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Heart-Lung Interactions from the Lung's Perspective

Dr. Fernando Suarez Sipmann
******@***surgsci.uu.se

Consultant in Intensive Care -
Uppsala University Hospital

Dr. Gerardo Tusman
******@***hotmail.com

Anesthesiologist - Department of
Anaesthesia Hospital Privado de
Comunidad Mar del Plata

In this article we describe the characteristics of the interaction between lung protective ventilation and pulmonary and right ventricular function in ARDS. We highlight and discuss the concept that protective ventilation should be directed towards all components of the functional unit, and discuss how mechanical ventilation can modulate the interaction between them.

The heart and the lungs share a common physical space inside the thorax in which they are anatomically and functionally linked by the pulmonary circulation. These three elements are the main components of a functional unit specialised in fulfilling the physiological task of gas exchange and oxygen delivery. Tidal breathing results in cyclic changes in intra-thoracic pressure that affects the interaction between the components of this functional unit in a complex manner. During normal spontaneous breathing these pressure changes are of low magnitude, ranging from slightly negative (i.e. sub-atmospheric) to slightly positive, resulting in low transpulmonary pressure swings. Such cyclic changes are beneficial as they facilitate venous return and improve the matching between pulmonary perfusion and ventilation. Mechanical ventilation significantly alters this physiological scenario. The baseline operating pressure in the thoracic cavity increases from atmospheric to a continuous positive level, the positive end-expiratory pressure (PEEP). In addition cyclic tidal mechanical ventilation above this new operating level occurs at significantly higher than normal transpulmonary pressures to which the functional unit must adapt. When higher tidal volumes and/or pressures are delivered, especially in pathological conditions such as acute respiratory distress syndrome (ARDS), the adaptation capability of the system is critically challenged. The pathophysiological changes of ARDS, which include inflammation, interstitial and alveolar oedema and loss of lung volume make the functional unit particularly vulnerable to the negative effects of mechanical ventilation. In heterogeneous ARDS lung tidal volume is unevenly distributed, imposing an increased mechanical stress on lung structures, which can be greatly amplified at a regional level where normally aerated areas inflate next to collapsed areas. The resulting ventilatorinduced lung injury (VILI) can amplify lung damage (Slutsky and Ranieri 2013). One of the major advances in ARDS management has been the introduction of lung protective ventilation strategies. Aimed at minimising VILI by reducing the delivered cyclic tidal volumes and pressures, they have significantly contributed to reduce mortality to levels around 35-40% (Rubenfeld et al. 2005). However, lung protection has mainly focused on preventing the deleterious effects of mechanical ventilation on the alveolar compartment. However, the impact of positive pressure ventilation on the vascular compartment of the functional unit has received much less attention. This omission is surprising as pulmonary artery hypertension, increased pulmonary vascular resistance (PVR) and right ventricular (RV) failure are pathophysiological components of ARDS and have been known for a long time (Zapol and Snider 1977; Villar et al. 1989; Squara et al. 1998).

Pulmonary Vascular Dysfunction in ARDS

The term pulmonary vascular dysfunction (PVD), introduced more than 30 years ago, (Zapol and Snider 1977) refers to the pathophysiological involvement of the vascular and heart components of the functional unit in ARDS. It can be defined as the increase in pulmonary arterial pressure and/or PVR resulting in different degrees of right ventricular (RV) dysfunction. Causes of PVD include structural factors affecting the vascular component during ARDS, that include: pulmonary vasoconstriction induced by hypoxia and/or vasoactive inflammatory mediators; microvascular thrombotic phenomena; reduced lung volume; interstitial oedema that compresses the microcirculation; endothelial damage due to the direct inflammatory insult and vascular remodelling. PVD should be considered a continuum during the course of ARDS that can range from mild pulmonary hypertension, invariably present in most ARDS patients, to severe pulmonary hypertension with overt right ventricular failure. Clinically the overall estimated incidence of PVD approaches 70% and nearly 20% of ARDS patients evolve to its most severe form, the acute cor pulmonale (Bull et al. 2010; Boissier et al. 2013). Although still under debate (Ryan et al. 2014), there are accumulating clinical data that strongly support an existing link between PVD and ARDS outcome. Direct evidence from recent clinical studies has shown that PVD is independently associated with higher morbidity and mortality (Bull et al. 2010; Boissier et al. 2013). In addition the presence of a high physiological dead space, as an expression of endothelial/microcirculatory dysfunction has consistently shown to be a very strong predictor of mortality in ARDS (Matthay and Kallet 2011). More indirectly the analysis of a large randomised placebo-controlled clinical trial on the use of inhaled nitric-oxide concluded that among survivors those who received nitric-oxide had better functional outcomes at six months compared to controls (Dellinger et al. 2012).

Heart-lung Interactions and PVD: The Role of Mechanical Ventilation

Whether the clinical expression of PVD remains as a mild pulmonary hypertension or evolves to acute cor pulmonale depends on the extent of the intrinsic vascular involvement related to ARDS, as described above, but also on the pharmacological (i.e. selective vasodilators) and ventilatory management. The role of mechanical ventilation is of particular interest as it constitutes a potentially modifiable factor that can

modulate the interaction between the heart, the lung and the pulmonary circulation. In fact, high tidal volume ventilation has been shown to directly cause (Menendez et al. 2013) or worsen PVD (Vieillard-Baron et al. 1999). In a recent study the increase in driving pressure (i.e. plateau pressure – PEEP) was an independent factor associated with the development of cor pulmonale (Boissier et al. 2013). Interestingly, driving pressure was also recently identified as the isolated ventilation variable that better predicted mortality in the analysis of a large cohort of ARDS patients (Amato et al. 2015). Driving pressure is directly related to the cyclic strain imposed on preserved ventilated units and is expressed as the ratio between tidal volume and lung compliance. Lung protective ventilation strategies can also potentially prevent the occurrence and progression of PVD (Bouferrache and Vieillard-Baron 2011; Jardin and Vieillard-Baron 2007). The routine use of echocardiography evaluation of the RV in ICU has contributed to the first description of a specific strategy named the RV protective approach (Bouferrache and Vieillard-Baron 2011). This strategy, based on simple and easy to apply rules, combines the use of low tidal volumes (limiting plateau pressure to < 28cmH2O), low PEEP and the early use of prone positioning. The proponents of this strategy summarised their approach with the assertion: "what is good for the right ventricle is good for the lung" (Repessé et al. 2012), as they found echocardiographic signs of improved RV function in response to such a strategy. Unfortunately, the reported incidence of PVD in the era of lung protective ventilation is still high (Bull et al. 2010; Boissier et al. 2013). Maybe additional factors such as the lung condition expressed by the lung volume status and the characteristics of pulmonary haemodynamics should be taken into account for improving pulmonary vascular-RV protection.

Lung Volume Status

The lung protective effects of using low tidal volumes are strongly supported by clinical and experimental evidence. However, low tidal volume ventilation can be associated with lung collapse, hypercapnia and respiratory acidosis, all of them potentially causing an increase of the pulmonary vascular load on the RV. Lung volume status (i.e. end-expiratory lung volume) may have a particular role in the development of PVD as it affects PVR in a u-shaped fashion (Whittenberger et al. 1960). Low lung volumes can promote lung collapse, which triggers hypoxic pulmonary vasoconstriction, and alters the extraalveolar vessels' geometry, reducing their diameter and eventually leading to capillary derecruitment. At high lung volumes the compression of alveolar capillaries accounts for most of the increase in pulmonary vascular resistance. During mechanical ventilation lung volume is critically affected by the level of PEEP. Both low levels when associated with lung collapse and high levels when inducing excessive lung inflation increase PVR. These effects are enhanced in the heterogeneous ARDS lung where overinflated lung regions may coexist with sometimes extensive regions of dependent lung collapse. In such a condition, the beneficial effects of low PEEP on pulmonary circulation and RV function could be offset by the negative effects associated with lung collapse, whereas a higher level of PEEP could be beneficial if associated to a recruitment effect. In other words, how PEEP affects lung volume is a major determinant of its haemodynamic effects. This probably accounts for the conflicting haemodynamic responses to PEEP reported in the literature. **Pulmonary Vascular Haemodynamics**

To accommodate the entire output of the RV that perfuses the lung, pulmonary vessels are highly distensible, offering a low resistance to forward flow. A low arterial elastance is also essential to maintain RV efficiency, that is the effective transfer of power from the ejecting ventricle to the pulmonary circulation at the lowest energetic cost. This ensures an optimal coupling between the RV and the load imposed by the pulmonary circulation. An increase in pulmonary arterial elastance is probably as important as an elevated PVR in increasing RV load (Milnor et al. 1969). In patients with primary pulmonary hypertension, the ventricular-vascular decoupling caused by an increased arterial stiffness is the hallmark of the shift from a compensated RV dysfunction to right ventricular failure. It is reasonable to think that an increased arterial elastance is also an important component of PVD during ARDS, due to the predominant vasoconstrictive state caused by hypoxaemia, acidosis and vasoactive mediators. Another factor that impairs ventricular-vascular coupling is related to wave reflection phenomena. When the forward pressure (or flow) wave generated by the RV systole meets the backward returning wave reflected from the distal arterial tree, pressure is increased and flow decreased. In the normal pulmonary circulation wave reflection phenomena are minimal and the reflected wave arrives during the ventricular diastolic period. However, in pathological conditions in which arterial elastance or resistance are increased, reflected waves are regularly present and arrive during systole, affecting RV ejection and decreasing RV efficiency. Interestingly, timing of reflected wave arrival is influenced by the location of the predominant vascular pathological condition. If the problem affects distal small-sized vessels wave reflections will arrive later and vice versa (Castelain et al. 2001). Unfortunately, these phenomena are not easy to detect clinically. During early stages the contractile function of the overloaded right ventricle may be preserved (Stein et al. 1979), and the decreased efficiency may not be detected with routine RV function assessment methods. PVR and pulmonary artery pressure are insufficient for the evaluation of all the forces that oppose RV ejection. Nevertheless, pulmonary wave reflections have been documented in patients with primary and thromboembolic pulmonary hypertension by time domain analysis of the pulmonary artery pressure waveform (Castelain et al. 2001), but have not been studied in ARDS patients. A visible notching on the systolic portion of the pressure wave form indicates the site of the reflected wave arrival and the pressure increase above the notching is an indication of the magnitude of the reflected wave.

We have recently evaluated the wave reflection phenomena by time domain analysis of the pulmonary arterial waveform in an experimental porcine model of ARDS (Oviedo et al. 2013). We hypothesised that the lung condition could dynamically modulate wave reflection phenomena, and found that lung collapse increased the magnitude of wave reflections which arrived during mid-systole. When collapse was minimised, reflected waves decreased and arrived later in the systolic phase, even at similar levels of pulmonary artery pressure.

Towards a More Integrative Protective Ventilation Approach

The pathophysiological aspects of heart-lung interactions discussed could help in introducing additional interventions to confer improved protection to the functional unit as a whole that is the lung, the pulmonary circulation and the RV. Given the importance of lung volume these interventions should be aimed at restoring and maintaining end-expiratory lung volume. A lung recruitment manoeuvre, when effectively performed, can restore lung volume by re-expanding collapsed lung regions. This results in a more homogenous distribution of tidal volume that is redistributed to more dependent lung regions, eventually decompressing non-dependent hyperinflated regions (Borges et al. 2006). In addition, by increasing the gas exchange area, recruitment improves oxygenation and carbon dioxide elimination, which can diminish the pulmonary vascular tone by reducing hypoxic pulmonary vasoconstriction. An expanded lung could also reduce the presence and effects of wave reflection phenomena and thus RV efficiency by two potential mechanisms: capillary recruitment and a decrease in pulmonary arterial elastance. The restored lung volume is then maintained by an individualised level of PEEP. Clinically this individualised PEEP level can be identified by means of a decremental PEEP trial after recruitment, searching for the level resulting in maximal lung compliance (Suarez Sipmann et al. 2007). Ideally this level should provide an optimal balance between minimal lung collapse and overdistension and would correspond to the lowest point of the PVR-lung volume curve. Furthermore, best compliance results in the lowest driving pressure for a given tidal volume that would then be adjusted to the size of the functional lung (Amato et al. 2015). Once the lung is stabilised with the individualised PEEP level, tidal volume and plateau pressure should be maintained as low as possible. The RV unloading effect of lung recruitment and PEEP has been described in cardiac surgery patients (Miranda et al. 2006). A recruitment effect may also account for the RV unloading of ARDS patients ventilated in the prone position (Vieillard-Baron et al. 2007).

Conclusion

The components of the functional unit interact in a complex manner. Mechanical ventilation and the lung condition have an important modulation role in this interaction. Pulmonary vascular dysfunction frequently complicates the course of ARDS and negatively affects patient's outcome.

Implementing a protective ventilatory strategy extended to the lung, the pulmonary circulation and the right ventricle should constitute an early target during mechanical ventilation in ARDS patients. Such a ventilation strategy should aim at restoring and maintaining lung volumes by means of recruitment and individualised PEEP selection in combination with a strict limitation of tidal volume and inspiratory pressures. An improved understanding of pulmonary vascular haemodynamics and its response to mechanical ventilation will help in further refinements of global protective strategies. Summarising, protective ventilation should be good for both lung and the heart!

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