transesophageal approach[51] and *via* a transthoracic approach[50]. Electrical impedance tomography (EIT) can provide a good estimate of the amount of tidal recruitment and may be useful to individualize ventilatory settings[52,53]. Even though LUS and EIT offer, at the bedside, an easy, alternative way to evaluate lung recruitment, both are inappropriate to detect hyperinflation.

Response to RMs and/or lung recruitability cannot be predicted a priori, and require individualized assessment. Recently, Cressoni *et al*[47] showed that extent of lung inhomogeneities increases as poorly aerated tissue increases from mild to severe ARDS (from 14% to 23%). In this study, high lung recruitability was considered in patients in whom the poorly aerated tissue area decreased with increasing PEEP, unlike in patients in whom poorly aerated tissue increased with increasing

pressure[47]. Additionally, poorly aerated tissue areas, *i.e.,* areas of tidal recruitment/derecruitment, are the primary targets of the inflammatory process in ventilator-induced lung injury[54]. In this context, severe ARDS is more recruitable than mild or moderate disease[42,47], and extrapulmonary ARDS is more recruitable than cases of pulmonary etiology. Several studies[55-57] have demonstrated that focal lung injury (pulmonary etiology) is associated with lower recruitability and alveolar overinflation in response to increased PEEP levels. In contrast, within the group of ARDS responders, in those with diffuse loss of aeration (extrapulmonary etiology), alveolar recruitment resulting from PEEP is not accompanied by lung overinflation[42,55].

Recently, Caironi *et al*[58] retrospectively analyzed a large cohort of patients with ARDS, aiming to describe lung edema and recruitability according to the Berlin definition and elucidate whether assessment of PaO_2/FiO_2 at standardized PEEP (5 or 15 cm H_2O) allows a more accurate description of ARDS severity as compared to its clinical assessment. They reported that the clinical PEEP applied when assessing PaO_2/FiO_2 may mask the underlying ARDS severity, and that application of the Berlin definition at 5 cm H_2O PEEP more accurately matches ARDS lung injury severity and recruitability, providing important information to guide ventilator strategies and to assess mortality risk.

TITRATION OF POSITIVE END-EXPIRATION PRESSURE

PEEP is required to recruit or maintain recruitment in the heterogeneous ARDS lung. The most common method for PEEP level selection is the use of $PEEP/FiO_2$ tables, introduced by the ARDS Network[3] and the LOVS study[29]. Although high PEEP values improve oxygenation and decrease alveolar stress[44], they can sometimes result in lung overdistension and hemodynamic instability[59]. An explanation for this discrepancy may be found in the heterogeneity of ARDS: A subpopulation of non-responders (patients with low recruitability) experience no change in arterial oxygenation with higher PEEP[60], and may be at greater risk of ventilator-induced lung injury from overdistention[61]. On the other hand, patients with predominantly recruitable lung (severe ARDS; PaO_2/FiO_2 < 150 mmHg) exhibit an association of oxygenation response and PEEP adjustment, as well as lower risk of death[62]. Recently, a Cochrane review of seven trials concluded that high PEEP levels are unrelated to hospital outcome as compared with low levels[63]. A relationship between higher PEEP and low mortality could be achieved in patients with more severe ARDS, in whom lung recruitability is higher[59]. In the era of identification of PEEP responders and/or high recruitability, attention to prevention of intratidal collapse and decollapse ("open the lung and keep it open!")[64] and lung function seems to be more relevant than oxygenation.

In a study of 57 patients with ARDS, Huh *et al*[65] compared daily decremental PEEP titration according to the best dynamic compliance performed after an RM *vs* PEEP selection as suggested by ARDSnet[3], based on a $PEEP/FiO_2$ table. In this protocol, an initial improvement in oxygenation occurred in patients who received decremental PEEP titration after RM compared to those in whom the $PEEP/FiO_2$ table method was used. This earlier improvement in oxygenation was not related to any advantage in respiratory mechanics within 1 wk, nor with 28-d intensive care unit mortality.

Cressoni *et al*[66] reported that, in mechanically ventilated patients in the supine position, collapse occurs first in the most dependent areas and overinflation in the less dependent regions, as observed on computed tomography analysis. This finding calls into question the use of a single pressure parameter to reflect the entire lung structure. Pintado *et al*[67], in a randomized controlled pilot study, suggested that PEEP application according to the highest compliance was associated with more organ dysfunction-free days and a trend toward lower mortality at 28 d as compared with FiO_2-guided PEEP selection, with no differences in oxygenation ratio or PEEP level among groups.

The new concept of transpulmonary pressure to titrate PEEP during the decremental method has emerged as a measurement of alveolar stability and alveolar stress. Rodriguez *et al*[68] showed that high and low transpulmonary pressure values were associated with lung overdistension and with reductions in oxygenation and collapse, respectively. In addition, a positive correlation has been observed between transpulmonary and airway pressures. Transpulmonary pressure reflects pleural pressure surrounding dependent lung regions at a given point, while airway pressure only reflects opened alveolar units. In this context, transpulmonary pressure could be a more representative measure to guide PEEP selection and prevent alveolar unit instability.

"Open-lung PEEP", first described more than 2 decades ago by Lachmann *et al*[64], represents the level of PEEP that combines the minimal tidal recruitment/derecruitment, overinflation, and dead space with optimal oxygenation and lung compliance. Open-lung PEEP should be achieved after an application of RM[44], which may open collapsed alveolar units, and should then be titrated gradually toward the minimum value that can stabilize the previously recruited lung[67]. RMs and PEEP titration are interdependent events for the success of ventilatory management.

CONCLUSION

RMs are a simple, low-cost, feasible intervention that can be performed at bedside in intensive care units. A wealth of experimental and clinical data has demonstrated improvements in oxygenation, lung mechanics, and lung re-aeration after application of RMs. Recent systematic reviews and meta-analyses suggest that RMs are associated with lower mortality in patients with ARDS. However, the optimal RM method (*i.e.,* that with the

best balance of benefit and harm) and the effects of RMs on clinical outcome are still under discussion, and further evidence is needed.

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ORIGINAL ARTICLE

Basic Study

In vivo analysis of intestinal permeability following hemorrhagic shock

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Abstract

AIM: To determine the time course of intestinal permeability changes to proteolytically-derived bowel peptides in experimental hemorrhagic shock.

METHODS: We injected fluorescently-conjugated casein protein into the small bowel of anesthetized Wistar rats prior to induction of experimental hemorrhagic shock. These molecules, which fluoresce when proteolytically cleaved, were used as markers for the ability of proteolytically cleaved intestinal products to access the central circulation. Blood was serially sampled to quantify the relative change in concentration of proteolytically-cleaved particles in the systemic circulation. To provide spatial resolution of their location, particles in the mesenteric microvasculature were imaged using *in vivo* intravital fluorescent microscopy. The experiments were then repeated using an alternate measurement technique, fluorescein isothiocyanate

(FITC)-labeled dextrans 20, to semi-quantitatively verify the ability of bowel-derived low-molecular weight molecules (< 20 kD) to access the central circulation.

RESULTS: Results demonstrate a significant increase in systemic permeability to gut-derived peptides within 20 min after induction of hemorrhage (1.11 ± 0.19 *vs* 0.86 ± 0.07, $P < 0.05$) compared to control animals. Reperfusion resulted in a second, sustained increase in systemic permeability to gut-derived peptides in hemorrhaged animals compared to controls (1.2 ± 0.18 *vs* 0.97 ± 0.1, $P < 0.05$). Intravital microscopy of the mesentery also showed marked accumulation of fluorescent particles in the microcirculation of hemorrhaged animals compared to controls. These results were replicated using FITC dextrans 20 [10.85 ± 6.52 *vs* 3.38 ± 1.11 fluorescent intensity units ($\times 10^5$, $P < 0.05$, hemorrhagic shock *vs* controls)], confirming that small bowel ischemia in response to experimental hemorrhagic shock results in marked and early increases in gut membrane permeability.

CONCLUSION: Increased small bowel permeability in hemorrhagic shock may allow for systemic absorption of otherwise retained proteolytically-generated peptides, with consequent hemodynamic instability and remote organ failure.

Key words: Small bowel ischemia; Hemorrhagic shock; Peptides; Microcirculation; Proteolysis

Core tip: Although the concept of systemically circulating molecules from the bowel in response to shock is not new (*e.g.*, bacterial "translocation"), the premise that small, proteolytically-derived molecules transit the bowel early in shock has not previously been examined. We offer evidence that proteolytically-derived peptides formed in the gut reach the systemic circulation in experimental hemorrhagic shock. The time-course and spatial disposition of low-molecular weight peptides *in vivo* was examined using real-time fluorescent intravital microscopy of the microcirculation and systemically as a first step towards demonstrating a pivotal role that these factors may play in affecting hemodynamic instability in early shock.

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INTRODUCTION

The small intestinal mucosa normally serves as a selective barrier to uncontrolled transport of large-molecular weight bowel contents into the systemic circulation, while simultaneously allowing the absorption of low-molecular weight nutrients necessary to sustain life. Severe hemorrhagic shock leads to decreased organ perfusion, especially to the bowel. Resultant ischemia to the gut adversely affects its function, and in particular the ability of the small bowel to act as a selective barrier to the uncontrolled egress of lumenal molecules into the systemic circulation. It has previously been shown that destruction of the small gut lumenal surface occurs very early in shock, and that this destruction appears to be mediated by enzymatic (proteolytic) activity at the bowel mucosa[1,2]. Under normal circumstances the bowel is protected from enzymatic degradation by a proteolytically-impermeant mucus layer. Maintenance of this layer requires ATP, and the ability of the protective mucus layer to prevent digestive enzyme attack of the mucosal wall is degraded with ischemia[3]. With the mucus layer compromised in shock, digestive enzymes in the bowel are able to destroy the underlying enterocyte layer, cell-cell junctions and the serosa, leading to increases in bowel permeability[1].

Enteral infusion of (serine) protease inhibitors into the small bowel lumen has been shown to be protective in multiple forms of experimental circulatory shock that result in gut ischemia, including hemorrhagic, endotoxic, and peritonitis shock[4]. Infusion of protease inhibitors enterally (but not systemically[5]) prevents or mitigates mortality in different species[6] after shock, including man[7], presumably by decreasing permeability of the small bowel to inflammatory mediators that otherwise cause systemic inflammation and multiple organ failure[8]. However, the mechanisms by which the mitigation of bowel injury improves outcomes after shock are largely unexplored.

Hemorrhagic shock has been reported to increase intestinal permeability, but this has largely been studied *ex-vivo* (*e.g.*, Ussing chambers[9]) or using small markers such as radio-labeled sugars[10] or at single or later time points[11,12]. As such, the time-course and the extent of bowel permeability changes in this condition are largely unexplored. We hypothesized that proteolytically-derived peptides may be among the earliest mediators to cross the bowel mucosal barrier in shock and sought to determine their time-course *in vivo*, in order to further delineate the role and timing of bowel-mediated inflammation and remote organ injury in hemorrhagic shock.

MATERIALS AND METHODS

Ethics statement

The animal protocol was reviewed and approved by the University of California, San Diego Institutional Animal Care and Use Committee and conforms to the Guide for the Care and Use of Laboratory Animals by the United States National Institutes of Health (NIH Publication No.

85-23, 1996).

Animals and surgical procedure

Eight-week-old non-fasted male Wistar rats (300-350 g, Charles River Breeding Laboratories, Wilmington, Mass) were randomly assigned to either hemorrhagic shock (n = 11) or sham shock control groups (n = 11). The animal protocol was designed to minimize pain or discomfort to the animals. The animals were acclimatized to laboratory conditions (23 ℃, 12 h/12 h light/dark, 50% humidity, ad libitum access to food and water) for over one week prior to experimentation. Animals were not fasted before experiments.

Animals were anesthetized (pentobarbital sodium, Abbott Laboratories, North Chicago, IL, 50 mg/kg, *im*) and the left femoral vein and artery were cannulated to facilitate continuous cardiovascular monitoring and blood withdrawal for the experimental procedure. Further pentobarbital was given intravenous (*iv*) as necessary to maintain adequate anesthetic plane. Heparin was given (10 U/mL *iv*) to facilitate exsanguination and prevent clotting in all animals. The animals breathed spontaneously without tracheotomy.

Shock protocol

Hemorrhagic shock was induced by careful removal of blood *via* the femoral vein in 1 mL aliquots until a mean arterial pressure (MAP) of 35 mmHg was achieved. The MAP was maintained at 35 mmHg for 100 min, at which time shed blood was re-warmed to 37 ℃ and slowly reinfused in 1 mL aliquots, analogous to blood withdrawal, *via* the femoral vein. Animals were then observed for 100 min (Reperfusion) before termination of the experiment (Beuthanasia®, 0.22 mL/kg, *iv*). This model of hemorrhagic shock has previously been shown to result in ischemia-mediated damage to the small bowel[2,4]. Sham-shock animals were instrumented and manipulated as above without hemorrhage as the comparator group.

Fluorophore-coupled casein injection into the small bowel

To determine the ability of bowel-generated proteolytically-cleaved peptides to diffuse into the central circulation, fluorescently-labeled casein (EnzChek Protease Assay kit, red-fluorescent BODIPY® TR-X, Invitrogen, Life Technologies, Grand Island, NY) was injected into the small bowel before the shock procedure (n = 6, both shock and sham shock control groups). The casein is labeled with multiple fluorophores and only fluoresces upon proteolytic cleavage. In confirmatory separate experiments, and because the molecular weight of the fluorescent casein-derived peptides was unknown, fluorescein isothiocyanate (FITC)-dextrans 20 (Sigma, St Louis), as a known molecular weight marker (20 kD MW) was substituted for the fluorescently-labeled casein (n = 5, both shock and sham shock control groups). Before induction of hemorrhagic shock (or analogous time period in the sham-shock control group) a midline incision was made and the small intestine was carefully exteriorized from the abdomen onto moist warmed (37 ℃) gauze. Either one ml casein solution or FITC-dextrans 20 was injected sequentially along the length of the small bowel from the cecum proximally to the duodenum (10 mL of fluorescent solution total).

In vivo intravital fluorescent imaging of the rat mesentery

The rat mesentery was gently exposed and draped over a transparent pedestal on a heated animal stage (at 37 ℃) as previously described[13]. The mesentery preparation was continuously superfused (2.0 mL/min) with Krebs-Henseleit solution (37 ℃) containing a 95% N_2-5% CO_2 gas mixture, with care taken to maintain adequate fluid superfusion of the tissue. The mesenteric microcirculation was imaged using an intravital microscope [water immersion objective lens (× 25, numerical aperture = 0.60, Leitz; Wetzlar, Germany)] by a color charge-coupled device camera (DEI-470, Optronics Engineering; Goleta, CA; frame rate 1/125 s for bright field and 1/2 s for fluorescence light). All images were recorded (Model AG-a270P, Panasonic; Tokyo, Japan) and digitally stored for analysis. Fluorescent images were elicited using a 200-W mercury lamp. The light was passed through a quartz collector, heat filter (KG-2, Zeiss; Oberkochen, Germany), and fluorescent filter set (Excitation/Emission: 590/625 nm for casein peptide-derived fluorescence, Excitation/Emission: 485/535 nm for FITC dextrans-20 fluorescence (in separate experiments), L3 filter cube, Ploempak, Leitz). Single microscopic fields (approximately 300 μm × 350 μm) containing arterioles and venules were examined. Wright's stain was used to identify the presence of inflammatory cell types. Briefly, mesentery sectors were excised, fixed in cold acetone (10 min) and subsequently stained with Wright's stain (1 min). Slides were washed, dehydrated and cover-slipped for imaging.

Plasma and organ fluorescence assay

After injection of fluorescent casein into the lumen of the small intestine, blood (50 μL) from the femoral artery was collected every 20 min for the duration of the experiment (200 min total) and plasma fluorescence was read immediately (SpectraMax Gemini XS, Molecular Devices, Sunnyvale, CA). In animals injected with FITC-dextrans 20, plasma was collected before the shock period and at reperfusion. At the end of the experiments heart, liver and lungs were collected, homogenized and fluorescence readings were performed to determine casein-derived peptide concentrations in these organs.

Statistical analysis

Results are presented as mean ± SD, where applicable. Unpaired comparisons of means between two groups in time were carried out using Repeated Measures ANOVA or two-tailed Student's t-test where appropriate;

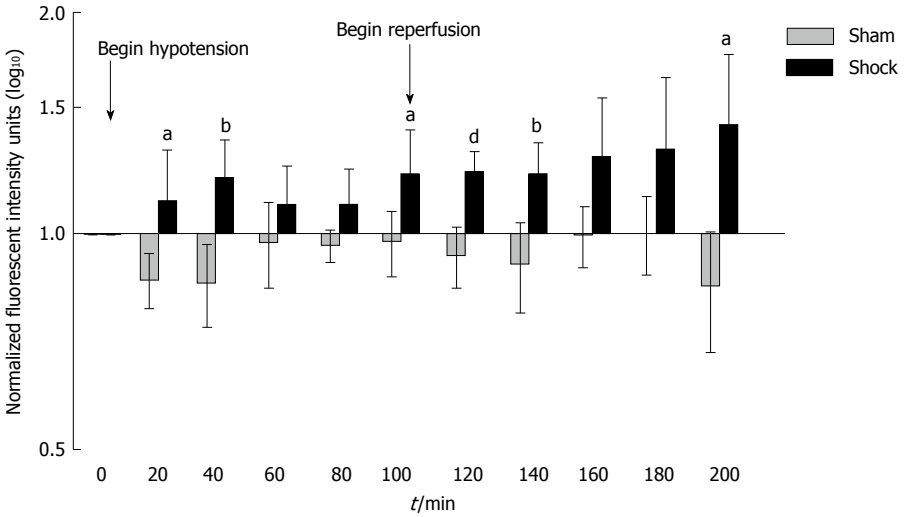

Figure 1 Increased bowel permeability to casein peptides after hemorrhagic shock. Small bowel permeability as measured by systemic concentrations of proteolytically-generated peptides from fluorescently labelled casein injected into the small bowel. Note the early increase in bowel permeability at 20 min, followed by a second, sustained increase in bowel permeability at reperfusion. Values normalized to background fluorescent levels in the systemic circulation at time T = 0 and plotted as $\log_{10}$ concentrations. Results reported as Mean ± SD. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{d}P < 0.001$ using Repeated Measures ANOVA for hemorrhagic shock ($n = 6$) *vs* sham-shock control ($n = 6$) groups at each time point.

comparisons between measurements in the same group were conducted using two-tailed Student's paired *t*-test. Because of significant differences between pre-ischemic values in the (plasma) casein-derived peptide experiments data were normalized prior to conducting statistical comparisons. $P < 0.05$ was considered to be significant.

RESULTS

Concentrations of fluorescent casein-derived peptides increase in the plasma of shocked animals in a time-dependent fashion

Hemorrhagic shock (average volume of blood withdrawn and subsequently reperfused: 6.6 ± 2.9 mL) led to time-dependent increases in small bowel permeability compared to that of sham-shock control animals as measured by increases in bowel-derived proteolytically-generated peptide fluorescence in the central circulation (Figure 1). A significant increase in small bowel permeability was apparent by as early as 20 min ($P < 0.05$ compared to the sham-shock control group), and was followed by a second and sustained increase in measured permeability upon reperfusion of shed blood ($P < 0.05$ and 0.01 compared to the sham-shock control group).

Fluorescence-conjugated casein peptides enter the systemic circulation and circulate in the mesentery tissue and microvasculature

Co-incident with increased plasma concentrations in shock animals, the number of fluorescently-conjugated casein-derived peptides was substantially greater in the parenchyma and microvasculature of the mesentery of shocked animals ($n = 6$) compared to their non-shocked controls ($n = 6$) (Figure 2). Of note, there appeared to be extensive co-localization of casein-derived peptides with white blood cells in the microcirculation (Figure 3), suggesting that some of these casein-derived peptides may be inflammatory. In order to quantify the increases in bowel permeability to small molecular-weight molecules, in confirmatory experiments the larger FITC-dextrans 20 (molecular weight approximately 20 kD) tracer was injected into the small bowel instead of fluorescent casein at the initiation of the experimental procedures. These results demonstrate a significant increase in measured FITC fluorescence in the plasma of shocked animals ($n = 5$) compared to sham-shock controls ($n = 5$) after reperfusion [10.85 ± 6.52 *vs* 3.38 ± 1.11 fluorescent intensity units ($\times 10^5$, $P < 0.05$)]. There were also significant increases in permeability-mediated FITC fluorescence after 100 min reperfusion compared to initial values in both shocked animals (10.85 ± 6.52 *vs* 3.97 ± 4.52, $\times 10^5$, $P < 0.05$, $n = 5$) and controls (3.38 ± 1.11 *vs* 1.44 ± 0.64, $\times 10^5$, $P < 0.05$, $n = 5$) (Figure 4). Intravital microscopy of the rat mesentery confirmed increases in microvascular permeability to FITC-dextrans 20 after hemorrhagic shock (Figure 5). However, less extravasation of FITC-dextrans 20 into the surrounding tissues was observed compared to that seen with casein-derived peptides, suggesting a possible differential increase in vascular permeability to the larger FITC-dextrans 20 molecule. Fluorescence of casein-derived peptides in remote tissues ($n = 4$ for both groups) displayed no significant differences in heart tissue (3210.7 ± 493.8 *vs* 2406.2 ± 841.8, $P = 0.15$) liver (4124.6 ± 1193.2 *vs* 6234.8 ± 1894.4, $P = 0.11$), and lung (2860.4 ± 1149.6 *vs* 3055.8 ± 1117.8, $P = 0.81$) in the shock group compared to sham-shock controls.

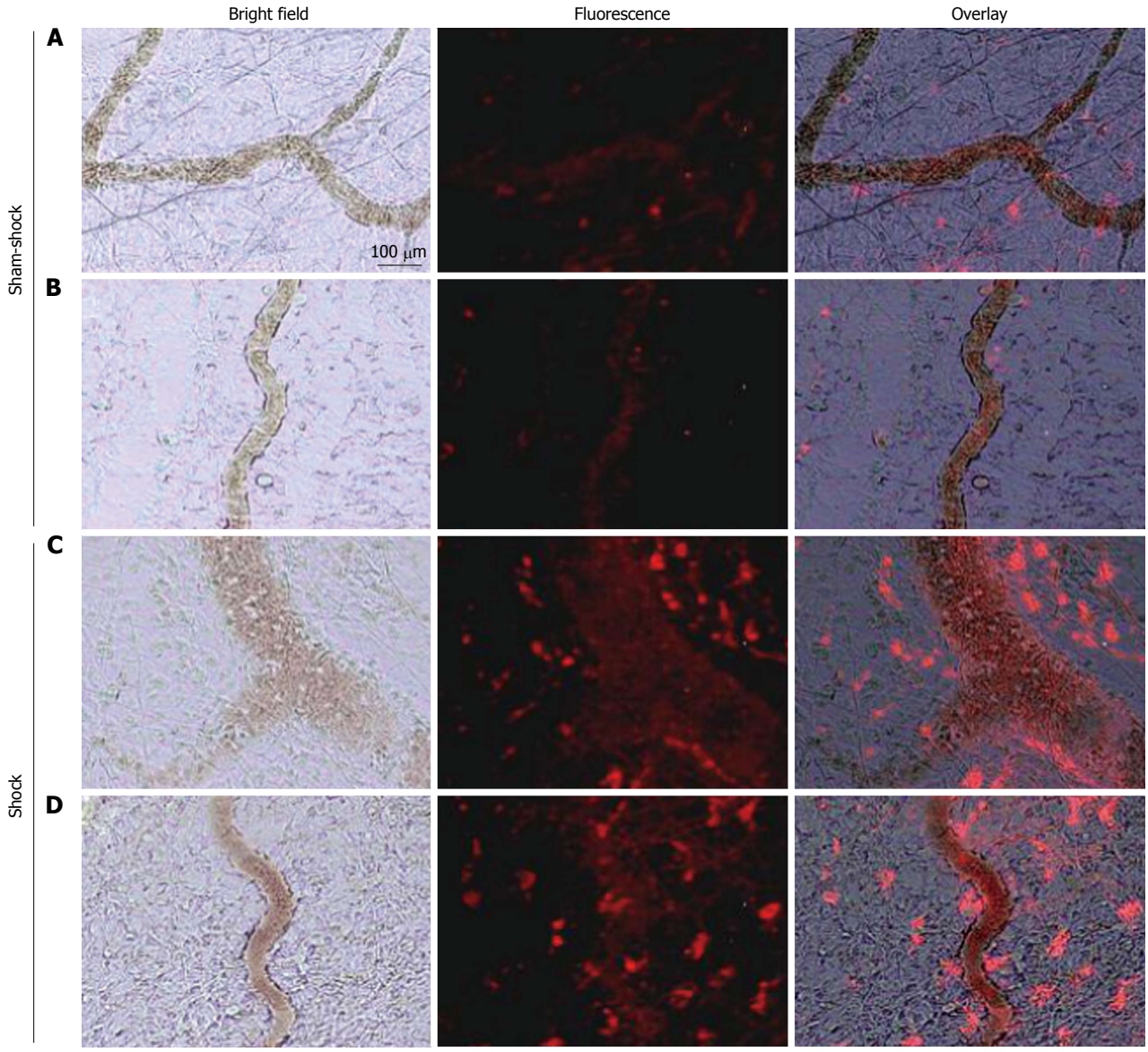

Figure 2 Selected *in vivo* microvascular images from two different sham-shock control (A and B) and shock (C and D) animals (*n* = 6, both groups) after hemorrhagic shock or sham-shock and reperfusion. Note the significantly higher levels of red fluorescent casein-derived peptides in the microvasculature and within the interstitium in shock animals (C and D) compared with their sham shock counterparts (A and B).

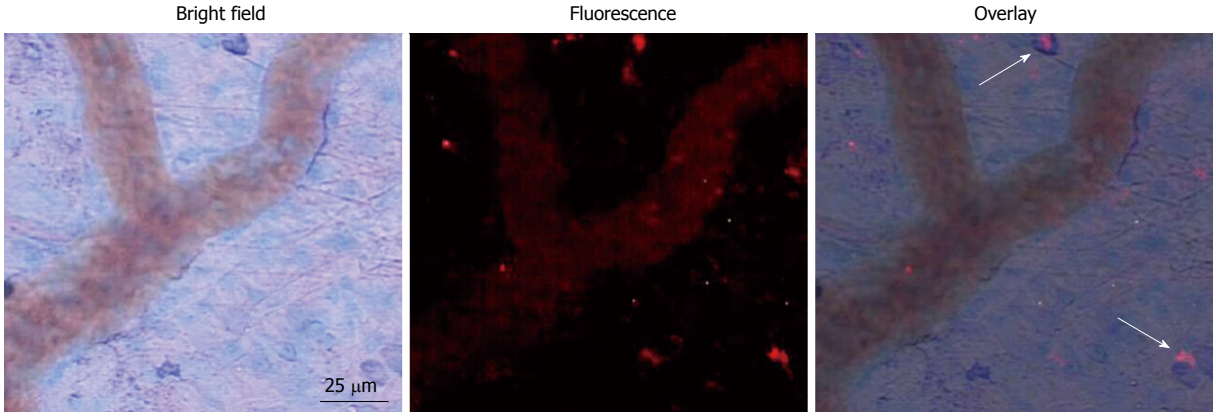

Figure 3 Representative micrograph with overlays depicting infiltration of white blood cells into the mesentery following shock. Arrows indicate co-localization of fluorescent casein-derived peptide with white blood cells, suggesting a possible inflammatory component to the casein-derived peptides.

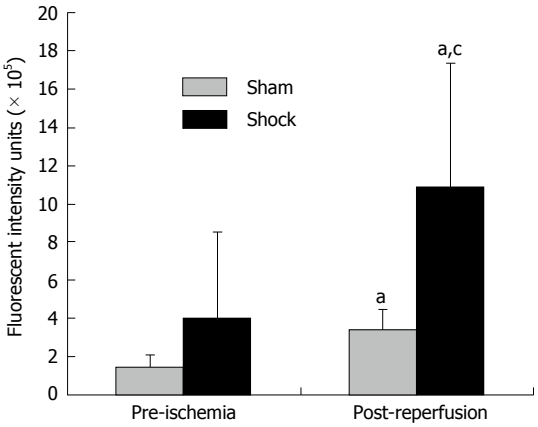

Figure 4 Increased bowel permeability after fluorescein isothiocyanate-Dextrans-20 after hemorrhagic shock. Small bowel permeability after experimental hemorrhagic shock as measured by systemic concentrations of FITC-Dextrans-20 injected into the bowel. $^{a}P < 0.05$ post-reperfusion *vs* initial values using two-tailed paired Student's *t*-test, $^{c}P < 0.05$ shock group ($n = 5$) *vs* sham-shock controls ($n = 5$) using two-tailed unpaired Student's *t*-test.

DISCUSSION

It has become increasingly apparent that fulminate circulatory shock, regardless of origin, results in small bowel ischemia[4]. Likewise, there is increasing evidence to suggest that prevention of bowel ischemia is beneficial to the organism, and preventing proteolytic digestion of the bowel mucosa, arising as a consequence of bowel ischemia, leads to improved outcomes in experimental shock[3,14,15]. The mechanisms by which bowel ischemia results in multiorgan failure and shock, are however, incompletely understood. It has long been hypothesized that "translocation" of bacterial product from the bowel to the systemic circulation contributes to deleterious outcomes in shock[16,17], but data supporting this theory are sparse and contradictory[10,18]. More importantly, there has been very little progress from a clinical perspective in attempting to modify or mitigate bacterial "translocation", which lessens enthusiasm for this approach[19].

Alternatively, bowel ischemia, as we demonstrate here in response to experimental hemorrhagic shock of non-gastrointestinal origin, leads to very early increases in microvascular permeability to relatively low molecular weight products from the lumen of the bowel into the systemic circulation. Gut-derived peptides lie on a continuum from approximately 0.1-10 kD, several orders of magnitude smaller than bacteria and their generated inflammatory products[20], and can be found in a myriad number of forms and configurations. Therefore, it is reasonable to suggest that gut-derived peptides are among the first molecules from the bowel to enter the central circulation and subsequently reach remote organs. That many of these peptides have vasoactive and/or inflammatory potential is well-established, including peptides derived from casein[21,22].

We propose that some of the initial inflammatory mediators that circulate systemically in early experimental hemorrhagic shock are gut-derived proteolytically-generated peptides. Although increased bowel permeability in response to shock and other stressors has been well-documented as a general concept[23] and to fixed molecular weight tracers[24], we demonstrate here under real-time *in vivo* observation that in experimental hemorrhagic shock there is a significant increase in small bowel permeability compared to sham-shock control animals within 20 min of ischemia to proteolytically generated peptide products from the gut, implicating bowel compromise as an early and perhaps inciting event in this model. The rapid increase in measured bowel permeability during early ischemia occurs during a low-perfusion state with concomitant limited flux of fluorescently-labelled peptides, implying an under-estimation of the permeability changes occurring at the bowel mucosa at this time. Conversely, sustained increases in small bowel permeability measured after blood reperfusion, where there is increased flux and possible "wash-out" of fluorescent tracer, may represent an over-estimation of increased bowel permeability rather than a second "reperfusion" injury.

An interesting observation from the study was the noticeable and frequent co-localization of casein-derived peptide fragments with possible inflammatory cells (mast cells *vs* macrophages, *etc*.). Although inflammatory activity of casein-derived peptides has previously been reported, this has not been directly confirmed *in vivo*[25-27]. Further investigation is necessary to confirm the robustness and clinical relevance of these findings, as fluorescently-labelled casein and FITC-dextrans 20 were used as markers of permeability and not for assessment of their intrinsic biologic activities. It is appreciated that there are limitations to the use of fluorescently-labelled markers when assessing permeability; it was for this reason that we chose to study small-molecule permeability using two different markers[28].

There are several limitations to this study. Among these includes our inability to categorize precisely the molecular weights of the fluorescently-bound casein-derived peptides secondary to the extreme heterogeneity of the cleavage products and the non-linear distribution of the fluorophores on the parent protein. However, it can be reasonably inferred that the MW's of these fluorescent compounds are between 0.1-10 kD, (parent compound MW: 19-25 kD) and smaller than native casein[29]. Previous studies indicate that these peptides are produced in the bowel rather than proteolytically generated in the circulation after becoming systemic[3,30,31]. Although there is a lack of ancillary temporal data correlating *in vivo* effects with increases in permeability, confirmatory measurements using FITC-dextrans 20 support the assertion that *in vivo* permeability to larger molecular-weight particles also increases to some extent in shock[23,24]. Further studies using calibrated tracers at discrete time-points and anatomic locations are necessary to completely quantify these findings. Heparin given systemically before experimental hemorrhage is a possible confounder to our

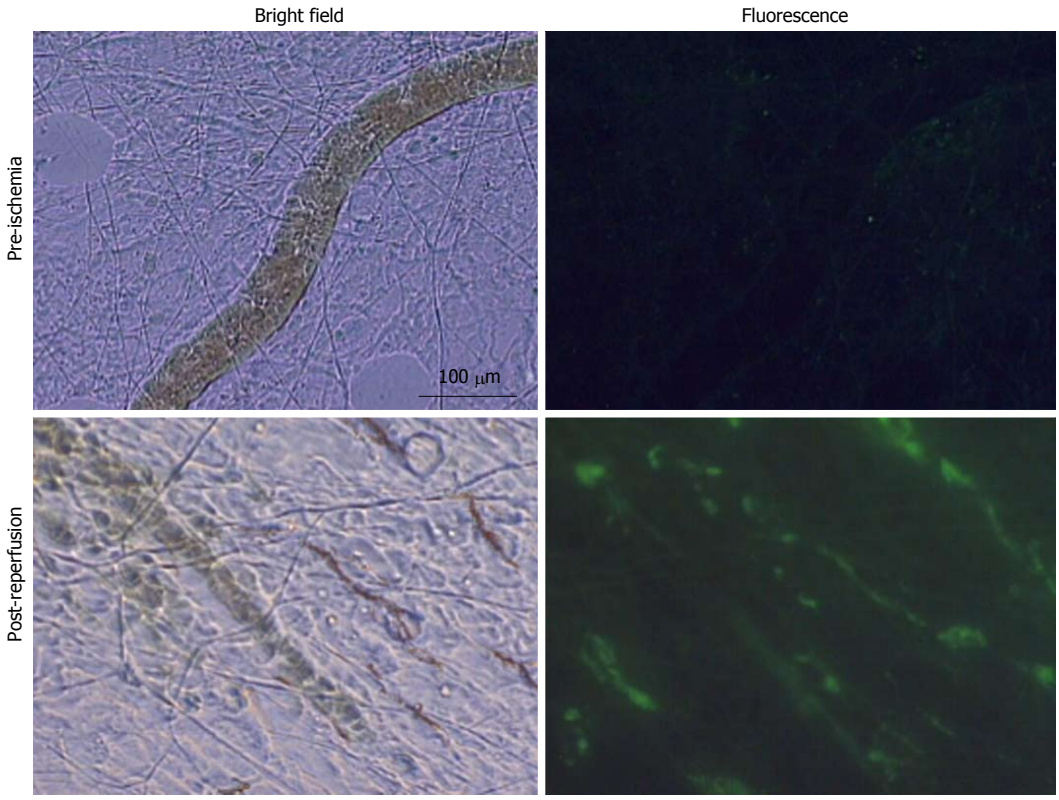

Figure 5 Selected *in vivo* microvascular images of the mesentery from a shock animal pre-ischemia and 100 min post-reperfusion (*n* = 5). Note the significantly higher levels of fluorescein isothiocyanate-dextrans-20 in the microvasculature *vs* initial values and the relative lack of flow after reperfusion.

results when the coagulopathy of hemorrhage/trauma is considered. This is an unavoidable aspect of our hemorrhage model in which blood otherwise clots the catheters and while stored during the ischemic period. An unanticipated result was the heterogeneous accumulation of the fluorescently-labelled peptides in remote tissues. Because of the marked increase in fluorescently-labelled peptides in the mesentery and systemic circulation of animals exposed to experimental hemorrhagic shock compared to sham shock controls it was anticipated that remote tissues would demonstrate similar increases in gut-derived peptide concentrations after shock. The reasons for this lack of difference are unclear but could be due to preferential absorption in other non-measured tissues, heterogeneous accumulation in the selected organs, or simply minimal measured peptide uptake relative to organ tissue mass. Finally, it is acknowledged that the definition of "permeability" as used in these studies is semi-quantitative, in that what is measured is the resulting accumulation of tracer in the measured (vascular or tissue) compartment. As all variables except the changes in permeability are held constant between groups, the permeability results presented here are, strictly speaking, a ratio of permeability changes between the control and shock groups and as such are necessarily semi-quantitative[32].

In conclusion, this study demonstrates that early increases in small bowel permeability occur during experimental hemorrhagic shock and that proteolytically-derived peptides may be the defining molecules that instigate early inflammation and hemodynamic compromise. Further studies are needed to determine precisely the identity of these putative gut-derived inflammatory mediators and their origin, as well as strategies for preventing their egress into the systemic circulation.

COMMENTS

Background

Ischemia resulting from acute hemorrhage compromises the intestinal barrier, leading to increased permeability of the membrane to bowel-derived contents. Some of these molecules may be intrinsically inflammatory and may possibly contribute to the organ dysfunction and mortality seen in shock.

Research frontiers

The ability of intestinal products, particularly those that are proteolytically generated, to escape into the central circulation following acute blood loss and their subsequent fate is not well understood. The authors were interested in determining *in vivo* the time course and the extent to which these particles access the central circulation following hemorrhagic shock.

Innovations and breakthroughs

The authors demonstrate in this manuscript that early increases in small bowel permeability occur very early during experimental hemorrhagic shock.

Applications

Proteolytically-derived peptides from the bowel enter the systemic circulation early in shock and may be defining molecules that instigate early inflammation and hemodynamic compromise in shock and associated poor bowel perfusion states.

Peer-review

This is a well written study investigating intestinal permeability after shock in a

rodent model.

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ORIGINAL ARTICLE

Retrospective Study

Therapeutic temperature modulation is associated with pulmonary complications in patients with severe traumatic brain injury

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Author contributions: O'Phelan KH and Gonzalez C designed the research; Zaila KE and Gonzalez C performed the research; Denny KG performed the statistical analysis; O'Phelan KH and Merenda A wrote the paper.

Institutional review board statement: This study was reviewed and approved by the IRB (institutional review board) for the University of Miami and the Jackson Memorial Hospital.

Informed consent statement: Informed consent was waived due to negligible risk of harm and the significant importance of evaluating a complete data set. All personal identifiers were removed prior to analysis.

Conflict-of-interest statement: None of the authors have any conflicts of interests. This work was performed without funding.

Data sharing statement: Technical appendix, statistical code and dataset available from the corresponding author at kophelan@med.miami.edu.

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Abstract

AIM: To examine complications associated with the use of therapeutic temperature modulation (mild hypothermia and normothermia) in patients with severe traumatic brain injury (TBI).

METHODS: One hundred and fourteen charts were reviewed. Inclusion criteria were: severe TBI with Glasgow Coma Scale (GCS) < 9, intensive care unit (ICU) stay > 24 h and non-penetrating TBI. Patients were divided into two cohorts: the treatment group received therapeutic temperature modulation (TTM) with continuous surface cooling and indwelling bladder temperature probes. The control group received standard treatment with intermittent acetaminophen for fever. Information regarding complications during the time in the ICU was collected as follows: Pneumonia was identified using a combination of clinical and laboratory data. Pulmonary embolism, pneumothorax and deep venous thrombosis were identified based on

imaging results. Cardiac arrhythmias and renal failure were extracted from the clinical documentation. acute respiratory distress syndrome and acute lung injury were determined based on chest imaging and arterial blood gas results. A logistic regression was conducted to predict hospital mortality and a multiple regression was used to assess number and type of clinical complications.

RESULTS: One hundred and fourteen patients were included in the analysis (mean age = 41.4, SD = 19.1, 93 males), admitted to the Jackson Memorial Hospital Neuroscience ICU and Ryder Trauma Center (mean GCS = 4.67, range 3-9), were identified and included in the analysis. Method of injury included motor vehicle accident (n = 29), motor cycle crash (n = 220), blunt head trauma (n = 212), fall (n = 229), pedestrian hit by car (n = 216), and gunshot wound to the head (n = 27). Ethnicity was primarily Caucasian (n = 260), as well as Hispanic (n = 227) and African American (n = 223); four patients had unknown ethnicity. Patients received either TTM (43) or standard therapy (71). Within the TTM group eight patients were treated with normothermia after TBI and 35 patients were treated with hypothermia. A logistic regression predicting in hospital mortality with age, GCS, and TM demonstrated that GCS (Beta = 0.572, P < 0.01) and age (Beta = -0.029) but not temperature modulation (Beta = 0.797, *ns*) were significant predictors of in-hospital mortality [χ^2 (3) = 22.27, P < 0.01] A multiple regression predicting number of complications demonstrated that receiving TTM was the main contributor and was associated with a higher number of pulmonary complications (t = -3.425, P = 0.001).

CONCLUSION: Exposure to TTM is associated with an increase in pulmonary complications. These findings support more attention to these complications in studies of TTM in TBI patients.

Key words: Hypothermia; Fever; Pneumonia; Traumatic brain injury; Head injury

Core tip: Therapeutic hypothermia and normothermia (fever control) are used in patients with traumatic brain injury. This is most commonly done for intracranial hypertension control. The potential complications associated with this therapy when it is used outside of the scope of a closely regulated clinical trial are not well known. This is a retrospective review of patients with traumatic brain injury treated with therapeutic temperature modulation carried out to quantify the non neurological complications associated with this therapy.

O'Phelan KH, Merenda A, Denny KG, Zaila KE, Gonzalez C. Therapeutic temperature modulation is associated with pulmonary complications in patients with severe traumatic brain injury. *World J Crit Care Med* 2015; 4(4): 296-301 Available from: URL: http://www.wjgnet.com/2220-3141/full/v4/i4/296.htm DOI: http://dx.doi.org/10.5492/wjccm.v4.i4.296

INTRODUCTION

The systemic cooling of patients with severe traumatic brain injury (TBI) has become an established second tier treatment modality for refractory intracranial hypertension (ICP)[1-5].

Basic science evidence, anecdotal clinical reports and several low quality trials have suggested that the prophylactic application of this strategy (*i.e.,* primary therapeutic hypothermia) may also exert neuroprotective effects in severe TBI[6]; however, these benefits have not been confirmed by high-quality human randomized controlled studies. Thus, outside of well-designed clinical trials, the implementation of therapeutic hypothermia after head injury remains justified for and largely limited to patients with uncontrolled ICP elevation. Yet, there are concerns that induced hypothermia may be associated with hemodynamic, pulmonary and infectious complications, as significant pathophysiological changes are known to occur with its induction and maintenance, especially when prolonged for more than 48 h[7]. However, overall rates of serious hypothermia-related adverse events remain poorly studied in TBI[8]. Given the knowledge that systemic, non-neurological complications are an independent contributor to morbidity and mortality after TBI[9], a more rigorous evaluation of the potential adverse effects associated with the use of hypothermia becomes of crucial importance to better determine the safety profile of this strategy in the setting of TBI. The purpose of this study is to examine types and rates of clinical complications in our severe TBI population who are treated with therapeutic temperature modulation (TTM).

MATERIALS AND METHODS

The protocol was reviewed and approved by the institutional review board of our institution. This is a retrospective, observational cohort study. We carefully reviewed the charts for 114 patients with severe TBI admitted to our trauma center between 2007 and 2009. Inclusion criteria included a post resuscitation Glasgow Coma Scale (GCS) < 9, admission to the intensive care unit (ICU) > 24 h and non-penetrating TBI. Patients were divided into two cohorts: The treatment group that received TTM and the control group, which did not. Patients in the temperature modulation group received continuous surface cooling and temperature measurement *via* an indwelling bladder probe. This group included both therapeutic hypothermia with a target temperature of < 36 ℃ or induced normothermia with a target temperature of 36 ℃-37 ℃. The control group received intermittent acetaminophen as need to treat fever. The decision to use TTM and the degree of cooling were determined on an individual basis by the

Table 1 Baseline characteristics

	Temperature modulation	Control
No. of patients	44	70
M:F	1:4.5	1:4.4
Mean GCS (SD)	4.6 (1.9)	4.7 (1.9)
Mean age (SD)	33.3 (14.2)	46.5 (20.2)
Mortality	15.9%	31.4%

GCS: Glasgow Coma Scale.

clinical team. The clinical record was reviewed to identify the following events: pneumonia, pneumothorax, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), acute renal failure, cardiac arrhythmias, pulmonary embolism (PE) and deep venous thrombosis (DVT). Pneumonia was identified using a combination of the following criteria: purulent sputum, chest imaging with an infiltrate or consolidation, fever > 38 ℃, leukocytosis (> 12000 wbc/mm^3 or leukopenia < 4000 wbc/mm^3) or worsening oxygenation. Pneumothorax and DVT and PE were identified based on imaging and ARDS and ALI were identified using a combination of imaging and arterial blood gas findings. Data on length of stay in the intensive care unit, duration of mechanical ventilation and in hospital mortality were also collected.

Statistical analysis

All data were analyzed using IBM SPSS version 21. A logistic regression was conducted to predict hospital mortality and a multiple regression was used to assess number of complications. Independent variables for both models were age, GCS on admission, and temperature modulation.

RESULTS

Baseline characteristics

One hundred and fourteen patients with severe TBI (mean age = 41.4, SD = 19.1, 93 males), admitted to the Jackson Memorial Hospital Neuroscience ICU (mean GCS = 4.67, range 3-9), were identified and included in the analysis. Method of injury included motor vehicle accident (n = 29), motor cycle crash (n = 20), blunt head trauma (n = 12), fall (n = 29), pedestrian hit by car (n = 16), and gunshot wound to the head (n = 7). Ethnicity was primarily Caucasian (n = 60), as well as Hispanic (n = 27) and African American (n = 23); four patients had unknown ethnicity. Patients received either temperature modulation (*i.e.*, aggressive temperature control, as detailed below) or no continuous modulation (*i.e.*, permissive temperature management), and were monitored for number and type of complications, as well as in hospital mortality.

Temperature modulation

Forty-three patients underwent temperature modulation (TM). Specifically, eight patients were treated with induced normothermia (mean temp = 36.25 ℃, SD = 0.85) and 35 with mild therapeutic hypothermia (mean temp 34.8 ℃, SD = 0.75). Temperature modulation was achieved by application of antipyretic agents (acetaminophen) and surface cooling techniques.

Temperature modulation was combined for the remaining analyses (Table 1). In-hospital mortality and number of complications did not statistically differ between normothermia and hypothermia groups [pearson χ^2 (4) = 4.99, ns].

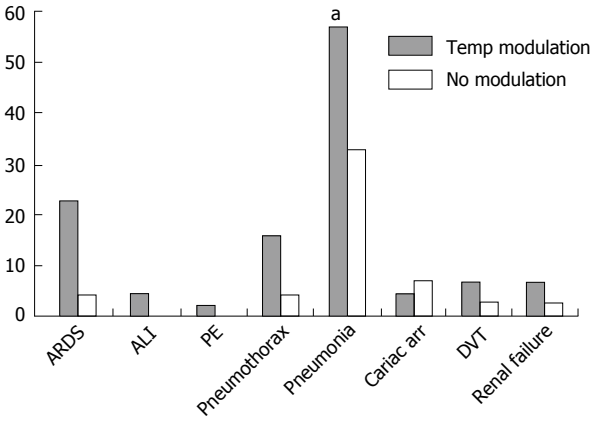

Figure 1 Complications by group. ARDS: Acute respiratory distress syndrome; ALI: Acute lung injury; PE: Pulmonary embolism; DVT: Deep venous thrombosis. $^aP < 0.05$.

Association of in hospital mortality with temperature modulation

Initially, an unadjusted analysis of mortality suggested a lower rate of mortality in TTM group (6% *vs* 19%, P = 0.06). However, the mean age in the TTM group was younger (33 years, SD 14) *vs* 46 years (SD 20). As expected, a logistic regression predicting in hospital mortality with age, GCS on admission, and temperature modulation demonstrated that GCS (Beta = 0.572, P < 0.01) and age (Beta = -0.029) but not temperature modulation (Beta = 0.797, *ns*) were significant predictors of in-hospital mortality [χ^2 (3) = 22.27, P < 0.01 when mortality was adjusted for age the difference between the groups was not significant.

Association of clinical complications with temperature modulation

A multiple regression predicting number of complications with age, GCS on admission, and temperature modulation demonstrated that receiving temperature modulation was the main contributor and was associated with a higher number of complications [F(3) = 4.59, P < 0.005, t = -3.425, P = 0.001]. Age (t = 0.71, *ns*) and admission GCS (t = 1.42, *ns*) were not significant contributors. Temperature modulation was significantly associated with ARDS, pneumothorax, and pneumonia (Figure 1).

DISCUSSION

The present study examined rates of medical com-

plications associated with the application of TM in patients with severe TBI. However, it was not designed to assess potential clinical benefits of TM as we did not measure long-term functional outcome.

Many physiological effects of hypothermia make its use theoretically attractive in the TBI setting. These include: (1) attenuation of neuro-excitotoxicity, *via* suppression of glutamate release, and ensuing stabilization of the intracellular influx of calcium (effects that ultimately reduce the magnitude of mitochondrial damage and cell demise secondary to the post-injury activation of multiple intracellular enzymatic cascades); (2) stabilization of the blood-brain barrier and blunting of the neuroinflammatory response from microglia, which may limit the development of cerebral edema and oxidative stress[10-12]; and (3) reduction in the cerebral metabolic rate of oxygen consumption (CMRO2) by approximately 7% for each degree Celsius decline in body temperature; the latter effect has the dual benefit of preserving brain oxygen stores (thereby conferring protection against cerebral hypoperfusion) and promoting cerebral vasoconstriction with ensuing decrease in ICP[13,14]. Nevertheless, despite these potential beneficial properties multiple randomized, controlled trials have failed to provide data in support of the primary application of induced hypothermia as a neuroprotective strategy aimed at improving mortality and functional outcome in TBI patients. In addition, concerns have been voiced about possible detrimental effects in trauma patients, with some evidence suggesting an increased risk for hemodynamic and pulmonary complications[7,15-17]. While data from a recent randomized controlled trial of 48-h hypothermia in TBI patients revealed "no significant differences in the percentage of patients with any individual complication or group of complications, whether critical or non-critical, between groups"[18], other clinical studies (mostly in patients with stroke and TBI) have reported a higher risk of adverse events, such as pneumonia, when cooling was carried out over longer periods of time (> 48-72 h)[19,20]. Nevertheless, the inadequate control for possible confounding influences (*e.g.*, poor glycemic control, barbiturate use) in those studies has left uncertainty over a causative link between induced hypothermia and risk of pneumonia or other complications.

The results of our study show that temperature modulation, applied for > 48 h, in the form of normothermia or hypothermia, is not a predictor of in-hospital mortality, but is associated with a significantly increased risk for pulmonary complications (pneumonia, ARDS, and pneumothorax). We were unable to detect a difference between the patients treated with normothermia *vs* those treated with hypothermia because the sample size was quite small. With regard to pneumothorax, we speculate that the increased incidence of pneumothorax may reflect a more prolonged and aggressive course of mechanical ventilation, with use of higher positive end expiratory pressure levels, in patient developing severe hypoxemia secondary to pneumonia or ARDS. Thus, the major systemic complications associated with the implementation of temperature modulation in TBI patients appear to be pneumonia and ARDS.

Our finding of an increased incidence of pneumonia with temperature modulation in a purely clinical setting is consistent with the results of 5 published systematic reviews and meta-analyses of randomized controlled clinical trials on the effectiveness of hypothermia in TBI[8,17,21-23], which identified 6 trials reporting a significant higher rate of pneumonia with induced hypothermia. Similarly, a more recent meta-analysis, which included 23 randomized controlled trials involving adult patients treated with therapeutic hypothermia of various duration (from several hours to several days) and for different indications (including TBI), revealed that patients undergoing systemic cooling were more likely to develop pneumonia (risk ratios, 1.44) compared to control groups[15].

An increased susceptibility to pneumonia may result from impaired central immune suppression after acute neurological injuries, including TBI. It is also possible that TM may promote the emergence of clinically apparent pneumonia by counteracting the ability of the body to fight infection. A substantial body of evidence from animal studies supports the concept that fever plays a central role in the host response to infection. The immunological effects of temperature elevation within a physiologic febrile range are multiple and beneficial. They include stimulation of neutrophil cell motility and phagocytosis, enhanced expression of receptors involved in mediating antibody responses, promotion of lymphocyte migration to sites of infection, and reduced growth of intracellular bacteria[24]. While these potentially beneficial consequences of fever cannot be disregarded, they come at the cost of a substantial increase in cerebral metabolic rate of oxygen consumption (CMRO2), neuroinflammation, activation of calcium-mediated intracellular enzymatic cascades, all of which may promote and exacerbate secondary brain injury. Thus, in TBI patients, a balance must be struck between the benefits of suppressing the above processes with temperature modulation and the potential detrimental effects on host defence mechanisms leading to an increased risk for infection.

It has been suggested that a longer duration of cooling increases risk of infection. This is consistent with the observation, in some clinical studies (mostly in patients with stroke and TBI), of a higher risk of pneumonia when cooling was carried out over more than 48 h duration[19,20]. This might explain why Clifton's second randomized trial, which limited the use of hypothermia to 48h, did not detect any significant difference in the rates of non-neurological organ dysfunction between hypothermic and normothermic patients. Unfortunately, this adds a layer of complexity to the management of TBI because a period longer than 48 h may be needed to sufficiently control brain edema. This longer

duration may expose the patient to an increased risk of complications. This may offset the potential benefits of prolonged cooling. Severe respiratory failure as a result of ARDS and/or pneumonia may adversely affect cerebral oxygenation and brain energy metabolism, and contribute to secondary brain injury. It is unknown if regional methods of cooling using new devices such as intranasal cooling[25,26] will offer the neurological benefits of TTM with fewer systemic side effects.

Our findings demonstrate that TM is associated with an increased incidence of pulmonary complications which may restrict the neuroprotective potential of this strategy. Inclusion of protocols to prevent pneumonia in patients with TBI undergoing TM may improve the efficacy of this strategy and should be included in future study protocols.

Our study has several limitations including the retrospective design, a small sample size and no functional measure of neurologic outcome. The questions raised here will need to be demonstrated in a larger study with a prospective design.

In conclusion, our study demonstrates that in patients with TBI, exposure to temperature modulation is associated with a significant increase in pulmonary complications, specifically, pneumonia, ARDS and pneumothorax. These findings support more detailed collection of information about these complications in studies of therapeutic temperature modulation in TBI patients to determine their relevance to outcome. Prospective studies are needed to determine possible detrimental effects on functional neurological recovery that could result from hypothermia-related complications such as ARDS and pneumonia.

COMMENTS

Background

The benefit of hypothermia used for neuroprotection is still debated. The benefits of this therapy have not been proven in large prospective randomized trials for patients with traumatic brain injury. However, the therapy is effective for lowering intracranial pressure. Therefore it is sometimes used for this population. Therefore it is important to understand the potential complications associated with its use.

Research frontiers

Current research efforts focus on the potential benefits of local or regional therapies for temperature management. These studies include trans nasal evaporative cooling which has been studied in cardiac arrest and stroke patients.

Innovations and breakthroughs

This study provides data taken from patients being treated outside of clinical trials. It may be more generalizable than data from carefully controlled trials with a very specific patient population.

Applications

This study should provide support for future studied to more carefully consider and collect data on pulmonary complications in patient being treated with therapeutic temperature modulation. Additionally, these data may inform the cost benefit analysis in a larger prospective study utilizing temperature management in this population.

Terminology

Therapeutic hypothermia or targeted temperature management: Is a therapy that tries to achieve and maintain a specific body temperature to mitigate tissue injury and improve outcome.

Peer-review

This retrospective review has issues with lack of definitions of the key outcome measures used.

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