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Review

Role of biomarkers in acute traumatic lung injury

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ABSTRACT

In severely injured patients severe thoracic trauma is common and can significantly influence the outcome of these critically ill patients by increased rates of mainly pulmonary complications. Furthermore, patients who sustained thoracic trauma are at increased risk for Acute Lung Injury (ALI) or Adult Respiratory Distress Syndrome (ARDS). Therapeutic options are limited, basically consisting of prophylactic antibiotic therapy and changing patient's positions. It is known, that ALI and ARDS differ clinically and pathobiologically from ALI/ARDS caused by other reasons, but the exact pathology remains elusive. Due to that no reliable predictive or surveillance biomarkers could be established for clinical diagnosis and identification of patients at high risk for acute traumatic lung injury. Nevertheless, there are plenty of promising markers that need to be further elucidated in larger case numbers and multicenter studies. This article sums up the recent status of those promising clinical biomarkers.

Contents

Abbreviations: AIS, Abbreviated Injury Scale; ALI, Acute Lung Injury; Ang-2, Angiopoietin-2; ARDS, Acute Respiratory Distress Syndrome; AUC, Area under the curve; BAL-F, Broncheoalveolar lavage fluid; BNP, Brain Natriuretic Peptide; CC16, Club Cell protein 16; DAMP, Damage Associated Molecular Pattern; ELISA, Enzyme Linked Immunosorbent Assay; HMGB-1, High Mobility Group Protein 1; ICAM-1, Intracellular Adhesion Molecule 1; IL, Interleukin; kDa, Kilodalton; LTB-4, Leukotriene B4; NFκB, Nuclear Factor Kappa B; PAI-1, Plasminogen Activator Inhibitor 1; PC, Pulmonary Contusion; PCP III, Procollagen Peptipe III; PMNL, Polymorphonuclear Leukocyte; RAGE, Receptor for Advanced Glycation End Products; SP-A/B/C/D, Surfactant Protein A/B/C/D; TLR, Toll Like Receptor; TNFα, Tumor Necrosis Factor α; VEGF, Vasoendothelial Growth Factor; VWF, Von Willebrand Factor.

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Introduction

In patients suffering from multiple injuries, severe thoracic trauma is common [1,2]. Out of all patients with an Injury Severity Score ≥ 16, 54.9% sustain severe chest trauma indicated by an Abbreviated Injury Scale (AIS) ≥3. Especially in these critically ill patients with concomitant chest trauma, high complication rates crucially deteriorate outcome [3–5]. Typical complications include disseminated intravascular coagulation and pneumonia, as well as acute lung injury (ALI) or its more severe form acute respiratory distress syndrome (ARDS) [6,7].

In Europe chest trauma is mainly caused by blunt mechanisms and rib fractures, pneumothorax and pulmonary contusion (PC) are frequently seen [8]. Especially patients with PC are at maximal risk for pulmonary complications, accordingly 50% of these patients show complications like pneumonia or ARDS during their clinical course [9,10]. Additionally, thoracic trauma is an independent risk factor for the development of ALI/ARDS in severely injured patients [11]. Treatment of patients at risk for these complications is limited to supportive care including prophylactic antibiotic therapy, mechanical ventilation with positive end expiratory pressure (PEEP), prone position or kinetic therapy [12,13].

In case of severe chest trauma, the cause of lung injury is multifactorial. First, the mechanical trauma itself causes direct damage to the lungs tissue. Second, an inflammatory response is activated, finally resulting in an increased leakage of the alveolocapillary permeability.

While main reasons for ALI and ARDS are non-pulmonary sepsis and pneumonia, major trauma is another common reason, whereby chest trauma increases the incidence of these syndromes [14]. Apart from trauma-associated acute lung injury, the pathology of ALI is due to injuries of the alveolocapillary membrane. Consequently, the increased permeability results in pulmonary edema and alveolar filling. Subsequently, inflammation cascades and activation of coagulation can compound the acute lung injury [15,16]. Among several other airway diseases, ALI and ARDS are associated with infiltration of the pulmonary wall by neutrophils. Consequently, lung tissue injury and micro vascular damage are caused by the release of proteolytic enzymes and oxidants. Caused by major trauma, indepently if including direct chest trauma or not, inflammatory responses are activated, which are usually mediated by toll like receptors (TLRs) and subsequently, through the activation of NFκB, inflammatory parameters are expressed [17]. Caused by the inflammatory response, polymorphonuclear neutrophils (PMNL) are recruited to the site of injury. Though the detailed pathophysiology of ALI remains unclear, the accumulation of neutrophils in the lung seems to be one major mechanism in developing ALI/ARDS after major trauma. The more severe form ARDS is defined as a bilateral radiographic infiltration and arterial hypoxemia without cardiac failure as primary cause [18]. ARDS is subclassified into cases with direct causes like bacterial or viral pneumonia, toxic inhalation, near drowning or lung contusion and indirect causes to whom sepsis, pancreatitis, massive blood transfusion and severe trauma can be allocated [18].

Despite its severity, outcome of patients suffering from trauma associated ALI/ARDS is better than for acute lung injury in patients with non-traumatic cause. This finding is not only due to a possible younger age and less co-morbidities in trauma patients [6]. Overall, in multiply injured patients the mortality after ALI is 10%, whereas the overall mortality of ARDS remains about 30% [19–22].

The search for a valid biomarker which could help to predict the development of ALI/ARDS or predict outcome is still ongoing.

The ideal biomarker should be sensitive, measurable, timely available and responsive, as Shehabi et al. designated a SMART biomarker [23]. Next to its predictive value, a reliable biomarker could influence clinical therapy and improve the knowledge of the pathophysiology pivotally. Regarding its role in endothelial injury, epithelial injury, coagulation, fibrosis, apoptosis or inflammation during the cellular injury a variety of potential biomarkers has already been tested. Although many promising biomarkers exist, none of them seems to be suitable as a solitary biomarker to predict patients at risk for impaired outcome, regardless of if ALI is trauma associated [16]. Additionally, most markers were evaluated in patients with ALI/ARDS without traumatic cause. Due to its possible different pathomechanisms, the results from biomarker studies investigating patients without trauma can not simply be transferred to patients suffering from trauma associated ALI [6].

Consequently, in severely injured patients no reliable biomarker for prediction or surveillance of these pulmonary injuries or complications is generally accepted, although there are a couple of biomarkers that showed a good correlation with acute traumatic lung injury and in parts with the complications during the clinical course of these trauma patients. In the following, these clinically tested markers are reviewed and described by their mechanistic role in the biological pathway during development of acute lung injury.

Methods

A systematic review of the literature was performed using the MedLine database, using the following search terms: (((biomarker [all fields] AND chest trauma [all fields] OR thoracic trauma [all fields] AND acute lung injury [all fields] OR adult respiratory distress syndrome [all fields] AND epithelial damage [subheading] or endothelial damage [subheading] or inflammation [subheading]))). Furthermore the search was extended to the Cochrane Library, Ovid Medline, AMED and Scopus Databases. To assess the current clinical role of the biomarkers, experimental studies were excluded from this review. Additionally, references of the retrieved documents were screened. Language was restricted to English and German.

Markers of epithelial damage

Club cell protein 16 (CC16)

Formerly known as Clara Cell protein, this protein is nearly exclusively secreted by the Club Cells of the terminal bronchial epithelium [24], whereas the production of CC16 by the prostate, endometrium and the kidneys is 10,000 fold lower than in the lung [25]. CC16 is a 15.8 kDa, antioxidant and anti-inflammatory protein that exerts its actions through modulation of phospholipase A2, interferon γ and tumor necrosis factor α. Over the past CC16 gained acceptance as a marker of acute and chronic non-traumatic lung injury [24,26,27]. The serum concentration of CC16 in healthy nonsmorkers is around 5–6 ng/ml with small deviation [28]. CC16 levels can easily be determined in serum and bronchoalvealor lavage fluid (BAL-F) via commercially available ELISA kits. Taken together, CC16 is accepted as a biomarker that correlates with the integrity of the pulmonary epithelium and can therefore be used as a marker for direct and indirect pulmonary damage [24,29–31].

Several studies examined the role of CC16 in acute traumatic lung injury. Wutzler et al. showed that serum levels of CC16 after multiple trauma were significantly higher in patients with severe thoracic injuries when compared to the multiply injured patients without chest trauma. Furthermore the serum levels revealed high correlation to the volume of lung contusion measured by computed tomography [28]. The results of Wu et al. showing markedly elevated CC16 serum levels in early stages of pulmonary contusion are in line with these findings [32]. The serum levels of patients who sustained severe chest trauma declined to baseline during the first 12–24 h, possibly due to its release after direct trauma and the short serum half-life by rapid glomerular filtration

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