Systemic Inflammation and Disseminated Intravascular Coagulation in Early Stage of ALI and ARDS: Role of Neutrophil and Endothelial Activation

Satoshi Gando,1,2 Takashi Kameue,1 Naoyuki Matsuda,1 Atsushi Sawamura,1 Mineji Hayakawa,1 and Hirokatsu Kato1

Abstract—To determine the existence of a close link between inflammation and coagulation in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) and to examine their prognostic value in the development of ARDS and clinical outcome, we made a prospective cohort study. The study subjects consisted of 57 patients: 19 patients with ARDS and 38 patients with ALI as defined by a Lung Injury Score of ≥2.5 and 1.0 to less than 2.5, respectively. According to the outcome, the patients were subdivided into the survivors and the nonsurvivors. Ten normal healthy volunteers served as control subjects. Plasma levels of soluble L-, P-, and E-selectins, intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (sVCAM-1), thrombomodulin (sTM), and neutrophil elastase were measured within 24 h after the diagnosis of ALI or ARDS. The number of systemic inflammatory response syndrome (SIRS) criteria being met by the patients and the disseminated intravascular coagulation (DIC) scores were determined simultaneously. The number of SIRS criteria and the DIC scores of the patients with ALI or ARDS showed high values, and more than half of the patients were complicated by DIC. The levels of sL-selectin in both groups of the patients were significantly lower than those of the control subjects. All other soluble adhesion molecules, neutrophil elastase, and sTM in the patients with ALI and ARDS were markedly elevated than those in the control subjects. The levels of sICAM-1, sVCAM-1, and sTM in the ARDS patients significantly increased compared with the ALI patients. The number of SIRS criteria and the DIC scores in the nonsurvivors showed higher values than those in the survivors. In addition, we found significant differences in the levels of soluble adhesion molecules, neutrophil elastase, and sTM between the survivors and the nonsurvivors. In conclusion, we found a concurrent activation of both inflammation and coagulation in the patients with ALI or ARDS. The results also suggest that systemic activation of inflammation and coagulation associated with endothelial injury has prognostic value for the development of ARDS and poor outcome.

KEY WORDS: acute lung injury (ALI); acute respiratory distress syndrome (ARDS); coagulation; inflammation; neutrophil; soluble adhesion molecules.

INTRODUCTION

The American-European Consensus Conference (AECC) committee described acute respiratory distress syndrome (ARDS) as a “syndrome of inflammation and increased permeability” and suggested the term acute lung injury (ALI) to describe the continuum of pathological responses to pulmonary parenchymal injury (1). They

1Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo, Japan.

2To whom correspondence should be addressed at Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo 060 Japan. E-mail: gando@med.hokudai.ac.jp
defined ALI and ARDS as a syndrome of inflammation. Primarily, inflammation is a physiological protective response to insult, which sometimes results in injury and organ dysfunction followed by endothelial injury. There is convincing evidence that leucocytes-endothelial interactions resulting from inflammatory reaction plays an important role in the pathogenesis of ALI and ARDS (2, 3).

Adhesion molecules mediate the interaction between leucocytes and endothelium as well as platelet and the endothelium. There are three families of adhesion molecules that play a central role in the leucocytes-endothelial interaction: the selectins, the integrins, and the immunoglobulin superfamily (4). The selectins are a group of surface glycoproteins essential to neutrophil margination and rolling along the vascular endothelium. Its members include endothelial E- and P-selectins and L-selectin expressed on leucocytes. The immunoglobulin superfamily comprises of intercellular adhesion molecules-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which are responsible for neutrophil attachment to endothelium (4). Proinflammatory cytokines and thrombin promote the synthesis and upregulation of these adhesion molecules, leading to adherence of neutrophils and activation of the endothelium. After adherence, neutrophils secrete several enzymes, such as myeloperoxidase and elastase from azurophil granules, which cause endothelial injury (4, 5). Now, the levels of circulating soluble adhesion molecules as a marker of leucocytes-endothelial activation, neutrophil elastase as a marker of neutrophil activation, and soluble thrombomodulin (sTM) as a marker of endothelial injury can be measured in a clinical setting.

In addition to inflammation, several studies have proposed the concept that coagulation abnormalities are involved in the pathogenesis of ALI and ARDS (2, 6, 7). Procoagulant pathways are upregulated and the fibrinolytic pathway is depressed, leading to florid alveolar deposition. Thrombin-induced intravascular coagulation enhances inflammatory responses by increasing vascular permeability, activating endothelial cells to produce proinflammatory cytokines and other mediators, inducing the accumulation of neutrophils (6–8). Intravascular and extravascular (intraalveolar) fibrin deposition is frequently found in the setting of ALI and ARDS (6, 7). These evidences suggest a critical link between coagulation and inflammation in ALI and ARDS (9). The role of inflammatory mediators including adhesion molecules in the development of ARDS has been studied (10, 11). We have demonstrated the important roles of coagulofibrinolytic abnormalities and neutrophil activation in the pathophysiology of ARDS (12–14).

It is now accepted that disseminated intravascular coagulation (DIC) can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction, and that DIC reflects an inflammatory disorder of the microvasculature (15). The derangement of coagulation and fibrinolysis in DIC is mediated by several proinflammatory cytokines (15). The persistent thrombin activity in DIC is closely linked to sustained systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) (15). These facts suggest that there are important links between the procoagulant and inflammatory mechanisms in the pathogenesis of organ failure in DIC patients.

Experimental and clinical investigations have examined the critical link between coagulation and inflammation in acute lung injury (6–9), however, few clinical studies have elucidated the systemic activation of coagulation and inflammation represented by DIC and neutrophil-endothelial interactions in patients with early stage ALI and ARDS. Thus, the aims of our study were systematic elucidation of changes in coagulation and neutrophil-endothelial activation markers at the early stage of ALI and ARDS, and to determine their predictive value for the development of ARDS and outcome.

**MATERIALS AND METHODS**

**Patients**

With approval of our Institutional Review Board and written informed consent from a relative, a total of 57 patients with ALI or ARDS were studied. Ten normal healthy volunteers served as control subjects. Approximately one-third of the patients overlapped with our previous studies (16, 17). Exclusion criteria for the study were patients <15 years of age or ≥90 years of age, patients with known clotting disorders or who were receiving anticoagulant therapy. The severity of illness of the patients was evaluated according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score (18).

**Definitions**

According to Murray’s Lung Injury Score (19), the patients were classified into two subgroups: those patients who met the definition of ARDS (with Lung Injury Score ≥2.5) and those patients at risk for but not developing