Extracorporeal Membrane Oxygenation and Novel Modalities in Management of ARDS

An essay

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List of Abbreviations

AECC	:	American-European Consensus Conference
ALI	:	Acute lung injury
APC	:	Activated protein C
ARDS	:	Acute respiratory distress syndrome
Arterial PO_2	:	Arterial partial pressure of oxygen
CV	:	Closing volume
ECCO2R	:	Extracorporeal carbon dioxide removal
ECLS	:	Extra-corporeal life support
ECMO	:	Extracorporeal membrane oxygenation
FIO_2	:	Fraction of oxygen inspired
FRC	:	Functional residual capacity
FVC	:	Forced vital capacity
HRQoL	:	Health-related quality of life
LPS	:	Lipopolysaccharide
MSCs	:	Mesenchymal Stem Cells
MVV	:	Maximal voluntary ventilation
NE	:	Neutrophil elastase
NOS	:	Nitric oxide synthase
PEEP	:	Positive end-expiratory pressure
RMV	:	Respiratory minute volume

List of Abbreviations (Cont.)

VD	:	Dead space
VILI	:	Ventilator-induced lung injury
VT	:	Tidal volume

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Introduction

Acute respiratory distress syndrome (ARDS) is an acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue with hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space and decreased lung compliance ***(Thille et al.,2013).***

There are a variety of predisposing factors for ARDS. Sepsis, multiple blood transfusions, pulmonary contusion, aspiration of gastric contents and drug abuse or overdose. Also, burns, pancreatitis, smoke inhalation, pneumonia and near drowning can cause this condition. The inhalation of irritants, chemical warfare agents such as phosgene, chlorine gas can also cause ARDS ***(Cherkas and David, 2011).***

In patients with severe hypoxemic and or hypercapnic respiratory failure, extracorporeal lung support techniques, including extracorporeal membrane oxygenation (ECMO), have been considered to be possible rescue therapies. The aim of this strategy is to overcome severe hypoxemia and respiratory acidosis while keeping the lung completely at rest ***(Peek et al., 2009).***

Over the last decade, several non-ventilatory treatments have been investigated to further improve the outcome of ARDS patients. As the role of conservative fluid strategy and the putative role of neuromuscular blocking agents ***(Papazian et al., 2010).***

Inhaled nitric oxide for its pulmonary vasodilator effects has been proposed to treat refractory hypoxemia

reestablishing an adequate ventilation perfusion matching ***(Taylor et al., 2004).***

Lack of effective therapies relies on the complex pathogenesis of the syndrome characterized by different overlapping signaling pathways. Gene therapy and Mesenchymal Stem Cells (MSCs) may be promising novel therapeutic strategies aimed at modulating key pathophysiologic mechanisms of ARDS ***(Mei et al.,2010).***

Aim of the Essay

This essay aims at revealing and highlighting the roles of extracorporeal membrane oxygenation therapy and other novel modalities in management of Acute Respiratory Distress Syndrome.

Anatomy and Physiology of the Respiratory System

The lung has two essential, interdependent functions. One function is ventilation-perfusion matching to deliver oxygen to the body and to remove carbon dioxide that is produced by the body (Fig. 1). The second function is host defense against the onslaught of airborne pathogens, chemicals, and particulates. These essential functions are emphasized through the gross, subgross, histologic, and ultrastructural determinants of respiratory gas exchange in the normal human lung. Secondary functions of the lung also are important, such as surfactant synthesis, secretion, and recycling; mucociliary clearance; neuroendocrine signaling; and synthesis and secretion of a myriad of molecules by its epithelial and endothelial cells ***(Albertine, 2016).***

Gross and Subgross Organization

In life the human lungs weigh 900 to 1000g, of which nearly 40% to 50% is blood. At end-expiration, the gas volume is approximately 2.5L whereas, at maximal inspiration, it may be 6 L. Thus overall lung density varies from 0.30 g/mL at *functional residual capacity* (FRC) to 0.14 g/mL at total lung capacity. But the density of the lung is not distributed uniformly, being approximately 1g/mL near the hilum and 0.1g/mL peripherally ***(Albertine et al.,1991).***

The increasing distention of vessels from apex to base also illustrates the increase in vascular distending pressures at the rate of 1 cm H2O/cm height down the lung. An amazing point is how little tissue is involved in the architecture of the alveolar walls. But this is as it should be because the major physical problem of gas exchange is the

slowness of oxygen diffusion through water. Thus the alveolar walls must be extremely thin. In fact, the thickness of the red blood cell forms a substantial portion of the air-blood diffusion pathway ***(Albertine et al., 1991).***

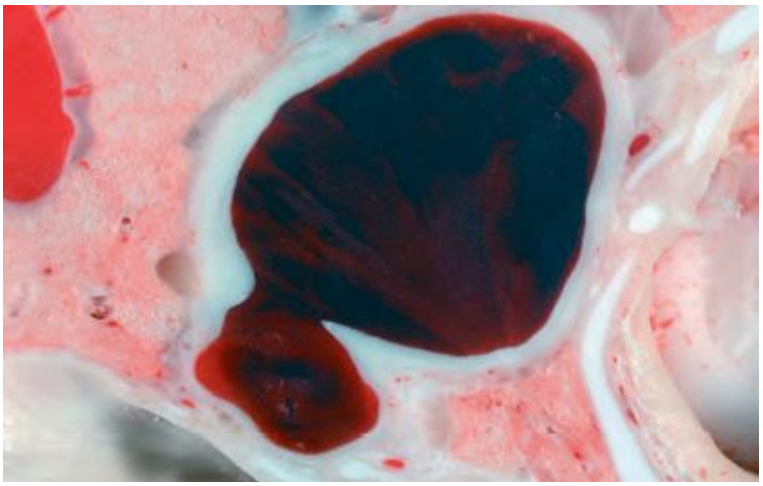

Fig. (1) Frozen block of lung tissue (***Albertine et al., 1991).***

The lung has two well-defined interstitial connective tissue compartments arranged in series, these are the parenchymal (alveolar wall) interstitium and the loose-binding (extra-alveolar) connective tissue (peribronchovascular sheaths, interlobular septa, and visceral pleura). The connective tissue fibrils (collagen, elastin, and reticulin) form a three-dimensional basket-like structure around the alveoli and airways. This basket-like arrangement allows the lung to expand in all directions without developing excessive tissue recoil ***(Sannes et al.,1998).***

Because the connective tissue fibrils in the parenchymal interstitium are extensions of the coarser fibers in the loose-binding connective tissue, stresses imposed at the alveolar wall level during lung inflation are transmitted not only to

adjacent alveoli, which abut each other, but also to surrounding alveolar ducts and bronchioles, and then to the loose-binding connective tissue supporting the whole lobule, and ultimately to the visceral pleural surface. These relations become more apparent in certain pathologic conditions. For example, in interstitial emphysema, air enters the loose-binding connective tissue and dissects along the peribronchovascular sheaths to the hilum and along the lobular septa to the visceral pleura. Interstitial pulmonary edema liquid enters and moves along the same interstitial pathways ***(Albertine, 2016).***

The bulk of the interstitium is occupied by a matrix of proteoglycans. Proteoglycans constitute a complex group of gigantic polysaccharide whose entanglements impart a gel-like structure to the interstitium. That structural role, although essential, is not the sole role of these important molecules. A growing view is emerging of the lung's extracellular matrix components as regulators of lung physiology, helping in determining epithelial cell phenotype; binding of and subsequent signaling by cytokines, chemokines, and growth factors; and mediating cell proliferation, migration, differentiation, and apoptosis ***(Frevert and Sannes,2005).***

In disease states, the degradation products may serve as endogenous sentinels of tissue damage and initiators of innate immune responses. Within this gel-like interstitium reside several varieties of interstitial cells (contractile and noncontractile interstitial cells, mast cells, plasma cells, and occasional leukocytes). The remainder of the interstitium is composed of laminin, collagens, elastin and reticulin fibrils, fibronectin, and tenascin ***(Kajikawa et al.,2005).***

Airways

The airways, forming the connection between the outside world and the terminal respiratory units, are of central importance to our understanding of lung function in health and disease. Intrapulmonary airways are divided into three major groups: *bronchi, bronchioles* (including the terminal bronchioles), and *respiratory bronchioles*. By definition, bronchi have cartilage in their wall, whereas bronchioles do not. Respiratory bronchioles serve a dual function as airways and as part of the alveolar volume (gas exchange) ***(Albertine, 2016).***

The trachea and bronchi are cartilaginous, do not change shape significantly with ventilation, and do not participate in gas exchange. Bronchioles, approximately 1 mm in diameter or less, have no cartilage and are exceedingly numerous and short. They consist of approximately five branching generations and end at the terminal bronchioles. In contrast to the bronchi, the bronchioles are tightly embedded in the connective tissue framework of the lung and therefore enlarge passively as lung volume increases ***(Hovenberg et al., 1996).***

Histologically, the bronchioles down to and including the terminal bronchioles ought to contribute approximately 25% to the anatomic dead space. In life, however, they contribute little because of gas-phase diffusion and mechanical mixing in the distal airways resulting from the cardiac impulse. By definition, the respiratory bronchioles and alveolar ducts participate in gas exchange and thus do not contribute to the anatomic dead space. The volume of the respiratory bronchiole-alveolar duct system is approximately one third of the total alveolar volume, and it is into this space

that the fresh-air ventilation enters during inspiration ***(Hovenberg et al., 1996).***

Most airway resistance resides in the upper airway and bronchi. Normally the large airways maintain partial constriction. The minimal airway diameter in the human lung, approximately 0.5 mm, is reached at the level of the terminal bronchioles; succeeding generations of exchange ducts (respiratory bronchioles and alveolar ducts) are of constant diameter ***(Albertine, 2016).***

The presence of apical junctional complexes between airway epithelial cells has important functional implications for metabolically-regulated secretion into and absorption of electrolytes and water from the lining liquid. Apical junctional complexes consist of three elements: *zonula occludens* (tight junction), *zonula adherens*, and *macula adherens* (desmosome). Tight junctions subserve two important functions: (1) restriction of passive diffusion by blocking the lateral intercellular space and (2) polarization of cellular functions (ion and water transport) between the apical and basolateral membranes ***(Chen et al.,2001).***

Polarization of chloride and sodium transport allows the airway epithelium either to secrete or to absorb ions, with associated water movement. Trapping of foreign material, such as particulates or bacteria, is accomplished by mucins. Mucins are complex glycoproteins that form gels, exemplified by MUC5A. MUC5A is present in the lung of humans. Other mucins (e.g., MUC5B, MUC7) become expressed by airway epithelial cells in diseases, such as cystic fibrosis. In that disease, MUC5B is produced by airway epithelial cells. Normally MUC5B is produced by