Critically ill patients are at risk of developing acute cardiovascular insufficiency or shock from any cause, defined as the imbalance between oxygen delivery and tissue oxygen consumption. This state is characterised by cellular dysoxia that, maintained over time, might progress to multi-organ failure and death. In order to prevent these consequences, haemodynamic resuscitation has to be started early and aimed at correcting tissue hypoperfusion. Since most common causes of shock have some degree of insufficient intravascular volume, volume expansion with fluids is recognised as the first step of resuscitation, and is one of the issues in critical care practice that shows a high level of controversy and debate in most of its aspects. In this review, we will analyse two fundamental questions: “which tools should we use to guide fluid management?” and “what strategies for fluid administration can improve the prognosis of our patients?”

**Applied Physiology at the Bedside: Current Approach to Fluid Administration**

According to the Frank-Starling law of the heart, there is a positive relationship between preload (defined as end diastolic volume) and stroke volume, and this relation follows a curvilinear shape. Consistently, a uniform increase in preload produces a significantly greater increase in stroke volume on the steep ascending portion of the curve, defining a preload-dependence area, where volume expansion significantly increases cardiac output. On the opposite, flatter part of the curve, we can define a preload-independence area, where volume expansion produces no significant changes in stroke volume. This increase in stroke volume as a result of volume expansion depends not only on the increase in end-diastolic volume, but also on ventricular function, since a decrease in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume (Pinsky 2005).

**Fluid Responsiveness**

Fluid responsiveness is arbitrarily defined as a \( \geq 15\% \) increase in cardiac output (CO) in response to a fluid challenge (normally 500 ml) (Michard et al. 2000). In the assessment of preload-dependence, the simplest method is to give a bolus of intravenous fluid and evaluate the haemodynamic response. This practical approach is also still considered to be the “gold standard” of fluid responsiveness. Volume expansion in normal individuals almost always produces an increase in stroke volume, but in shock states, the rate of response markedly falls to approximately 50%. Furthermore, fluid overload due to aggressive volume expansion may lead to deleterious effects, such as an increase in extravascular lung water or acute cor pulmonale, or both (Michard et al. 2002). Therefore, it seems of critical importance to detect if a shocked patient is on the preload-dependence part of the curve before starting fluid administration. For use in such instances, practical tools have been accessed to predict fluid responsiveness at the bedside.

- **Static Parameters for Assessing Fluid Responsiveness**

Static parameters are based on the evaluation of cardiovascular pressures and volumes, and they try to
estimate the absolute value of ventricular preload. However, predicting response to fluid challenge based on ventricular preload evaluation may be problematic.

1. Cardiovascular Filling Pressures

Commonly used measurements of preload include central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP). However, a significant relationship with reference to values of CVP and PAOP has not been found between fluid responsive and non-responsive patients (Michard et al. 2002). This can be explained by an inability of these static filling pressures to precisely estimate preload in different clinical scenarios, especially in those situations where intravascular pressure may overestimate transmural pressure (Pinsky 2003). However, it is accepted that extremely low values of filling pressures (<5 mmHg in CVP, and <7 mmHg in PAOP) can be considered as predictors of a positive response to fluid expansion (Teboul et al. 2004).

2. Cardiovascular Volumes and Areas

Although ventricular volumes are more accurately used for estimating ventricular preload than filling pressures, they are still far from being good predictors of fluid responsiveness. Fluid expansion is expected to increase right ventricular enddiastolic volume (RVEDV) as well as left ventricular end-diastolic volume (LVEDV). However, the relationship between ventricular volumes and telediastolic pressures depends also on ventricular compliance; so for a given telediastolic volume, the intravascular pressure will depend on ventricular compliance and not on the real value of preload.

The key concept that explains the inability of these static parameters to assess fluid responsiveness is again found in the Frank-Starling curve. For a given preload value, whatever the precision of the method used to assess it, cardiac output response might not be predicted unless it is known in which part of the curve the patient is operating (Sabatier et al. 2012). Despite their failure to do so, static volumes and filling pressures continue to be massively used in daily practice as tools for assessing fluid-responsiveness.

- Dynamic Parameters for Assessing Fluid Responsiveness

Recently, the use of a more dynamic approach to the prediction of fluid responsiveness has been proposed: a real-time evaluation of the cardiovascular response to temporary and reversible changes in preload, such as intrathoracic pressure secondary to mechanical ventilation or certain postural manoeuvres.

1. Changes in Left Ventricular Output Induced by Positive Pressure Ventilation: The Pulse Pressure Variation and the Stroke Volume Variation

During the inspiratory phase of positive pressure ventilation, rising intrathoracic pressure leads to increases in right atrial pressure and decreases in venous return, with a consequent fall in right ventricular output. Simultaneously, blood volume contained in the pulmonary circulation is squeezed, thus increasing left ventricular preload and left ventricular output. After two or three beats, the previous fall in right ventricular output will produce a decrease in left ventricular output in the expiratory phase. Thus, in preload dependent patients, cyclic changes in left ventricular stroke volume and its coupled arterial pulse pressure are seen, and the magnitude of these changes are proportional to the grade of volume-responsiveness (Magder 2004; Michard et al. 2000).

The stroke volume variation (SVV) measurement requires the use of Doppler echocardiography or analogue estimation of left ventricular stroke volume with pulse-contour analysis haemodynamic monitoring tools. Multiple studies have shown that SVV >10% predicts fluid responsiveness with high sensitivity and specificity (Marik et al. 2009). Since pulse pressure is primarily determined by left ventricular stroke volume in a given respiratory cycle, the pulse pressure variation (PPV) in this space of time will be dependent only on stroke...
volume variation. PPV is easily obtained at the bedside, automatically calculated from the signal of the arterial line in most haemodynamic monitors. Again, multiple studies have proven that PPV >13% predicts fluid responsiveness with high sensitivity and specificity (Marik et al. 2009).

Changes in the diameter of inferior vena cava (ΔDIVC) secondary to positive pressure ventilation, assessed non-invasively by transthoracic echocardiography, have also been explored. As occurs with SVV and PPV, the magnitude of inferior vena cava diameter change within a respiratory cycle is proportional to the grade of fluid responsiveness. Indeed, recent studies showed that ΔDIVC ≥12% predicted fluid responsiveness with high sensitivity and specificity (Feissel et al. 2004).

Some limitations of these parameters deserve mention. First, the patient has to have a stable and regular cardiac rhythm, as any kind of arrhythmia or frequent extra-systoles will interfere in the calculation of the parameters. Second, the patient has to be fully adapted to mechanical ventilation in a controlled mode, as spontaneous respiratory swings might lead to overestimation of those parameters. Third, patients with right ventricular dysfunction may generate false positives. Finally, the predictive power of these parameters is decreased through using tidal volumes set to <8 ml/Kg of ideal weight, since minimum modifications in intrathoracic pressure are required to observe the described haemodynamic effect (De Backer et al. 2005).

2. Passive Leg Raising

The passive leg raising (PLR) manoeuvre is a simple and reliable method to evaluate fluid responsiveness. It consists of a passive elevation of the legs to 45º while keeping the head at 0º, for three minutes (Monnet and Teboul 2008). The manoeuvre causes an autotransfusion of blood contained in the lower limbs to the central compartment, with a consequent increase in venous return and in cardiac pre-load. If the ventricles are operating in the preload-dependence area of the Frank-Starling curve, it also triggers a transient increase in cardiac output. It is considered a reversible fluid challenge equivalent to approximately 300cc. To evaluate the transitory cardiac response to PLR, it is important to use a haemodynamic monitoring device to assess rapid changes in cardiac output. PLR-induced increases ≥10% in cardiac output during the first 60-90 seconds predict fluid responsiveness with high sensitivity and specificity (Cavallaro et al. 2010). This manœuvre can be performed in ventilated or spontaneously breathing patients, and also in absence of sinus rhythm. Its primary limitations are: potential risk of increasing intracranial pressure, risk of aspiration, and decreases in test efficacy in patients with intrabdominal hypertension, extreme hypovolemia or cardiogenic shock (Monnet and Teboul 2008).

A huge amount of evidence endorses the superiority of these dynamic parameters over the static ones in assessing fluid responsiveness. However, these dynamic parameters have not been fully incorporated in current resuscitation guidelines (Dellinger et al. 2008), probably because of their limited applicability to certain patient populations.

Fluid Administration: Resuscitation Strategies

An accurate knowledge of fluid-responsiveness parameters is helpful in the haemodynamic resuscitation decision-making process, but it should be noted that the patient being preload-responsive does not imply that he/she needs volume. The clinician must bear in mind that recognising the need for further resuscitation (and when to stop) is just as important as being familiar with the tools used during the process, if not more so.

- Endpoints of Resuscitation

The goal of fluid therapy in critically ill patients is to restore tissue oxygenation, thus preventing or minimising tissue damage. From Shoemaker’s group studies to Rivers’ landmark early goal-directed therapy (EGDT) protocol, many groups have demonstrated that optimising oxygen delivery to tissues by means of standardised haemodynamic resuscitation protocols results in substantial improvements in morbidity and mortality of critically ill patients (Shoemaker et al. 1982; Rivers et al. 2001; Levy et al. 2010). Standardised care requires...
defined and validated endpoints, ranging from global DO2 to surrogates of global end-organ perfusion (such as lactate, and either central or mixed venous oxygenation) (Mesquida et al. 2011). Achieving these predetermined physiological endpoints would denote the culmination of the resuscitation process; therefore, volume administration or other interventions that aim to increase DO2 would no longer be indicated. However, during the last decade, overwhelming evidence has emerged indicating that, despite normalisation of global surrogates of tissue perfusion, local tissue hypoperfusion might persist, and these microcirculatory alterations are associated with worse outcome (De Backer et al. 2002). Regardless of the chosen endpoint, fluid administration is crucial for any of the proposed algorithms, and fluids are given while fluid responsiveness is suspected and global tissue perfusion surrogates have not normalised. Still, the response of the microvascular system, the ultimate target of the resuscitation process, might be independent to the behaviour of the macro-haemodynamic parameters. Then, macro-haemodynamic fluid responsiveness might not be equal to microcirculatory fluid responsiveness. The increasing proof of the uncoupling between macro- and microvascular compartments has taken us to the next query in resuscitation: should we monitor microcirculation to titrate the administration of fluids? Using video microscopic imaging techniques, several authors have reported persistent microcirculatory alterations, despite improvements in cardiac output after volume expansion, with dissociated response of the micro- and macrovascular compartments (Sakr et al. 2004; Trzeciak et al. 2007; Ospina-Tascon et al. 2010). In the near future, guiding fluid administration by using technologies that evaluate the microcirculatory perfusion seems unavoidable. Microcirculatory monitoring probably needs to be complementary to the macrovascular approach, and further clinical investigations should explore whether this combined approach results in better patient outcomes.

**Misleading Endpoints**

Despite the fact that current sepsis management guidelines offer well-established tissue perfusion endpoints, intravenous fluid administration remains highly empirical during the resuscitation process. The Surviving Sepsis Campaign guidelines for management of sepsis recommend an initial administration of repeated fluid challenges of >1000 ml of crystalloids or 300-500 ml of colloids (Dellinger et al. 2008). According to these guidelines, the infusion of fluids should be maintained until certain predetermined values of central venous pressure (CVP) are achieved. Importantly, CVP is presented as an endpoint per se, not only as a tool for assessing volume responsiveness. On a physiological basis, volume expansion should only be performed when an increase in stroke volume is expected and, as we already exposed, CVP has repeatedly failed in predicting preload dependency (Michard and Teboul 2002). Therefore, CVP seems to be an unreliable surrogate of the adequacy of intravascular volume status, and using CVP not only as a tool, but also as an endpoint in the resuscitation process, might be deleterious for patients. In the study by Rivers and colleagues (Rivers et al. 2001), patients in the EGDT treatment group, where CVP was used to guide fluid administration, received up to 1.5 litres more volume than patients in standard care within the first six-hour period; although, in the final 72-hour fluid balance, no difference between the EGDT and standard groups was recorded. Importantly, a more positive fluid balance has been associated with increased mortality (Vincent et al. 2006; Boyd et al. 2011), either within the first 12 hours or after four days of ICU stay (Boyd et al. 2011). Whether fluid balance independently affects outcome or it is just a confounder and a marker of severity of illness remains unclear, but aggravating fluid balance by using the wrong tools and the wrong endpoints should not take place in the context of current knowledge.

**Early Versus Late**

Finally, when analysing some failed goal-directed studies, it was noted that resuscitation interventions did not result in outcome improvements when initiated too late in the time course of the disease (Gattinoni et al. 1995; Kern and Shoemaker 2002), once tissue damage was presumably present. The EGDT study carried out by Rivers and his team (Rivers et al. 2001) also highlighted the importance of time: a six-hour initial resuscitation bundle, including aggressive fluid administration was associated to better prognosis. This fluid loading strategy has been adopted in sepsis management guidelines, with apparently favorable results (Levy et al. 2010).

However, compliance with current volume loading recommendations (within the initial resuscitation bundle) has not been independently associated to increased survival rates (Ferrer et al. 2009). Evidence appears more consistent when evaluating the effect of fluids administered late in the time course of the disease. On this behalf, several authors have reported the negative effect on outcome derived from positive fluid balance within three to seven days of ICU admittance (Rivers et al. 2001; Boyd et al. 2011; Murphy et al. 2009). Supporting these epidemiological findings, the significance of the time factor has been endorsed by some observations at
the microcirculatory level, where the response to fluid administration has proven to differ according to the elapsed time since the onset of the disease. Using sublingual video microscopy, Ospina-Tascon and colleagues (Ospina Tascon et al. 2010) detected improvements in perfusion of small vessels in response to volume expansion only when fluids were administered early (within 24 hours) after diagnosis of septic shock, but not when administered late in the course of the disease. Importantly, this effect was again independent from those at the global haemodynamic level.

Conclusions

In conclusion, there are still many grey zones regarding fluid management, but current knowledge permits to fill some pieces of the puzzle. Understanding our patients’ physiology, estimating their position in the Frank-Starling curve to better direct fluid administration, and targeting well-defined global tissue oxygenation endpoints in order to guide and/or finish the resuscitation process are key factors in providing a high standard of care and improving our critically ill patients’ prognoses. Whether incorporating additional targets such as microcirculatory variables will impact on outcome deserves further investigation.

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