# Updates in Management of Non Cardiogenic Pulmonary Oedema in Adults

***Essay***

*Submitted for partial fulfillment of the master degree* ***In Intensive care***

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**2013**

# Acknowledgement

*First of all, all gratitude is due to* **God** *almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

*Really I can hardly find the words to express my gratitude to* **Prof. Dr /Mostafa Kamel Fouad ,** *Professor of Anesthesia, Intensive care and Pain Therapy, faculty of medicine, Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.*

*I would like also to express my sincere appreciation and gratitude to* **Prof. Dr. Ehab Hamed Abdelsalam,** *Assistant Anesthesia, Intensive care , faculty of medicine , Ain Shams University, for his continuous directions and support throughout the whole work.*

*I Wish to express my deepest gratitude to* **Dr. Ibrahim Mamdouh Esmat,** *Lecture of Anesthesia, Intensive care faculty of medicine , Ain Shams University, for his encouragement support kindness his keen supervision and kind guidance which enabled med to go ahead and finish this work.*

*Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.*

**Tafreeh Bakheet Mehawed**

# Contents

# List of Abbreviations

| Abbrev | |
|---|---|
| AE | Alveolar epithelium |
| ALF | Alveolar lining fluid |
| ALI | Acute lung injury |
| APRV | Airway pressure release ventilation |
| ARDS | Acute respiratory distress syndrome |
| ARF | Acute respiratory failure |
| ASIC | Acid-sensing ion channel |
| ASL | Airway surface liquid |
| BAL | Brochoalveolar lavage |
| BNP | Brain natriuretic peptide |
| $CaO_2$ | Arterial oxygen content |
| CB | Capacity of blood |
| CF | Cystic fibrosis |
| CFTR | Cystic fibrosis transmembrane conductance regulator |
| CHb | Binding capacity of hemoglobin |
| CO | Cardiac output |
| CO | Carbon monoxide |
| CPAP | Continuous positive airway pressure |
| CT | Computed tomography |
| DLCO | Diffusing capacity of carbon monoxide |
| DLNO | Diffusing capacity for nitric oxide |
| $DO_2$ | Systemic oxygen delivery |
| ENaC | Epithelial sodium channel |
| eNOS | Endothelial nitric oxide synthase |
| FCD | Functional capillary density |
| FRC | Functional residual capacity |
| HACE | High-altitude cerebral oedema |
| HAPE | High-altitude pulmonary oedema |
| HFOV | High frequency oscillatory ventilation |
| HFV | High-frequency ventilation |
| ICU | Intensive care unit |
| IL | Interleukin-6 |
| IRV | Inverse ratio ventilation |

# List of Abbreviations

| | |
|---|---|
| KGF | Keratinocyte growth factor |
| MR | Magnetic resonance |
| MSOF | Multi-system organ failure |
| NFκB | Nuclear factor kappa B |
| NIV | Non invasive ventilation |
| NOS | NO synthase |
| NPPE | Negative-pressure pulmonary oedema |
| PAF | Platelet activating factor |
| PCL | Periciliary liquid |
| PEEP | Positive end-expiratory pressure |
| RCTs | Randomized controlled trials |
| $SO_2$ | Oxygen saturation |
| SP | Surfactant proteins |
| TNF | Tumor necrosis factor |
| TRPM8 | Transient receptor potential melastatin 8 |
| TV | Tidal volume |
| VILI | Ventilator associated lung injury |

# List of tables

# List of Figures

# Introduction

Acute pulmonary oedema is a life threatening emergency that requires immediate intervention with a management plan and an evidence based treatment protocol.

Ther is two types of pulmonary oedema occur in clinical medicine: cardiogenic pulmonary oedema (or hydrostatic pulmonary oedema) and non-cardiogenic pulmonary oedema. Non- cardiogenic pulmonary oedema is better known as acute lung injury or acute respiratory distress syndrome (ARDS) ***(Manne et al., 2011)***.

Their clinical manifestations are very similar, so the differentiation between them, based only on clinical grounds, may be very difficult, and knowing the precise etiology of the episode of acute pulmonary oedema has major implications in the treatment plan ***(Manne et al., 2011)***.

Acute respiratory distress syndrome (ARDS) is the most devastating form of acute lung injury (ALI) or pulmonary oedema. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are serious chest disorders with high mortality ***(Chen, 2009)***.

Non- cardiogenic pulmonary oedema may be due to Altered alveolar–capillary membrane permeability as in case of infectious pneumonia, Sepsis, inhaled toxins and aspiration of acidic gastric contents, decreased plasma oncotic pressure, increased negativity of interstitial pressure, lymphatic insufficiency, unknown or incompletely understood ***(Ware and Matthay, 2005)***.

Acute pulmonary oedema usually presents with rapid onset or aggravation of dyspnea at rest, tachypnea, tachycardia, extreme anxiety, signs of severe hypoxemia, hypertension due to endogenous release of catecholamines,

wheezes, frothy and blood-tinged sputum more commonly associated with cardiogenic cause ***(Ware and Matthay, 2005)***.

The correct diagnosis relies on clinical and radiological findings, despite some overlap in the clinical and imaging findings between the different causes. In order to avoid life threatening complication, prompt recognition of non-cardiogenic pulmonary oedema is important. The use of chest radiography in conjunction with the clinical presentation are generally sufficient to arrive at adiagnosis of non-cardiogenic pulmonary oedema ***(Baird, 2010)***.

Treatment is largely supportive and aimed at ensuring adequate ventilation and oxygenation. There are no specific treatment to correct the underlying alveolar-capillary membrane permeability problems, or to control the inflammatory cascade once triggered, beyond mechanical ventilator management and intensive care support ***(Perina, 2003)***.

When severe non-cardiogenic pulmonary oedema has developed, mechanical ventilation is necessary to achieve adequate ventilation and oxygenation. Because a significant portion of alveoli are fluid filled or collapsed, high airway pressures and positive end-expiratory pressure (PEEP) frequently are necessary ***(Antonelli et al, 2001)***.

## Aim of the work

The aim of this essay was to discuss & to review the advances in management of non-cardiogenic pulmonary oedema

## Functional Anatomy of the Respiratory Pathway:

## I. Pulmonary Epithelium:

In all surface epithelia of the conducting airways, various cell types can be found which consist mainly of ciliated cells, Clara cells, undifferentiated basal cells and goblet cells. These cells are expressed in different proportions in the airway epithelia (nasal, tracheal, bronchial) and their local distribution varies. The single cell types may also vary in their ultrastructural features between different species, as shown for the microvilli-containing bronchiolar epithelial Clara cells ***(Kim et al., 2007).***

The basic functions or the various cell types are similar among different species. Ciliated cells are known to be responsible for the transport of inhaled particles and the mucous layer in the oral direction by beating of their motile cilia. Most airway epithelial cell types such as ciliated cells, Clara cells and goblet cells secrete ions, phospholipids, mucus, surfactant and immunoprotective proteins such as the Clara cell secretory protein ***(Coppens et al., 2007)***.

Basal cells are undifferentiated and serve as stem cells for other airway epithelial cell types like ciliated cells ***(Rock et al., 2009).***

### A. Mucociliary Clearance and Airway Lining Fluid:

An intact mucociliary clearance is essential for a healthy lung and is part of the innate immune system. It is responsible for cleaning the airways from inhaled pathogens and particles. Its function is mainly dependent on two parameters: ciliary beat and ion transport. Thus, the ciliated cells occupy an essential role in the mucociliary clearance because of the coordinated beating of their cilia and the set of ion channels they express ***(Song et al., 2009)*.**

The periciliary liquid (PCL) together with the mucous layer that covers the PCL forms the airway surface liquid (ASL) (Fig. 1). The mucous layer with all its trapped particles and pathogens is transported orally by the ciliary beat and by that forms an important part of the innate immunity of the lung. Thus, severe effects such as respiratory infections are observed when ciliary beat is impaired due to defects in its regulation ***(Olbrich et al., 2002).***

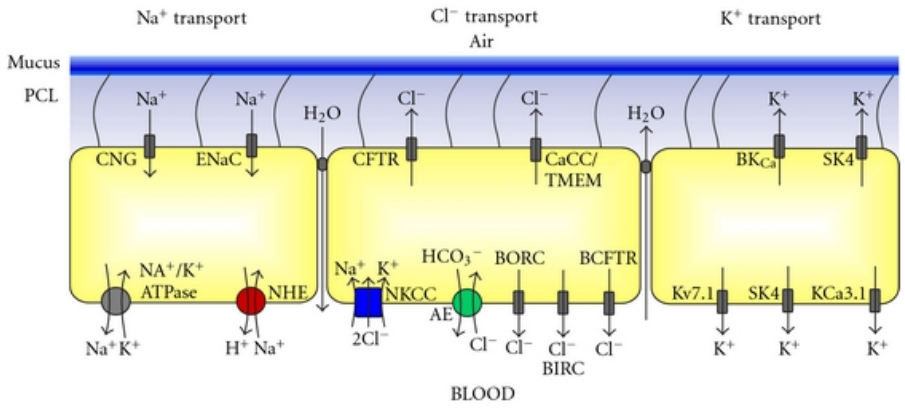


**Fig. 1:** Schematic drawing of ciliated airway epithelial cells with Na+, Cl− and K+ channels and transporters ***(Olbrich et al., 2002).***

Additionally the ASL of the conducting airways represents an important part of the innate immunity, because it contains immunoreactive proteins, such as the Clara cell secretory protein as well as the surfactant proteins A (SP-A) and D (SP-D) that are secreted by the airway epithelial cells. The endogenous function of Clara cell protein is not fully understood, but it is thought to have immunomo-dulatory functions ***(Coppens et al., 2007)***. SP-A and SP-D play an important role in recognising inhaled pathogens and the innate host defence. SP-A- and SP-D-deficient mice are more susceptible to death induced by respiratory pathogens like the fungus Aspergillus fumigatus ***(Madan et al., 2010).***

**B. Ion Transport Processes That Regulate the ASL:**

In agreement with the general dogma that all airway epithelia (nasal, tracheal, bronchial) are Na+ absorptive, an amiloride-sensitive, epithelial sodium channel (ENaC)-mediated component of baseline ion transport has been detected in airway epithelia of human and a variety of mammalian species such as rabbit, dog and mouse ***(Bangel et al., 2008).***

In addition to that, Cl− secretion on the apical side is an important parameter for airway epithelial function, because Na+ absorption and Cl− secretion regulate passive transepithelial H2O flow and, thus, the height of the ASL ***(Song et al., 2009).***

In this way, these ion transport processes are mainly responsible for providing optimal environment for ciliary beat. Human nasal epithelial cells have been shown to display a predominant Na+ absorption consisting of an amiloride-sensitive ENaC-mediated and an amiloride-insensitive component, whereas Cl− secretion plays only a minor role ***(Song et al., 2009).***

However, functional Cl− secretion mediated by the cystic fibrosis transmembrane conductance regulator (CFTR) is essential to regulate PCL viscosity and, thus, maintain functional ciliary beat as visible from cystic fibrosis (CF) patients with defective CFTR ***(Boucher, 2002).***

Additionally, there is increasing evidence for K+ transport playing an essential role in maintaining and regulating airway epithelial membrane potential and ASL ***(Manzanares et al., 2011).***

In addition to Na+, Cl− and K+ channels, a variety of other ion channels has been detected in the airway epithelium.

One example is the acid-sensing ion channel 2 (ASIC2) which belongs to the ENaC/degenerin family of ion channels and has been found in ciliated tracheal cells of rats and ciliated cells in the embryonic rat nasal septum epithelium ***(Kikuchi et al., 2010).***

These channels might be important for pH sensing at birth and for detection of pathogens due to altered pH in the environment and by this may contribute to the function of the innate immune system of the lung ***(Kikuchi et al., 2008).***

Another example is the truncated variant of the transient receptor potential melastatin 8 (TRPM8) channel that has been characterized in human bronchial epithelial cells. Since this channel is permeable for Ca2+ and sensitive to cold stimuli such as cold air, a role in cold-induced alterations of lung physiology has been suggested for this channel by the authors ***(Sabnis et al., 2008).***

## II. The Alveolar Epithelium:

The most important requirements for an efficient air-exchanging structure are: a) First, it must have a wide surface area and this is achieved by the miniaturization. B) Second, it must be thin to facilitate gas exchange between the environment and the organism. This has been realized by an anatomical characteristic that is referred to as the three-ply design and is accomplished by the alveolar epithelial barrier, the basal lamina and the endothelial barrier ***(Maina and West, 2005).***

The alveoli are composed of a continuous layer of epithelial cells referred to as the alveolar epithelium (AE). The AE is very thin (0.1-0.2μm) ***(Matthay et al., 2005).***

The AE is very close to the vascular endothelium which facilitates efficient gas exchange due to the relative short diffusion distance for the breathing gases. The surface of the alveolar epithelium is separated from the gas phase by a fluid layer (alveolar lining fluid, ALF) which covers the entire alveolar epithelium ***(O'Grady and Lee, 2003).***

The ALF originates primarily from fluid infiltration into the alveolar airspace and this is the product of a pressure gradient between the blood capillaries and the alveolar airspace. The amount and volume of ALF in the alveoli affects gas exchange, because it impairs the diffusion distance for the gases. Therefore, one of the most important functions of the AE is the control and regulation of the volume and electrolyte composition of the ALF ***(Bardou et al., 2009).***

In order to avoid excessive fluid infiltration into the alveolar airspace, the AE must exhibit an impermeable barrier to limit solute diffusion to keep the alveoli relatively dry. This is mainly achieved by tight junctions (zonula occludens) which form a continuous and gasket-like seal near the apical surfaces