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Fluids for the Patient with Leaky Lungs

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Acute respiratory distress syndrome (ARDS) is characterised by increased permeability pulmonary oedema (Ware and Matthay 2000). Patients with ARDS often experience haemodynamic instability, due either to an associated sepsis or to the consequences of mechanical ventilation with positive end-expiratory pressure (PEEP) (Fougères et al 2010). Clinicians can be tempted to administer fluids in such situations where cardiac preload is often reduced. However, in patients with ARDS, fluid management is a real therapeutic dilemma. On the one hand, failure to restore adequate cardiac preload and hence cardiac output can promote organ hypoperfusion and multiple organ failure. On the other hand, fluid administration can enhance pulmonary oedema formation in such conditions of increased pulmonary vascular permeability. This can result in worsening of hypoxaemia and of lung mechanics.

Back to Physiology: The Starling Equation

The transfer of fluid from the lung capillary vessels compartment to the lung interstitium across the capillary-interstitial barrier is classically described by the Starling equation: $Q_f = K_f (P_c - P_i) - \sigma(\pi_c - \pi_i)$, where Q_f is the net fluid movement across the lung capillary membrane, K_f is the filtration coefficient, P_c the capillary hydrostatic pressure, P_i the interstitium hydrostatic pressure, σ the reflection coefficient for proteins, the πc the capillary oncotic pressure and πi the interstitium oncotic pressure. Thus there are forces that promote fluid transfer such as the hydrostatic pressure gradient and forces that oppose fluid transfer such as the oncotic pressure gradient. It is noteworthy that K_f and σ are functions of vascular endothelial cell integrity and the intraluminal glycocalyx (Chelazzi et al. 2015; Lira and Pinsky 2014). The importance of the opposing forces (oncotic pressure gradient) depends on the permeability to proteins of the transvascular barrier, which is represented by σ. If vascular permeability is normal, σ is close to one and the net interstitial oedema formation will be minimal unless the capillary hydrostatic pressure reaches a certain critical level above which the interstitial oedema formation overwhelms the capacity of drainage by the lymphatic system. If vascular permeability is abnormally increased, σ decreases and tends to zero in cases of markedly leaky lungs. This can happen when excessive lung and/or systemic inflammation result in damaged intraluminal glycocalyx (Chelazzi et al. 2015; Lira and Pinsky 2014) and vascular endothelial tight junction disruption (Lira and Pinsky 2014). In such leaky lungs, the forces that oppose the fluid transfer are minimal and pulmonary oedema can develop even when the capillary hydrostatic pressure is not high. The higher the degree of alteration of vascular permeability, the lower the critical capillary pressure above which the capacity of lymphatic drainage is overwhelmed and thus pulmonary oedema develops (see Figure 1). Above this critical level, even a small increase in capillary hydrostatic pressure could result in a large increase in the amount of pulmonary oedema given that the K_f is abnormally increased in such a situation of increased vascular permeability (see Figure 2).
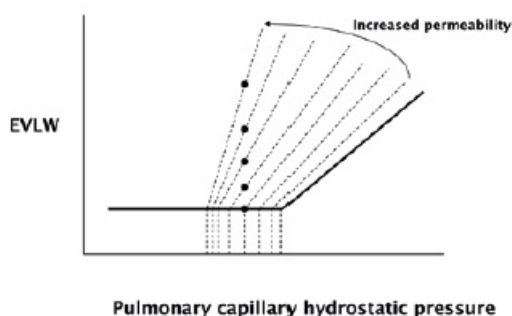

Figure 1. Relationship Between Pulmonary Capillary Hydrostatic Pressure and Extravascular Lung Water (EVLW) In case of normal permeability of the transvascular barrier (bold lines), pulmonary oedema does not develop until a certain level of capillary hydrostatic pressure is reached. Beyond the critical capillary pressure, pulmonary oedema develops because capacity of the lymphatic system to drain the interstitial oedema is

overwhelmed. In this case EVLW increases along with capillary pressure. In case of increased permeability of the lung transvascular barrier, the critical capillary hydrostatic pressure is lower than normal and the slope of the relationship is greater (dashed lines). The more altered the permeability, the lower the critical capillary pressure and the greater the slope. For a given capillary pressure, the more altered the permeability, the higher the EVLW (black circles).
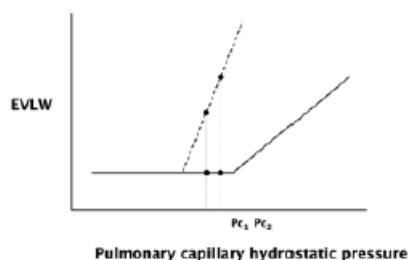

Figure 2. Effect of an Increase in Capillary Hydrostatic Pressure on Extravascular Lung Water (EVLW)
A similar increase from P_{c_1} to P_{c_2} results in a large increase in EVLW in case of increased vascular permeability but in no EVLW change in case of normal vascular permeability.

Fluid Therapy in ARDS

Many ARDS patients experience haemodynamic instability because of associated sepsis or the application of PEEP. In such conditions, central blood volume and cardiac preload can be reduced and fluid therapy can be beneficial. Alternatively, a depressed right ventricular dysfunction, either sepsis- or PEEP-related, or a sepsis-induced left ventricular dysfunction can be responsible for haemodynamic instability such that fluid infusion is not always the appropriate therapeutic solution. We have learned from studies in intensive care unit (ICU) patients that around 50% of patients are fluid responsive in terms of increase in cardiac output (Michard and Teboul 2002). This underlines the fact that fluid responsiveness must be assessed before any fluid administration in ICU patients, and particularly in patients with ARDS, where the lung vascular permeability is altered (see above). There is a lot of evidence that excessive fluid balance is an independent predictor of mortality in septic patients (Vincent et al. 2006; Boyd et al. 2011). In ARDS patients a liberal strategy of fluid management was demonstrated to be deleterious in terms of duration of mechanical ventilation and length of ICU stay, when compared to a conservative strategy in a randomised multicentre study (National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network et al. 2006). Given the uncertainty of the benefits and the potential risks of lung overload, the decision of fluid administration must be carefully made in each ARDS patient when a treatment is judged to be necessary to maintain or restore haemodynamic stability. The decision of fluid administration must be based individually on three elements:

1. The presence of haemodynamic instability or signs of peripheral hypoperfusion;

2. The presence of preload responsiveness, which can predict the benefits of fluid administration, and;

3. Limited risks of fluid overload.

It is thus important to assess the benefit/risk ratio of fluid therapy in each individual patient.

How Should we Assess the Benefit/ Risk Ratio of Fluid Therapy? Predicting the Benefits by Predicting Preload Responsiveness

The general issue of preload responsiveness and preload unresponsiveness has been extensively investigated over the last 15 years (Michard and Teboul 2002; Monnet and Teboul 2013). Schematically, there are two different approaches, the "static" and the "dynamic" approaches. The "static" approach, which is advocated by the Surviving Sepsis Campaign (SSC) (Dellinger et al. 2013), consists of administering fluids until a certain level of central venous pressure (CVP) is reached, assuming that beyond this level the heart is certainly preload unresponsive. The SSC recommends targeting a CVP of between 8 and 12 mmHg and between 12 and 15 mmHg in septic patients receiving mechanical ventilation, such as those suffering from ARDS associated with sepsis. The "dynamic" approach, which is advocated by the recent task force of the European Society of Intensive Care Medicine (Cecconi et al. 2014), consists of performing tests to predict preload responsiveness before making any decision on fluid administration. Heart-lung interaction indices based on the arterial pressure curve analysis such as pulse pressure variation (PPV) (Michard et al. 2000) and stroke volume variation (SVV) (Berkenstadt et al. 2001) have been shown to be superior to static indices such as CVP to predict fluid responsiveness (Michard and Teboul 2002; Michard et al. 2000; Berkenstadt et al. 2002; Marik et al. 2009). In many cases, especially in ARDS patients, PPV and SVV cannot be interpreted reliably (Teboul and Monnet 2013), because of the presence of spontaneous breathing activity, low tidal volume ventilation, reduced lung compliance or cardiac arrhythmias (Monnet and Teboul 2013). In such cases alternative tests such as passive leg raising (PLR) or end-expiration occlusion can be used (Monnet and Teboul 2013). The PLR test can accurately predict fluid responsiveness in cases of spontaneous breathing activity (Monnet et al. 2006), cardiac arrhythmias (Monnet et al. 2006), low tidal volume and reduced lung compliance (Monnet et al. 2012). This postural manoeuvre, which mobilises venous blood from the lower limbs and the abdominal compartment towards the intrathoracic compartment, mimics a fluid challenge, but unlike fluid challenge its effects are reversible (Monnet et al. 2006). The validity of PLR as a preload responsiveness test relies on strict rules, which need to be respected (Monnet and Teboul 2015): the postural manoeuvre consists of adjusting the bed (not manually raising the patient's legs) from a semi-recumbent position (not a horizontal position) to a position where the head and trunk are horizontal and the lower limbs elevated at 45°; the haemodynamic response to PLR must be assessed by real-time changes in cardiac output or stroke volume (and not by real-time changes in arterial pressure); the heart rate must not increase during the test, ensuring that no sympathetic stimulation occurs. Another possibility to predict fluid responsiveness in ARDS patients is to perform an end-expiration occlusion, which is a test consisting of interrupting the ventilator during 15 seconds and in measuring the real-time changes in cardiac output or in arterial pulse pressure (Monnet et al. 2009). This test can also be considered as a reversible preload challenge. Indeed it abolishes the impediment of venous return induced by mechanical insufflation, thus transiently mobilising venous blood to the heart. An increase in cardiac output or in pulse pressure greater than 5% during this test predicts fluid responsiveness with good accuracy. It is still reliable in case of ARDS and low tidal volume ventilation (Monnet et al. 2012).

Predicting the Risks by Estimating Extravascular Lung Water (EVLW) and Pulmonary Vascular Permeability

The role of capillary hydrostatic pressure in pulmonary oedema formation is particularly important during ARDS, given that a small increase in pressure can result in a large increase in the amount of interstitial oedema in leaky lungs (see Figure 2). Although a high pulmonary capillary pressure should be associated with a high risk of pulmonary oedema formation and its worsening after fluid infusion, there is no magic value below which this does not occur. In addition pulmonary capillary pressure is difficult to measure at the bedside, and is not well reflected by the pulmonary artery occlusion pressure (PAOP) obtained after balloon inflation of a pulmonary artery catheter, especially during ARDS where the pulmonary venous resistance is abnormally increased (Nunes et al. 2003; Teboul et al.1992). Finally PAOP cannot reflect EVLW (Boussat et al. 2002), which is obviously in agreement with physiologic principles.

A more direct estimation of EVLW is obviously a better approach to evaluate the amount of pulmonary oedema already developed at the time of the therapeutic decision. For 15 years it has been possible to estimate EVLW in ICU patients by using transpulmonary thermodilution devices. The normal EVLW value is below 10 mL/kg (Tagami et al. 2013). The EVLW was demonstrated to be an independent predictor of mortality in ARDS patients (Jozwiak et al. 2014), confirming its validity and its relevance in this category of patients. The EVLW was also shown to be higher in severe versus moderate ARDS and higher in moderate versus mild ARDS when the Berlin definition of ARDS is used (Kushimoto et al. 2013). Interestingly, baseline EVLW and not PaO_2/FiO_2 can predict the progression to acute lung injury in patients with increased risks (LeTourneau et al. 2012). Finally, in cardiac surgery and in aortic vascular surgery patients, the maximal value of perioperative EVLW was recently shown to predict clinically significant postoperative pulmonary oedema (Kor et al. 2015). All these arguments support the interest in estimating EVLW before making any decision on fluid infusion in patients with ARDS or even at risks of ARDS. Transpulmonary thermodilution also allows the automatic calculation of pulmonary vascular permeability index (PVPI), which is assumed to reflect the permeability of the pulmonary transvascular barrier. The PVPI was demonstrated to distinguish well between pulmonary oedema of hydrostatic origin and ARDS with a cut-off value of 3 (Kor et al. 2015). It is also an independent predictor of mortality in ARDS patients (Jozwiak et al. 2013), and is well linked to the severity of ARDS according to the Berlin definition (Kushimoto et al. 2013). Knowledge of both EVLW and PVPI are of major importance, since they allow the clinician not only to evaluate well the severity of the lung injury (PVPI) and its consequences (EVLW), but also to predict what would be the lung tolerance to a subsequent fluid administration. In case of a moderately high EVLW (e.g. 14 mL/kg) but a high PVPI (e.g. 5), there is a high risk of excessive lung oedema formation with fluid infusion. In case of a moderately high EVLW (e.g. 14 mL/kg) associated to a moderately high PVPI (e.g. 3.5), fluid could be carefully infused if there are both haemodynamic instability and preload responsiveness conditions.

In some patients a high EVLW value and high PVPI value can be associated with a high degree of fluid responsiveness (e.g. high PPV or large CO response to PLR). This situation represents a therapeutic conflict, and the decision of administering fluids or not would be based on the respective degree of lung injury and its consequences (hypoxaemia, hypercapnia, etc) versus the degree of circulatory failure and its consequences (hypotension, organ failures, etc). Thus similar values of EVLW, PVPI and PPV can result in opposite decisions in terms of fluid administration, depending on the presence and the severity of organ dysfunctions. This underlines the importance of taking into consideration the complete and often complex picture of the patient's state rather than reducing the patient's care to a too simplistic protocol based on three to four numbers only.

Conclusion

Fluid administration in case of ARDS is a real therapeutic challenge since there are risks of worsening of pulmonary oedema even in preload responsive patients. Assessment of the benefit/ risk ratio in each individual patient is thus very important before making any therapeutic decision. Use of dynamic indices of preload responsiveness allows assessment of the potential benefits (the numerator), whereas the risks (the denominator) can be assessed at best by measurements of EVLW and PVPI. It must be emphasised that assessment of the benefit/risk ratio should be continued during fluid administration to help to make the decision to stop fluid infusion.

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