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Review Article

Role of Adhesion Molecules in Ventilator Induced Lung Injury

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Abstract

Adult Respiratory Distress Syndrome (ARDS) affects the lung in a patchy pattern with variability in compliance between areas of the lung. This syndrome of acute lung injury often requires mechanical ventilation which in itself may contribute to the propagation of the injury through high inflation pressure and over distention of lung tissue. This injury termed ventilator induced lung injury (VILI) involves multiple complex mechanisms but is characterized by microvascular leak and inflammatory cell influx. Foremost amongst the inflammatory cells is the polymorphonuclear cells (PMN) important in multiple inflammatory pathways including that of VILI. It's transmigration into lung tissue requires adhesion to the endothelium and then extravasation across the endothelial barrier along a cytokine gradient. Adhesion molecules on the surface of the PMN are responsible for endothelial adhesion, transendothelial migration and also have a role in signal transduction. These molecules have been the target of inhibition to attenuate VILI and are increasingly recognized as a potential therapeutic target and marker for this injury. We review the evidence for the role of these adhesion molecules in VILI referencing both animal and human studies hoping for a renewed interest in this complex mechanism of injury.

Keywords: *Ventilator-induced Lung Injury; Adult Respiratory Distress Syndrome; Cell Adhesion Molecules; Integrin; Antigens, CD18; Respiration, Artificial*

Abbreviations

ARDS: Adult Respiratory Distress Syndrome; VILI: Ventilator-induced Lung Injury; PMN: Polymorphonuclear Cell; MV: Mechanical Ventilation; CD11/CD18: Cluster of Differentiation 11/18; PECAM: Platelet Endothelial Cell Adhesion Molecule; VCAM: Vascular Cell Adhesion Molecule; V_T: Tidal Volume.

Introduction

Mechanical ventilation (MV) is the most important intervention in the management of critically ill patients with respiratory failure due to Adult Respiratory Distress Syndrome (ARDS). ARDS affects the lungs in a patchy pattern with variability in compliance between different areas [1,2]. A ventilator delivered breath goes preferably to the most compliant part of the lung over-distending alveoli in that region while the less compliant areas remain unventilated and collapsed. In severely damaged lungs a ventilator breath, however small, could cause over-distention and injury to the less damaged and more compliant part of lung thus propagating the injury [3]. Hence the lung damage caused by exposure to high inflation pressures, regional alveolar over-distension, and cyclical opening and closing of alveoli is referred to as Ventilator induced lung injury (VILI). In addition to direct structural damage to the lungs, mechanical forces induced by high tidal volumes have been shown to increase inflammatory mediators and lung levels of inflammatory cells [4,5]. Conversely lower tidal vol-

ume (V_T) ventilation has also resulted in a lower mortality at the bedside. In a clinical study by the ARDS network involving 800 patients comparing conventional V_T ventilation with lower V_T ventilation (6 cc/kg) a mortality benefit in the lower V_T group was observed [6].

Cell stretch *in vitro* has been shown to increase vascular permeability and induce chemo-attractant cytokines (chemokines) including IL-8, known to attract polymorphonuclear cells (PMN) [7]. On the other hand activation, adhesion and extravasation of PMNs across the vascular endothelial cells have been shown to contribute to increased permeability through alterations in endothelial barrier function [8]. This in turn could contribute in sustaining the initial stretch induced microvascular leak of VILI.

PMN migration into lung tissue is a complex process involving adhesion to the endothelium and then transmigration across the endothelial barrier. Adhesion to the endothelium is a prerequisite for PMN recruitment to inflammatory sites. This process is regulated by adhesion molecules like the CD11/CD18 adhesion receptors on the surface of PMN and by chemokine gradients critical for directing the PMN to the site of inflammation. The CD11/CD18 membrane surface adhesion molecule is an example of integrins which are transmembrane receptors composed of both α and β subunits that mediate cell to extracellular matrix adhesion and also signal transduction from the site of adhesion to the cell [9]. It has been shown that antibodies to the common ß subunit of ß2-integrins (CD18) inhibit PMN adhesion to endothelial cells, aggregation, and other adhesion dependent functions such as chemotaxis [10]. Inhibition of integrins (CD11/CD18) on the surface of PMNs, with antibodies to the common CD18 subunit protected against acute lung injury following peritonitis in a rabbit model of multiple organ failure [11]. This protective effect was accompanied by a reduction in PMN lung infiltration. This same protective effect of antibodies to CD18 was also seen in a rabbit model of lung injury where intra-tracheal and intravenous endotoxin was administered [12].

In a study, looking at the effects of PMN adhesion on VILI, Rimensberger., *et al.* reported that administration of leumedins, known to inhibit the expression of adhesion molecules on the surface of leukocytes specially PMNs, attenuated ventilator-induced lung injury [13]. The dynamic compliance and arterial oxygenation improved in animals receiving leumedin vs. those without and this was associated with reduction in PMN influx in the leumedin group. In another animal study the protective effect of adhesion molecule inhibition was observed by inhibiting a different adhesion molecule E-selectin [14]. In this study clarithromycin reduced ventilator-induced lung injury and decreased neutrophil recruitment into the alveolar spaces. The clarithromycin effect was mediated by preventing the increase in adhesion molecule E-selectin after VILI.

Another adhesion molecule Platelet-endothelial cell adhesion molecule-1 (PECAM1) is a cell adhesion molecule that is constitutively localized at cell-cell junctions that connect endothelial cells to one another. PECAM1 can be cleaved from endothelial cells in response to endothelial damage resulting in a secreted, shed protein (sPECAM1). Animals on high tidal volume ventilation had a four to six fold increase of mean sPECAM1 serum levels than the unventilated group, hence suggesting that circulating sPECAM1 may represent a promising biomarker for the detection and monitoring of ventilator-induced lung injury [15].

In human studies, increased concentrations of circulating soluble adhesion molecules have been reported in patients with systemic inflammatory response syndrome, septic shock, and cardiovascular diseases. Increased concentrations of adhesion molecules have also been associated with multiple organ dysfunction, disease severity, or death [16,17].

In a recent human study looking at serum adhesion molecules as outcome predictors in adults with severe sepsis requiring mechanical ventilation in the emergency department, adhesion molecule VCAM-1 levels was found to be a more powerful outcome predictor of hospital mortality than lactate and other conventional parameters on admission [18]. In this study increased plasma VCAM-1 concentration was suggested as useful in predicting in-hospital mortality among severely septic patients requiring MV.

Conclusion

In conclusion, adhesion molecules on the surface of PMNs are responsible for endothelial adhesion, transendothelial migration and signal transduction all of which represent important steps in the pathophysiology of VILI. Despite the abundance of animal studies only a few human studies exist. The role of adhesion molecules in VILI needs further investigation in human studies to determine if these molecules may qualify as potential targets to ameliorate VILI. Serum concentrations of adhesion molecules are increasingly recognized as markers for early organ injury and future studies are needed to explore whether these levels maybe incorporated in predictive models for prognostication and triage.

Conflict of Interest

No conflict of interest to be declared.

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