

## SYNERGISTIC EFFECT OF HYPEROXIA AND BIOTRAUMA ON VENTILATOR-INDUCED LUNG INJURY

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### ABSTRACT

Patients undergoing mechanical ventilation in intensive care units (ICUs) may develop ventilator-induced lung injury (VILI). Beside the high tidal volume ( $V_t$ ) and plateau pressure ( $P_{plat}$ ), hyperoxia is supposed to precipitate lung injury. Oxygen toxicity is presumed to occur at levels of fraction of inspired oxygen ( $FiO_2$ ) exceeding 0.40. The exposure time to hyperoxia is certainly very important and patients who spend extended time on mechanical ventilation (MV) are probably more exposed to severe hyperoxic acute lung injury (HALI). Together, hyperoxia and biotrauma (release of cytokines) have a synergistic effect and can induce VILI. In the clinical practice, the reduction of  $FiO_2$  to safe levels through the appropriate use of the positive end expiratory pressure (PEEP) and the alignment of mean airway pressure is an appropriate goal. The strategy for lung protective ventilation must include setting up  $FiO_2$  to a safe level that is accomplished by using  $PaO_2/FiO_2$  ratio with a lower limit of  $FiO_2$  to achieve acceptable levels of  $PaO_2$ , which will be safe for the patient without local (lungs) or systemic inflammatory response. The protocol from the ARDS-net study is used for ventilator setup and adjustment. Cytokines (IL-1, IL-6, TNF $\alpha$  and MIP-2) that are involved in the inflammatory response are determined in order to help the therapeutic approach in counteracting HALI. Computed tomography findings reflect the pathological phases of the diffuse alveolar damage. At least preferably the lowest level of  $FiO_2$  should be used in order to provide full lung protection against the damage induced by MV.

**Keywords:** hyperoxia, ventilator-induced lung injury, cytokines, lung-protective ventilation strategies

### INTRODUCTION

Providing effective life-support with minimized risk and optimized comfort in patients with respiratory failure are still the principal objectives of mechanical ventilation (MV) [1]. Despite its life saving effects, MV might have adverse effects: ventilator-associated pneumonia, impaired cardiac performance, and difficulties with sedation and paralysis. The mechanical ventilation may also lead to serious damage in both healthy and diseased lungs; a process called ventilator-induced lung injury (VILI).

In the past the inadequate ventilation strategy was considered to be responsible for the onset of VILI, that is, histopathologically identical with the acute lung injury (ALI). However, recently, more detailed factors for development of VILI have emerged: loading of alveolocapillary membrane, duration of exposure to MV, intensity of the exposure (tidal volume;  $V_t$ ), end-expiratory pulmonary volume, magnitude of the available “baby lung” heterogeneity (which includes atelectasis, consolidation and edema) and hyperoxia. Endotoxin, vascular pressures and fluid/transfusions are additional factors leading to VILI

[2,3]. High Vt and high plateau pressure (Plat) can give excessive distension, or “stretch,” of the aerated lungs, thus resulting in volutrauma and barotrauma. Besides the volutrauma and barotrauma, atelectrauma is another important causative factor leading to VILI. Ventilator-induced lung injury arises not only from repeated application of high mechanical forces that tear fragile tissue directly, but also from initiation of signaling that culminates in inflammatory changes [4]. The term “biotrauma” denotes release of cytokines (mediators) secondary to epithelial injury caused by barotrauma or volutrauma [5]. Ventilator-induced lung injury greatly assists patients with the most severe form of lung injury, acute respiratory distress syndrome (ARDS) [6].

A question arises why hyperoxia, especially if it lasts long, is not being considered as a risk factor for the development of VILI along with the other factors. Oxygen therapy has been used in the care of critically ill patients since early years of the last century. However, from the beginnings of the 1970s an increasing understanding emerged that oxygen therapy can cause pulmonary toxicity [7]. Hyperoxia is detrimental for mechanically ventilated patients and even fraction of inspired oxygen ( $\text{FiO}_2$ ) levels of 0.40 and lower can provoke pulmonary toxicity, thus leading to VILI. The exposure time to hyperoxia is certainly very important and patients who spend extended time on MV are probably more exposed to severe hyperoxic acute lung injury (HALI) [8].

Hyperoxia is supposed to precipitate lung injury through the production of reactive oxygen intermediates [9]. Hyperoxia provokes cytokine release, which is involved in the inflammatory response. Endothelial and epithelial cells injury, increased pulmonary capillary permeability and a marked increase in the inflammatory cells are the main manifestations of HALI [10]. Microscopically the prominent findings are: hyaline membrane formation in alveoli, alveolar septal edema and fibrosis, and diffuse hyperplasia of the alveolar lining layer with formation of a cuboidal epithelial lining [7]. The combination of high Vt and hyperoxia causes significantly greater reductions in the lung compliance, increased alveolar-capillary membrane permeability, gives more severe pulmonary surfactant dysfunction [11], and increases expression of pro-inflammatory mediators [12,13]. These notions have been confirmed in a several number of studies, which showed that cyclic opening and collapse of the alveoli even at low inspiratory pressures and low inspiratory volumes increased stretch and shear forces resulting in lung injury and surfactant dysfunction [14,15]. Inflammation and more specifically, cytokines such as tumor

necrosis factor - alpha ( $\text{TNF}\alpha$ ) and interleukin (IL)-1 are thought to decrease surfactant components either directly [14-17] or indirectly by inducing alveolar leakage of proteins that subsequently inhibit surfactant function [14-18]. Cytokines play the most important role in inflammation. They are low molecular weight soluble proteins that transmit signals between the cells involved in the inflammatory response [19]. Cytokines are produced by bronchial, bronchiolar, and alveolar epithelial cells but also by alveolar macrophages and neutrophils [20]. In almost all studies in-vitro, ex-vivo and in-vivo models, using different species and applying various techniques, hyperoxia induced elevation of cytokines. Furthermore, in almost all studies, cyclic overstretch has increased alveolar levels of IL-8 or its rodent equivalent macrophages inflammatory protein (MIP)-2. MIP-2 is the most potent leukocyte chemoattractant and its role in the pathogenesis of VILI is very important [21,22]. Other proinflammatory cytokines such as IL-1 and IL-6 were elevated in a large number of studies.

### **FIO<sub>2</sub> LEVELS: DIFFERENT ATTITUDES, BELIEFS AND PRACTICES**

Considerable variations exist in the attitudes, beliefs, and stated practices relating to the management of oxygen therapy in the ICUs patients. A Canadian questionnaire study has shown that most respondents believed that the levels of  $\text{FiO}_2$  up to 0.40 are not harmful and this is the ideal value when partial pressure of oxygen in arterial blood ( $\text{PaO}_2$ ) permits this [23]. Another newer study from the Netherlands investigated the beliefs and actual clinical practice regarding the oxygen therapy in critically ill patients where the majority of ICUs clinicians acknowledged the potential adverse effects of prolonged exposure to hyperoxia and reported a low tolerance for high oxygen levels, in actual clinical practice; a large proportion of their ICUs patients was exposed to higher arterial oxygen levels [24, 25].

However, there is evidence of poor outcomes after hyperoxia in a number of patients mechanically ventilated, but in most cases this did not lead to adjustment of ventilator settings [10]. All the doctors in ICUs have their “own” mode of setting the ventilator, but almost always patients on MV are exposed to greater than normal concentration of oxygen. Additionally, in some patients it is not possible to develop a ventilation strategy that is non-injurious in all lung regions and hence the problem becomes more complex.

Clinical practice shows that whenever we have a low  $\text{PaO}_2$ , the first step we undertake is to set the  $\text{FiO}_2$  on a higher level. It is well-known that this is not the right way to increase  $\text{PaO}_2$ , but in spite of that, we

are used. In this protocol, higher PEEP with lower  $\text{FiO}_2$  is used. The higher PEEP levels are set and adjusted according to each patient's arterial-oxygenation response to the PEEP/ $\text{FiO}_2$  settings [29]. (Table 1).

**Table 1.** Higher PEEP levels with Lower  $\text{FiO}_2$

|                                  |     |     |     |     |     |     |     |     |
|----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| <b><math>\text{FiO}_2</math></b> | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.5 |
| <b>PEEP</b>                      | 5   | 8   | 10  | 12  | 14  | 14  | 16  | 16  |

always repeat it and moreover, for a longer period of time.  $\text{FiO}_2$  setting value is usually about 0.4, but even oxygen toxicity is presumed to occur at levels of  $\text{FiO}_2$  exceeding 0.40, there are no studies which have examined the effect of  $\text{FiO}_2$  value less than 0.4 on the lungs. It would be of great benefit to perform studies that will apply protective ventilation strategies with different levels of  $\text{FiO}_2$ , but especially with  $\text{FiO}_2$  under 0.4.

### RATIONALE STRATEGY FOR LUNG PROTECTIVE VENTILATION

In order to achieve lower  $\text{FiO}_2$  level than 0.4, which is safe for the patient, it is necessary to decrease  $\text{FiO}_2$  to safe levels through appropriate use of the positive end expiratory pressure (PEEP) and the alignment of the mean airway pressure. An acceptable level of  $\text{PaO}_2/\text{FiO}_2$  ratio with a lower limit of  $\text{FiO}_2$  must be accomplished. This way, adequate tissue oxygenation with  $\text{FiO}_2$  levels less than 0.40 will be achieved.

The modes of mechanical ventilation are adjusted according to the protocol of the ARDS-net study (based on open lung concept) [26]. The ARDS network study gives a golden protocol for lung protective ventilation. Ventilation protective strategies are used routinely without fulfilling the criteria for ALI/ARDS [27]. The ARDS network study demonstrated a compelling survival advantages when using low tidal volumes rather than conventional MV with high tidal volumes in patients with ALI or ARDS [28].

According to the protocol, the ventilator set up and adjustment is as follows: MV is adjusted to the body mass, with an initial  $\text{Vt}$  of 8 ml/kg/bw and reducing  $\text{Vt}$  by 1 ml/kg/bw at intervals not more than 2 hours, until reaching the  $\text{Vt}$  of 6 ml/kg/bw, with plateau airway pressure ( $\text{P}_{\text{plat}}$ ) not exceeding 30 cmH<sub>2</sub>O. Furthermore,  $\text{PaO}_2$  between 55-80 mmHg or saturation of the arterial blood oxygen ( $\text{SaO}_2\%$ ) 88-95% and minute ventilation of 6-35 respirations per minute adjusted to achieve arterial pH  $\geq 7.30$  if possible and inspiration:expiration time 1:1-1:3 are accepted values. A minimum PEEP of 5 cmH<sub>2</sub>O, and incremental PEEP/  $\text{FiO}_2$  combinations

From the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. N Engl Med 2004; 351:327 [29].

However, it is still unclear which is the optimal PEEP that has to be used to avoid overdistension of the alveoli and de-recruitment, and to minimize VILI [30,31].

Regarding  $\text{P}_{\text{plat}}$ , to reach  $\text{P}_{\text{plat}} \leq 30$  cm H<sub>2</sub>O after each change in PEEP or VT,  $\text{P}_{\text{plat}}$  (0.5 second inspiratory pause) has to be checked [27].

Recruitment maneuvers are performed to maximize the amount of open lung while avoiding the high tissue stresses that lead to VILI. Extended sigh recruitment maneuver has better improvement of oxygenation in arterial blood than CPAP recruitment maneuver [32,33].

Additionally, bedside the monitoring, the following is necessary: heart rate, electrocardiogram, non-invasive mean arterial pressure, respiratory rate, oxygen saturation,  $\text{FiO}_2$ , arterial blood gas analysis (monitored half an hour after every MV adjustment), serial chest X-ray and chest/lung computed tomography that reflect the pathologic phases of diffuse alveolar damage [34]. Immunological analyses of cytokines: IL-1, IL-6, TNF $\alpha$  and MIP-2 also have to be made.

Precise control of the arterial oxygenation to minimize the possible harms of hypoxemia is an issue that is extremely important, as at present there is no direct evidence to support the implementation of permissive hypoxemia [35].

The effects of open lung ventilation with reduced  $\text{FiO}_2$  of 0.4 will prevent not only local, but systemic inflammatory response as well. Furthermore, the effects of setting  $\text{FiO}_2$  values at 0.3 will be more reliable. The effects will of course depend on the condition of the lungs (healthy or diseased prior to MV). Evidence for oxygen use in different medical conditions where efficacy and/or safety are uncertain relies on anecdotal experiences, case reports, or small, underpowered studies and require large randomized controlled clinical trials [36].

The rationale of this approach will determine the exact  $\text{FiO}_2$  level necessary for safe MV.



## CONCLUSION

Patients undergoing MV might develop VILI. Hyperoxia is detrimental for mechanically ventilated patients and may lead to VILI. VILI can appear as a result of too much O<sub>2</sub>, large tidal volumes, high inspiratory pressures, cyclic opening/closing of the alveoli and all these lead to release of cytokines. The release of cytokines leads to biochemical injury, which is the concept of biotrauma. The lungs are metabolically active organs composed of epithelium and endothelium that create many substances. They are a door to many pathogens and may be source of systematic inflammation. Alveolar epithelial cells are important for maintaining alveolocapillary barrier and can act as immune effector cells in response to exogenous stimuli (MV). The mechanical ventilation together with hyperoxia are responsible for the cytokine increase and may play a role in initiating a possible systematic inflammatory response. Together, hyperoxia and biotrauma have a synergistic effect and can induce VILI.

The prevention of VILI means also prevention of HALI. Lung-protective ventilation strategies provide avoidance of cyclic opening and closing of alveoli, limitation of inspiratory pressures and volumes, appropriate level of the end-expiratory pressure and together with the appropriate (preferable lowest) level of FiO<sub>2</sub> can give full lung protection against the damage induced by mechanical ventilation.

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**Резиме****СИНЕРГЕТСКИ ЕФЕКТ НА ХИПЕРОКСИЈА И БИОТРАУМА НА ВЕНТИЛАТОР-ПРЕДИЗВИКАНА ПОВРЕДА НА БЕЛИТЕ ДРОБОВИ**

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**Апстракт**

Во единиците за интензивна нега (ЕИЛ) пациентите што се поставени на механичка вентилација (МВ) можат да развијат вентилатор-предизвикана повреда на белите дробови (ВИЛИ). Покрај големиот дишен волумен (Vt) и плато-притисок (Pplat), и хипероксијата ја влошува белодробната повреда. Се претпоставува дека кислородна токсичност се јавува при вредности на инспираторен кислород (FiO<sub>2</sub>) што се поголеми од 0,40. Времето на изложеност на хипероксијата е, секако, многу важно и пациентите што поминуваат подолго време на МВ се веројатно повеќе изложени на тешка хипероксична акутна белодробна повреда (ХАЛИ). И двете, хипероксијата и биотраумата (ослободување на цитокини) имаат синергистички ефект и можат да предизвикаат ВИЛИ. Во клиничка практика целта е намалување на FiO<sub>2</sub> на безбедни вредности со соодветна примена на позитивен притисок на крајот на експириумот (РЕЕР) и усогласување на притисокот во дишните патишта. Стратегијата на белодробна протективна вентилација мора да вклучи поставување на FiO<sub>2</sub> на безбедно ниво, кое се постигнува со користење на односот PaO<sub>2</sub>/FiO<sub>2</sub>, со долна граница на FiO<sub>2</sub> за да се постигне прифатливо ниво на PaO<sub>2</sub>, кое ќе биде безбедно за пациентот без локален (белите дробови) или системски инфламаторен одговор. Протоколот од ARDS-нет студијата се користи за поставување и приспособување на вентилаторот. Се испитуваат цитокините (IL-1, IL-6, TNFα и MIP-2) што се вклучени во инфламаторен одговор, со цел да помогнат во терапевтскиот пристап на ХАЛИ. Наодите од компјутеризираната томографија ги одразуваат патолошките фази на дифузното алвеоларно оштетување. Потребно е да се користи најниско ниво на FiO<sub>2</sub> за да се обезбеди целосна заштита на белите дробови од оштетување што е предизвикано од МВ.

**Клучни зборови:** хипероксија, вентилатор-индуцирана повреда на белите дробови, цитокини, вентилација стратегии за заштита на белите дробови