Soluble Receptor for Advanced Glycation End Products Quantifies Lung Injury in Polytraumatized Patients

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GENERAL THORACIC

Background. **Biomarkers caused by blunt chest trauma might leak into the vascular compartment and therefore reflect the severity of parenchymal lung injury (PLI). Five promising proteins were preselected after a literature scan. The objective of our study was to identify a biomarker that is released abundantly into the serum shortly after trauma and reliably quantifies the loss of functional lung tissue.**

Methods. **Polytraumatized patients (aged ≥18 years, Injury Severity Score [ISS] ≥16) were included in our prospective observational study if they were admitted directly to our level I trauma center during the first hour after trauma occurred. Immediately after stabilizing the patient's condition, blood samples were taken and a whole-body computed tomographic (CT) scan was obtained. Biomarker levels were measured directly after admission and on day 2. PLI volume was calculated using volumetric analysis.**

Results. **One hundred thirty patients met the inclusion criteria. Compared with a matched healthy control population, median levels of the soluble receptor for advanced glycation end products (sRAGE) was almost 3 times higher and decreased by 41% on day 2. Higher initial median sRAGE levels were detected in patients with PLI compared with patients without PLI and in individuals with severe PLI compared with those with mild PLI. Spearman correlation analysis and a univariate linear log regression model revealed a significant correlation/equation between initial sRAGE levels and relative PLI volume. Receiver operating characteristic (ROC) statistics identified the initial sRAGE level as an indicator of severe PLI.**

Conclusions. **sRAGE levels measured shortly after trauma seem to be a promising diagnostic tool to assess the severity of PLI in polytraumatized patients.**

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Blunt thoracic trauma is 1 of the most common injuries in polytraumatized patients [1]. It represents a major challenge for clinicians because it very often causes parenchymal lung injury (PLI). Of 22,613 polytraumatized patients with an Injury Severity Score (ISS) [2] of at least 16 and an Abbreviated Injury Scale Thorax (AIS_{Thorax}) [3] of at least 2, 48% experienced lung contusions, whereas lung lacerations were found in 12% [4]. PLI is caused by a substantial mechanical insult to the chest, usually from high-energy traffic accidents or falls from great heights [4]. Although the parenchyma or the interstitium, or both, get lacerated in a bursting manner, resulting in cavity formation [5], the pathophysiologic characteristics of a lung contusion results from both direct tissue damage and activation of inflammatory responses. As the strong force on the chest wall reduces the thoracic volume, the intrathoracic pressure increases consecutively and compresses the lung parenchyma, subsequently leading to increased alveolocapillary permeability and interstitial hemorrhage. This condition is followed by edema formation around the area of initial injury [6] and finally by severe damage of the surfactant system [7], with resulting alveolar collapse, atelectasis, and consolidation of the injured areas of the lung, peaking at 24 to 48 hours after the trauma [8]. PLI has a major impact on the treatment regimen in the emergency department and the intensive care unit [1]. The risk of expected complications increases if the percentage of PLI volume exceeds 20% of total lung parenchyma [9, 10]. Unambiguous identification of at-risk patients directly after hospital admission is crucial for starting an appropriate treatment regimen and adapting therapeutic procedures to the actual and expected respiratory status in due time. Currently, whole-body computed tomographic (CT) scans are obtained routinely after admission. They provide fundamental information about the severity of chest trauma and give surgeons the opportunity to measure the extent of PLI using volumetric evaluation, which is not implemented in routine clinical examinations because it is time-consuming and needs a trained specialist to perform. Triggered by the PLI, certain biomarkers might leak from the lung epithelium into the vascular compartment. Because searching for such biomarkers may be worth considering, we scanned the literature and finally decided on 5 proteins. Soluble secretory isoform of the receptor

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for advanced glycation end products (sRAGE) is a transmembrane protein and a multiligand pattern recognition receptor that belongs to the immunoglobulin superfamily of cell surface molecules. It is present at high levels in the lung, mainly in alveolar type I epithelial cells [11]. Increased sRAGE levels were found in patients with acute respiratory distress symptom (ARDS) if they were ventilated [12] or if they had severe infections [13]. The low-molecular-weight club cell protein (CC16), which is secreted throughout the airway mainly by nonciliated bronchial epithelial cells, is an immune-modulating and antiinflammatory agent [14]. It might be a diagnostic biomarker for ARDS in individuals with ventilator-associated pneumonia [15]. Cytokeratin 19 (CK19) is an acidic (type I) cytokeratin that belongs to the family of keratins; it is found as a major component in various types of respiratory epithelial cells [16]. Cytokeratin fragment 21-1 (CYFRA21-1), the soluble fragment of CK19, is rarely detected in the circulation of healthy individuals, but it is frequently released into the blood of patients with cancer [17]. Increased CYFRA21-1 levels are found in patients with non-small cell lung cancer [18] and in patients with nonmalignant respiratory diseases [19]. Krebs von den Lungen 6 (KL-6) is a submolecule of mucin 1 (MUC1), a transmembrane high-molecular-weight mucin glycoprotein that is expressed on alveolar type II epithelial cells [20]. Serum levels of KL-6/MUC1 increase in various interstitial lung diseases [21] and in ventilated patients with ARDS [22]. Surfactant protein D (SP-D) is a member of the collectin family. It is predominantly synthesized and secreted into the alveolar space by alveolar type II epithelial cells and Clara cells [23]. Serum SP-D has been reported to indicate the severity of pneumonia, chronic obstructive pulmonary disease, tuberculosis [24], and ARDS [25].

Complementary to CT scans, biomarker levels might serve as a reliable tool to assess the health risk represented by PLI. Therefore the objective of our study was to evaluate if the serum levels of sRAGE, CC16, CYFRA21-1, KL-6/MUC1, and SP-D significantly changed within 1 to 2 hours after polytrauma; if 1 or several of these initial biomarker levels could reliably quantify the loss of functional lung tissue caused by PLI; and if the levels of the 5 selected biomarker levels measured on day 2 (24–48 hours after trauma) were significantly different from the corresponding biomarker levels measured directly after admission.

Patients and Methods

Our prospective observational study was planned for a period of 4 years. The inclusion criteria were (1) multiply injured patients with an ISS of at least 16, (2) minimum patient age of 18 years, (3) direct admission to our level I trauma center within 1 hour after the trauma, (4) transfer to the intensive care unit after initial treatment because of a compromised medical condition, and (5) survival of at least 24 hours. To minimize possible misinterpretations, burn victims and patients with known malignancies or chronic inflammatory lung diseases were excluded from our trial. After approval by the local ethics committee (Project No. 368/2011) we started to enroll patients in June 2011.

Blood Sampling and Analysis

At admission, routine venous blood samples were taken from the polytraumatized patients, filling 1 additional separating gel tube (Vacuette 4 mL; Greiner Bio-One International GMBH, Frickenhausen, Germany) for biomarker measurement. These samples were immediately centrifuged at 3000*g* for 15 minutes at room temperature. Thereafter serum was removed and stored at –80°C until assayed. A sample was used only if informed consent could be obtained by the patient or family members afterward; otherwise, it was discarded. Biomarker levels of study participants were measured again on day 2 after admission.

By means of enzyme-linked immunosorbent assay (ELISA) kits, levels of sRAGE (Human RAGE Immunoassay, Quantikine ELISA; R&D Systems, Inc, Minneapolis, MN; catalogue numbers DRG00, SRG00, and PDRG00), CC16 (Human Uteroglobin Immunoassay, Quantikine ELISA; R&D Systems, Inc; catalogue number DUGB00), SP-D (Human SP-D Immunoassay, Quantikine ELISA; R&D Systems, Inc; catalogue number DSFPD0), CYFRA21-1 (Human TM-CYFRA 21-1 ELISA Kit; DRG International Inc, Springfield, NJ; catalogue number EIA-5070), and KL-6/MUC-1 (Human Kl-6/MUC1 ELISA Kit; Shanghai BlueGene Biotech Co, LTD, Shanghai, China; catalogue number E01K0061) were measured according to the manufacturer's instructions. All samples were analyzed in triplicate, and the mean values were calculated.

Measurement of PLI

Because a Somatom Sensation Open CT scanner (Siemens Healthcare, Forchheim, Germany) is located in our trauma resuscitation room, whole-body-CT scans could be obtained directly after admission following a standardized protocol: tube voltage, 120 kV; tube current, 170 mAs; rotation time, 0.5 seconds; dose modulation enabled; and collimation, 20 $\times$ 0.6 mm in spiral mode. Because no contraindications for the use of intravenous contrast agent were known, only contrast-enhanced scanning was performed in the venous phase (120 mL/3 flow/55 seconds) covering chest and abdomen. Images were reconstructed in the soft tissue and lung window with a slice thickness of 3 mm in axial and coronal orientations. For quantitative analysis, CT data were transferred to an OsiriX (Pixmeo, Geneva, Switzerland) workstation. To avoid interobserver variation, 1 author (LLN) performed all volumetric analyses by manually defining regions of interest (ROI) for the borders of PLI and the lung itself on every 1 to 3 axial CT images using a 64-bit version of OsiriX, version 5.9 (Fig 1). ROI between the images with defined ROI were interpolated automatically by the software and adjusted manually, if necessary. PLI and total lung volumes were calculated in cubic centimeters, and PLI volume was expressed as a percentage of the total lung volume. All analyses were

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