Acute Lung Injury

Pathogenesis of Adult Respiratory Distress Syndrome

Edited by

Homayoun Kazemi, MD
Albert L. Hyman, MD
Philip J. Kadowitz, PhD

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Introduction

Adult Respiratory Distress Syndrome (ARDS) is a multifactorial disorder of diverse etiology with a high mortality rate. The syndrome is associated with diffuse injury of pulmonary vascular endothelium and the alveolar epithelium. Proteolytic enzymes released by neutrophils, activation of the coagulation cascade, prostanoids and other vasoactive peptides all have been incriminated in the pathophysiology of this disorder.

This symposium on Acute Lung Injury and its relationship to ARDS focuses on new knowledge in areas of pulmonary physiology, pathology, biochemistry and pharmacology and their role in lung injury. The contributors have all been intensely involved in studies of pathophysiology of ARDS.

The symposium was organized under the auspices of the Cardiopulmonary Council of the American Heart Association and was held in Dallas, Texas, in September 1984. The organizers of the symposium gratefully acknowledge grants from the AHA, the Division of Lung Diseases, National Heart, Lung and Blood Institute, NIH, and the Upjohn Company.

We are also indebted to the staff of the AHA, in particular Mr. Leonard P. Cooke and Ms. Stephanie Stansfield, for their invaluable assistance in organizing the symposium.

Lastly, PSG Publishing Company and its president, Dr. Frank Paparello, have been particularly helpful in putting the proceedings of the symposium together and expediting their publication, and we express our special appreciation to them.

Albert J. Hyman
Philip J. Kadowitz
Homayoun Kazemi, Chairman
Program Committee for the Symposium
Cardiopulmonary Council of the
American Heart Association

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1 *The Pulmonary Vascular Bed in Acute Lung Injury– An Overview*

Homayoun Kazemi

This symposium addresses the pathophysiology and therapeutic approaches to acute lung injury. The concept of acute lung injury causing severe respiratory insufficiency, failure, and in many instances death, is relatively recent and has been identified as a clinical syndrome for less than 20 years.

Adult respiratory distress syndrome (ARDS) is one of varied etiology and is characterized by a constellation of clinical features and physiologic aberrations in the respiratory system. The cardinal features of ARDS are its relatively acute onset, presence of dyspnea and a rapid respiratory rate, arterial hypoxemia and decreased lung compliance, diffuse infiltrates on x-ray films of the chest and, physiologically, a leaky alveolar-capillary membrane.

The role of the pulmonary vascular bed is becoming more and more important in the pathogenesis of ARDS. In addition to the leaky alveolar-capillary membrane, there are other special features in the pulmonary vascular bed that are of particular interest and relevance to our understanding of this syndrome: There is significant loss of capillary units, there is invariably pulmonary arterial hypertension, there is clotting in large and small vessels, and on pathologic examination there is structural remodeling of precapillary pulmonary vessels. This intriguing and complex syndrome is believed to occur in about 150,000 persons per year in the United States and has a mortality rate of around 50% – in some series it may be as high as 90%[1] – and therapeutic modalities have not been particularly effective in saving patients with this syndrome in the past.

In their classic monograph on adult respiratory failure in 1972, Pontoppidan et al[2] devote a large part of their writing to the mechanical abnormalities of the lung and gas exchange derangements in ARDS and an equal amount to its management. However, little was said then about the vascular bed since at that time little was known about the role of the pulmonary vascular bed and particularly about the vascular endothelial

cells and interaction between formed elements in the blood and the vessels in the lung. In the recent past it has become apparent that the role of the vascular bed is a significant and possibly crucial part of the syndrome.

The pulmonary circulation and vascular bed, however, have been the subject of interest to physicians and physiologists going back to the thirteenth century. The first description of the vascular bed was given by Ibn-El-Nafis, a native of Damascus working in Cairo, who said that "the blood of the right ventricle passes through the vena arteriosa to the lung, spreads through its substance, mixes with air and becomes completely purified; then it passes through the arteria venosa to reach the left chamber of the heart." In Europe, Michael Servetus, the Spanish monk, working in Paris in the sixteenth century, wrote of "the vital spirit. It is generated in the lungs from a mixture of inspired air with elaborated subtle blood which the right ventricle of the heart communicates to the left . . . blood becomes reddish-yellow and is poured from the pulmonary artery into the pulmonary vein."[3] His book *Christianismi restitutio* was considered heretical by both Catholics and Protestants and he was burned at the stake by the Calvinists in Geneva in 1553.

In ARDS the area of particular interest in the pulmonary circulation is the alveolar-capillary (A-C) membrane. Looking at the ultrastructure of the A-C membrane, one can wonder about the behavior of the cell lining of both the epithelial and the endothelial surfaces of the membrane and their interaction with formed elements in blood in causing the disease. In terms of pathogenesis of ARDS, one point of view is that there is first injury and damage to the A-C membrane leading to development of the leaky membrane. Edema formation then creates the physiologic abnormalities in the lung, but at the same time there are alterations in the metabolic behavior of both epithelial and endothelial cells and in their interaction with leukocytes in the blood—all culminating in the development of the classic pictures of ARDS. Later chapters in this book will address the questions of how injury to the A-C membrane might occur and what role specific cells play. In considering the pulmonary vascular bed physiologically, two aspects of it need to be emphasized: (1) reactivity of the vessels and (2) permeability characteristics of the A-C membrane.

As far as reactivity is concerned, the pulmonary vessels may be more reactive than any other vascular bed in the body in reacting to changes in their environment. Specifically, the mechanical forces within the thorax, the interstitial pressure of the lung and the state of alveolar distention affect vessel caliber and blood flow. Furthermore, the pulmonary vessels are particularly sensitive to changes in oxygen tension in the alveolar air and to a lesser extent to oxygen saturation in blood. The response of the vessels to a fall in alveolar oxygen tension, as demonstrated by the shift of perfusion away from areas of alveolar hypoxia, is the major mechanism for adjustment of distribution of regional perfusion to ventilation. This

remarkable vasoreactivity to alveolar hypoxia is demonstrated in Figure 1-1, and was reported from our laboratory earlier.[4] In this example, the anesthetized dog is mechanically ventilated through a double-lumen endotracheal tube to separate ventilation of one lung from the other. Distribution of perfusion to the lungs is quantitated by intravenous (IV) injection of a bolus of nitrogen 13 (^{13}N) in solution and positron scintigraphy of the chest. When both lungs are ventilated on room air, blood flow is relatively equal to both lungs. As soon as the inspired gas mixture to one lung is switched to a low O_2 mixture, despite continued mechanical ventilation, blood flow to the hypoxic lung is markedly reduced.

The question in ARDS is whether this normally present hypoxic pulmonary vasoconstriction contributes to development of pulmonary hypertension and vascular remodeling. The evidence at hand would say yes. Mechanisms of vasoconstriction are probably several and among others include the sympathetic system[5] and a number of chemical mediators which are either elaborated in the lung or modified in their passage through the pulmonary vascular bed. Of these, histamine and prostanoids seem particularly relevant at the moment.

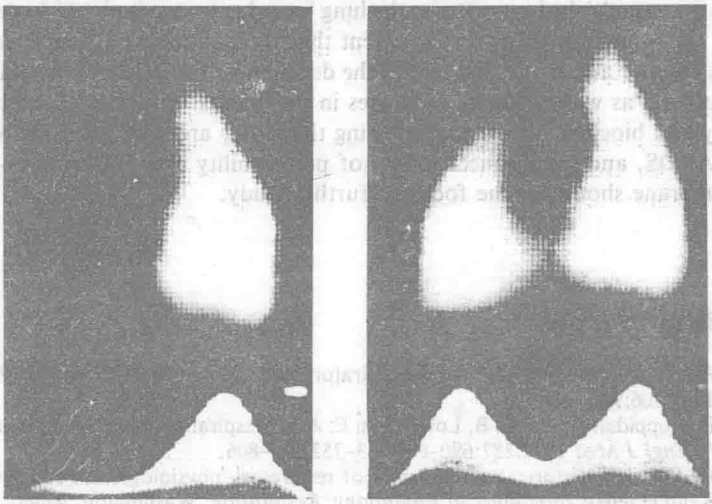

Figure 1-1 Positron scintigraphy of distribution of pulmonary perfusion with nitrogen 13 in the anesthetized supine dog. The upper half of the picture is the perfusion image and the lower half the summation of all counts from each lung. Left panel is control perfusion when both lungs are ventilated on room air and the right panel the pattern of perfusion after the right lung was ventilated with 100% nitrogen. Perfusion to the alveolar hypoxic lung is reduced by 54%. (Reproduced with permission from Hales et al.[4])

Despite the reduction in pulmonary capillary bed, the marked pulmonary hypertension, and the high pulmonary vascular resistance in ARDS, it is possible to increase flow through these vessels by increasing cardiac output.[6] This finding implies that there may be recruitment of new vessels with a possible critical opening pressure or further distention of already patent vessels or both.

The A-C membrane leaks in ARDS. Assessing permeability of the membrane and quantitating regional lung water has been one of the challenges to our understanding of ARDS. To quantitate regional lung water in an isolated lung model that spontaneously developed pulmonary edema, we have used the short-lived positron-emitting isotopes oxygen 15 (^{15}O) with a half-life of two minutes to measure total lung water with $H_2{}^{15}O$, the intravascular volume with carbon monoxide-labeled hemoglobin (Hgb-$C^{15}O$), and the difference between the two to calculate the extravascular lung water volume. With positron camera scintigraphy one can regionalize the extravascular lung water.[7] Using such a technique, we found that extravascular lung water increased in all regions of the lung from apex to base (Figure 1-2) as the wet/dry ratio increased from 3.6 to 6.0 and the increase in extravascular water matched the intravascular volume closely, suggesting that leakiness of the membrane is fairly uniform from apex to base of the lung, but that *fluid accumulation* after fluid leaving the vascular bed is greater at the lung base due to gravitational forces.

In summary, then, it is apparent that the pulmonary vascular bed has a major and significant role in the development of ARDS. There are structural as well as reactive changes in the vessels. Endothelial cell injury and biochemical events following the injury are significant factors in ARDS, and finally mechanisms of permeability changes in the A-C membrane should be the focus of further study.

REFERENCES

1. Rinaldo JE, Rogers RM: Adult respiratory distress syndrome. *N Engl J Med* 1982;306:900-909.
2. Pontoppidan H, Geffin B, Lowenstein E: Acute respiratory failure in the adult. *N Engl J Med* 1972;287:690-697,743-752,799-806.
3. Perkins JF: Historical development of respiratory physiology, in Fenn WO, Rahn H (eds): *Handbook of Physiology. Respiration.* Washington, American Physiological Society, 1964, vol 1 pp 1-62.

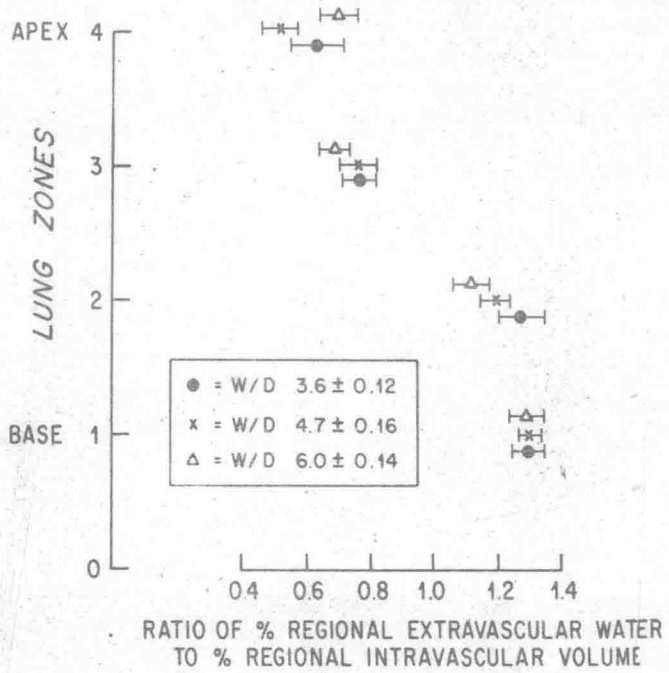

Figure 1-2 Distribution of regional extravascular lung water compared to regional intravascular volume in 17 isolated, perfused lungs which developed spontaneous pulmonary edema. There is no change in distribution of lung vater with increasing edema, but there is a gravity-dependent increase from apex to base of the same magnitude at all levels of pulmonary edema. (Reproduced with permission from Hales et al.[7])

4. Hales CA, Ahluwalia B, Kazemi H: Strength of pulmonary vascular response to regional alveolar hypoxia. *J Appl Physiol* 1975;38:1083–1087.
5. Dauber IM, Weil JV: Lung injury edema in dogs. Influence of sympathetic ablation. *J Clin Invest* 1983;72:1977–1986.
6. Zapol WM, Snider MT: Pulmonary hypertension in severe acute respiratory failure. *N Engl J Med* 1977;296:476–480.
7. Hales CA, Kanarek DJ, Ahluwalia B, et al: Regional edema formation in isolated perfused dog lungs. *Circ Res* 1981;48:121–127.

APEX 4
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LUNG ZONES

2 *Pathology of Pulmonary Vascular Bed in Adult Respiratory Distress Syndrome (ARDS)*

Lynne M. Reid
Rosemary C. Jones

There is a time "to lump" and a time "to split." In the clinical setting, we can be "lumpers" since treatment of patients with the acute respiratory distress syndrome (ARDS) is essentially similar, regardless of cause. Furthermore, as the care of ARDS patients has improved we less frequently see the acute stages of the injury, and in the subacute and chronic stages structural changes in the lung correlate with the duration of the disease rather than with the cause.

In considering the experimental studies of ARDS we can be "splitters" in the attempt to identify the particular pathogenetic pathways by which a given cause produces lung disease. It is necessary to analyze separately the mechanisms responsible for the early acute injury from those that lead to its amplification and fatal outcome. One set of questions concerns the way nonthoracic injury damages the pulmonary microvasculature to cause the increased permeability and hemorrhage that give us the symptoms and signs of acute respiratory failure. Another set of questions is concerned with the evolution of the acute changes, with or without artificial ventilation using high partial pressure of oxygen. Resolution, healing with varying degrees of scar, or fatal outcome are possibilities at this stage.[1-9].

The presence of edema and hemorrhage as hallmarks of the acute stage of ARDS and the early presence and steady progression of pulmonary hypertension point to injury of the pulmonary circulation at all stages. The most puzzling form of ARDS is the severe lung damage that follows a primary injury at some distance from the lung such as peripheral trauma or abdominal sepsis. In such cases its vascular channels are likely also to be the route by which attack on the lung is delivered.

The human disease is first described here after consideration of the normal microcirculation of the lung, then selected animal models are considered for their relevance either to the cause of ARDS or its treatment.