Neuromuscular Blockers In Acute Respiratory Distress Syndrome

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LIST OF ABBREVIATIONS

ABG: Arterial Blood Gases
Ach: Acetylcholine
AChE: Acetylcholinesterase
ACHR: Receptors protein molecules for acetylcholine
AECC: American-European Consensus Conference
ALI: Acute Lung Injury
AP: Action Potential
APACHE: Acute Physiology And Chronic Health Evaluation
ARDS: Acute Respiratory Distress Syndrome
ATN: Acute Tubular Necrosis
BAL: Broncho Alveolar Lavage
BALTI-2: Beta-Agonist Lung injury Trial-2
BNP: Brain Natriuretic Peptide
Ca^{2+}: Calcium
CT: Computed Tomography
CV: Conventional Ventilation
DAD: Diffuse Alveolar Damage
DIC: Disseminated Intravascular Coagulation
ECMO: Extracorporeal Membrane Oxygenation
ELSO: Extracorporeal Life Support Organization
EPA: Eicosapentaenoic Acid
EPPs: End-plate potentials
FIO2: Fraction of oxygen in the inspired air
FRC: Functional Residual Capacity
G-CSF: Granulocyte Colony-Stimulating Factor
GLA: Gamma-Linolenic Acid
HFOV: High Frequency Oscillatory Ventilation
ICU: Intensive Care Unit
IL: Interleukin

LIST OF ABBREVIATIONS (Cont.)

K^+ : Potassium
MAWP: Mean Airway Pressure
MEPPs: Miniature End Plate Potentials
Mg+: Magnesium
Na^+: Sodium
NHLBI: National Heart, Lung, and Blood Institute
NMBAs: Neuromuscular Blocking Agents
PaO2: Partial pressure of oxygen
PBW: Predicted Body Weight
PCP-III: Procollagen Peptide III
PCWP: Pulmonary Capillary Wedge Pressure
PEEP: Positive End Expiratory Pressure
Pplat: Plateau Pressure
RM: Recruitment Maneuvers
SI: Sustained Inflation
THAM: Tris-Hydroxymethyl Aminomethane
TNF: Tumor Necrosis Factor
TOF: Train-Of-Four
TPPr: Transpulmonary Pressure
V/Q: Ventilation-Perfusion matching
VALI: Ventilator-Associated Lung Injury
VAP: Ventilator Associated Pneumonia
VILI: Ventilator Induced Lung Injury
VT: Tidal Volume
VWF: Von Willebrand Factor

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a permeability pulmonary edema,characterized by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells, leading to hypoxemia that is refractory to usual oxygen therapy. In a national study in Iceland done by Sigurdsson and his coworker in 2013, the incidence of ARDS almost doubled but hospital mortality decreased during the 23 years of observation. Recently, the new definition of ARDS has been published; this definition suggested severity-oriented respiratory treatment by introducing three levels of severity according to partial pressure of oxygen to fraction of oxygen in inspired air (PaO2/FiO2) and positive end-expiratory pressure. ***(Koh,2014)***

The neuromuscular junction (NMJ), the most studied of all synapses, provides the link between myelinated motor nerves and skeletal muscle.It is composed of three regions the presynaptic, the synaptic cleft and the postsynaptic part. In health, it is an integral part of an impressively efficient biological amplification system, which converts minute nerve action potentials into muscle contraction. Acetylcholine (Ach) is the excitatory transmitter in the NMJ. Ach is stored at the motor nerve terminals in a large number of synaptic vesicles, each of which stores approximately 5,000 to 10,000 molecules of ACh. ***(Mori et al.,2014)***

Neuromuscular Blockers are used in the intensive care unit (ICU) to improve patient-ventilator synchrony, enhance gas

exchange, and diminish the risk of barotrauma. The most common reason for their administration is to facilitate mechanical ventilatory support. Administration of Neuromuscular Blockers eliminates the spontaneous breathing activity, thereby allowing tidal volume and the plateau pressure to be controlled within desirable target ranges. The use of them is especially helpful during non-conventional ventilator strategies such as permissive hypercapnia,prone positioning, use of high levels of PEEP and high frequency oscillatory ventilation. ***(Piriyapatsom et al.,2013)***

Despite intense research, there are no specific pharmacologic therapies proven to decrease mortality rate in ARDS. The only confirmed therapy is a lung protective strategy involving the use of relatively small tidal volumes with limitation of the end inspiratory lung stretch. Other examples of the minimalist approach include the administration of fewer transfusions, less bed rest, fewer intubations and less sedation.Now, many methods have been studied to improve the oxygenation like extracorporeal membrane oxygenation and Recruitment maneuvers. (***Matthay et al.,2013)***.

Acute Respiratory Distress Syndrome Overview

A-Background

Since World War I, it has been recognized that some patients with non thoracic injuries, severe pancreatitis, massive transfusion, sepsis and other conditions develop respiratory distress, diffuse lung infiltrates and respiratory failure, sometimes after a delay of hours to days. In 1967, Ashbaugh and his fellows described 12 such patients, using the term "Adult Respiratory Distress Syndrome" to describe this condition. Before research into the pathogenesis and treatment of this syndrome could proceed, it was necessary to formulate a clear definition of the syndrome. Such a definition was developed in 1994 by the American-European Consensus Conference (AECC) on Acute Respiratory Distress Syndrome (ARDS). The term "acute respiratory distress syndrome" was used instead of "adult respiratory distress syndrome" because the syndrome occurs in both adults and children ***(Bernard, 2005)***.

ARDS was recognized as the most severe form of acute lung injury (ALI), a form of diffuse alveolar injury. The AECC defined ARDS as an acute condition characterized by bilateral pulmonary infiltrates and severe hypoxemia in the

absence of evidence for cardiogenic pulmonary edema. According to the AECC criteria, the severity of hypoxemia necessary to make the diagnosis of ARDS is defined by the ratio of the partial pressure of oxygen in the patient's arterial blood (PaO_2) to the fraction of oxygen in the inspired air (FIO_2). In ARDS, the PaO_2/FIO_2 ratio is less than 200, and in ALI, it is less than 300. In addition, cardiogenic pulmonary edema must be excluded either by clinical criteria or by a pulmonary capillary wedge pressure (PCWP) lower than 18 mm Hg in patients with a pulmonary artery (Swan-Ganz) catheter in place **(*Wheeler and Bernard, 2007*)**.

Despite this unquestionable success, a number of issues regarding the AECC definition have emerged.

1- The AECC demanded the ‘‘acute onset’’ but does not explicitly define the time window (e.g., hours, days, or weeks), nor from when to judge the onset of the syndrome.
2- The chest X-ray criterion has been shown to have poor to moderate inter-observer reliability.
3- Although the definition requires a PCWP 18 mm Hg (when measured), patients with ARDS frequently have elevated PCWPs often because of transmitted airway pressures and/or vigorous fluid resuscitation.

4- There is evidence that ALI and ARDS as defined using the AECC criteria is under-recognized by clinicians, particularly the subgroup of patients with milder hypoxemia (i.e., those with PaO 2/FiO2 201–300).

5- PaO 2/ FiO2 is not constant across a range of both FiO2 and PEEP in individual patients. In 2007, Villar and coworkers in a study of four combinations of FiO2 and PEEP with standardized tidal volumes applied 24 hrs after ARDS onset, determined that the combination of PEEP [10 cm H2O and FIO2 0.5] with a tidal volume of 7ml/kg predicted body weight(PBW) demonstrated substantial reclassification of high- and low mortality groups in comparison to PaO 2/ FiO2 ratios determined on usual care ventilator settings at the time of diagnosis They proposed that standardized ventilator settings after a 24 h waiting period should be used to define ARDS.

(*Ranieri et al.,2013*).

To address these limitations of the AECC definition, the European Society of Intensive Care Medicine, with the endorsement of the American Thoracic Society and of the Society of Critical Care Medicine, convened an international expert panel to revise and adjust the AECC definition of ARDS. Feasibility, reliability, face validity and predictive validity were important considerations in developing the new

definition. An empiric evaluation of the preliminary draft using data from more than 4,000 patients with presumed ARDS recruited from several clinical trials and observational cohorts from North America, Europe and Australia was done to assess predictive validity. A requirement for standardized ventilator settings was considered but not thought to be feasible as this practice is not generally part of contemporary usual care(***Matthay et al.,2013)***.

The essential aspects of the new definition (The‘‘Berlin definition’’) are as follows:

1-Acute was defined as 1 week or less.

2- Chest radiograph criteria were clarified to improve inter-reliability and example radiographs provided.

3- The wedge pressure criterion was removed and clinical vignettes added in an effort to improve the ability to exclude cardiac causes of bilateral infiltrates.

4-The term acute lung injury was abandoned.

5- Measurement of the PaO 2/FIO2 ratio was changed to require a specific minimum amount of PEEP; three categories of ARDS were proposed (mild PaO2/FiO2 < 300 but >200 mm Hg, moderate PaO2/FiO2 < 200 but >100 mm Hg and severe PaO2/FiO2 < 100)

(*Ranieri et al.,2012*).

B-Epidemiology

ARDS represent approximately 5% of hospitalized, mechanically ventilated patients. The incidence of ARDS varies widely. For example, estimates from prospective US cohort studies using the AECC definition range from 64.213 to 78.912 cases/100,000 person-years, whereas estimates from Northern Europe (17 cases/100,000), Spain (7.2 cases/100,000) and Australia (34 cases/100,000) have shown substantially lower rates.Reasons for the large variation in ARDS incidence are unclear and may include major differences in demographics and healthcare delivery systems (***Rubenfeld et al., 2005***).

C-Etiology

Multiple risk factors exist for ARDS. Approximately 20% of patients with ARDS have no identified risk factor. ARDS risk factors include:

1- Direct lung injury (most commonly, aspiration of gastric contents). 2- Sepsis is the most common indirect risk factor for ARDS.

Other major risk factors associated with the development of ARDS include the following:

1- Bacteraemia

2-Trauma with or without pulmonary contusion

3-Fractures, particularly multiple fractures and long bone fractures

4- Burns,

5-Massive transfusion

6-Pneumonia

7- Drug overdose

8- Near drowning

9-Postperfusion injury after cardiopulmonary bypass

10-pancreatitis

11-Fat embolism.

General predisposing factors for ARDS have not been prospectively studied using the 1994 AECC criteria.

However, several factors appear to increase the risk of ARDS after an inciting event, including

1-advanced age

2-female sex (noted only in trauma cases)

3-cigarette smoking

4-alcohol use.

For any underlying cause, increasingly severe illness as predicted by a severity scoring system such as the Acute Physiology And Chronic Health Evaluation (APACHE) increases the risk of development of ARDS.

(Gajic et al., 2011)