Fluid bolus therapy: monitoring and predicting fluid responsiveness

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Purpose of review
When a condition of hypoperfusion has been identified, clinicians must decide whether fluids may increase blood flow or whether other therapeutic approaches are needed. For this purpose, several tests and parameters have been introduced in clinical practice to predict fluid responsiveness and guide therapy.

Recent findings
Fluid challenge is the gold standard test to assess the preload dependence of the patients. Moreover, several parameters and tests avoiding fluid administration are now available. Pulse pressure variation and stroke volume variation are based on heart–lung interaction and can be used to assess fluid responsiveness. These parameters have several limitations and can really be used in a limited number of critically ill patients. End-expiratory occlusion test and passive leg raising have been proposed to overcome these limitations. The aim of resuscitation is to increase blood flow and perfusion pressure. Dynamic arterial elastance has been recently proposed to predict the pressure response after fluid challenge in preload-dependent patients. Finally, the effects of volume expansion of hemodynamic parameters do not necessarily reach the microcirculation, which should also be assessed.

Summary
Nowadays, several parameters are available to assess fluid responsiveness. Clinicians need to know all of them, with their limitations, without forgetting that the final aim of all therapies is to improve the microcirculation.

Keywords
cardiac output, fluid responsiveness, haemodynamic monitoring, microcirculation, stroke volume

INTRODUCTION

One of the most important therapeutic approaches to patients affected by shock is the infusion of intravenous fluids. Fluids should be considered as other drugs, with beneficial but also adverse effects, especially in patients with a limited cardiac reserve. A positive fluid balance has been associated with an increased morbidity and mortality [1,2▪,3▪,4]. For this reason, it is helpful to know whether the patient will respond to the fluids before their infusion [5].

First, the term 'fluid responsiveness' needs to be defined. Changes in cardiac output (CO) or stroke volume (SV) of more than 10–15% are used to define a positive response to fluids [6]. This implies that the monitoring of blood pressure alone is not enough and blood flow must also be measured. Fortunately, several minimally invasive monitoring systems are able to continuously track changes in CO and SV and are now available, and their use should be encouraged, especially in complex situations [7▪▪].

No doubts currently exist about the role of filling pressures to estimate fluid responsiveness: absolute values of central venous pressure (CVP) and pulmonary artery occlusion pressure are not good predictors of cardiac preload or the change in CO or SV to a fluid challenge [8]. Volumetric parameters, such as right ventricle end-diastolic volume and global end-diastolic volume, are also no better at predicting fluid responsiveness [9,10]. The last consensus on circulatory shock and hemodynamic monitoring clearly recommends not to target fluid therapy on any ventricular filling pressure or volume [7▪▪].

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KEY POINTS

- Fluids should be considered as other drugs, with beneficial but also adverse effects, and only 50% of critically ill patients respond to fluid challenge.
- Just because a patient is fluid responsive, this does not mean that he or she necessarily needs fluids.
- Different parameters or tests should be considered together to increase their single accuracy to predict the changes of cardiac output after fluid infusion.
- The oxygen delivery to tissue can increase only if therapeutic interventions are able to reach the microcirculation.

A fundamental aspect to consider is that just because a patient is fluid responsive, this does not mean that he or she necessarily needs fluids. The first condition to define is an inadequate tissue perfusion, shown, for example, by hypotension, oliguria, elevated lactate level, prolonged capillary refilling time, mottled skin and altered mental status. Blood pressure should not be used alone to define shock state, because it can be maintained in the normal range by a compensatory mechanism despite concomitant peripheral hypoperfusion [7▪▪].

When a condition of hypoperfusion has been identified, clinicians must decide whether fluids may increase blood flow or whether other therapeutic approaches are needed. For this purpose, several tests and parameters have been introduced in clinical practice to predict fluid responsiveness and guide therapy (Table 1).

FLUID CHALLENGE

The easiest approach to evaluate fluid responsiveness is to perform a fluid challenge. This is a dynamic test of the cardiovascular system that assesses the preload reserve of the patient [6]. The volume of fluid given for this test must be sufficient to stretch the right ventricle, increasing the diastolic volume. Under this condition, SV may increase according to Frank–Starling's law [11]. Usually, 250 ml or 3 ml/kg of crystalloids is needed. The rate of administration is also a critical aspect. Fluids should be infused over a short period of time (5–10 min) and the response is considered positive when SV or CO increases more than 10–15%. If SV or CO increases, further fluids can be given in a controlled manner, repeating the fluid challenge so long as there is a positive response (SV maximization). This approach avoids fluid overload, as the only excess fluids are equivalent to one fluid challenge [6].

Table 1. Tests and parameters of fluid responsiveness

Test/parameter	Underlying mechanism	Advantages	Limits
Fluid challenge	Infusion of 250 ml of crystalloids over 5 min	Small amount of fluids	No prediction before fluids infusion
Mini fluid challenge	Infusion of 100 ml of crystalloids over 1 min	Small amount of fluids	No prediction before fluids infusion
SVV, PPV, ΔVTI, IVC/SVC variability	Heart–lung interaction in mechanically ventilated patients	No fluids infusion	Spontaneous breathing efforts Vt <8 ml/kg Cr <30 ml/cmH_2O HR/RR >3.6 Arrhythmias RV failure
EEO test	Heart–lung interaction in mechanically ventilated patients	No fluids infusion Independent of arrhythmias Independent from Cr	Strong spontaneous breathing activity
PLR	Self-volume challenge	No fluids infusion Reversible effect	IAH ICH
Eadyn	PPV/SVV	BP response in preload-dependent patients	No prediction on SV changes

BP, blood pressure; Cr, compliance of respiratory system; Eadyn, dynamic arterial elastance; EEO, end-expiratory occlusion; HR, heart rate; IAH, intra-abdominal hypertension; ICH, intracranial hypertension; IVC, inferior vena cava; PLR, passive leg raising; PPV, pulse pressure variation; RR, respiratory rate; RV, right ventricle; SV, stroke volume; SVC, superior vena cava; SVV, stroke volume variation; Vt, tidal volume; VTI, velocity time integral.

Although CVP has a poor significance itself to predict fluid responsiveness, it is helpful to evaluate the effect of fluid challenge and to determine the amount of fluid needed to perform this test. Sufficient fluid is given to achieve a minimal increase in CVP (up to 2 mmHg). At this stage, the right ventricle will have stretched because of the increased end diastolic volume. A concomitant increase in CO indicates that the patient is fluid responsive, whereas an increase in CVP without an increase in CO shows that further fluids are not indicated [12].

Changes in circulating blood volume generated by a fluid challenge can also be assessed by mean systemic filling pressure (Pmsf) [13]. It is defined as the pressure in the cardiovascular system when the heart is stopped and there is no fluid motion. The Pmsf depends on the 'stressed volume', which is the blood that stretches the blood vessels and causes intravascular pressure, and the compliance of the cardiovascular system. After a fluid challenge, an increase in blood volume is related to an increase in Pmsf.

Recently, a mini-fluid challenge has been proposed [14,15]. It consists of giving only 100 ml of fluids over 1 min with a contemporaneous assessment of changes in CO or its surrogates. This test predicted fluid responsiveness in critically ill patients with a sensitivity and specificity of 95% and 78%, respectively, with an area under the receiver operating characterizing curve (AUC ROC) of 0.92 [95% confidence interval (CI): 0.78–0.98] [15]. This approach is based on a high rate of infusion rather than on the absolute volume of fluid given.

Because it has been estimated that only 50% of critically ill patients respond to fluid challenge [16], clinicians are interested in knowing whether the patient will increase SV as a consequence of fluid challenge before fluid administration, especially in the case of patients with a limited cardiac reserve or increased lung capillary permeability. For this purpose, several dynamic parameters and tests have been developed.

HEART–LUNG INTERACTION

In mechanically ventilated patients, the cyclical variation in intrathoracic pressure produces hemodynamic effects useful to determine whether the patient's heart is working on the steep or the flat portion of the Frank–Starling curve. During positive pressure ventilation, the increase in intrathoracic pressure that occurs during inspiration reduces the preload of the right ventricle (RV). At the same time, RV afterload increases in relation to the inspiratory increase in trans-pulmonary pressure. All together, these modifications are responsible for a decrease in RV SV. After two to three heart beats, the reduction of RV ejection leads to a reduction of left ventricle (LV) filling. Thus, LV preload reduction may induce a decrease in LV SV, with a minimum value during the expiratory phase. The magnitude of the respiratory changes in SV depends on the volume status and on the preload dependence of both ventricles. In the case of hypovolemia, these cyclic increase and reduction of SV are more pronounced.

STROKE VOLUME VARIATION AND PULSE PRESSURE VARIATION

Nowadays, several hemodynamic monitors are able to calculate SV continuously, providing dynamic parameters such as stroke volume variation (SVV) and pulse pressure variation (PPV).

Changes in peripheral pulse pressure are related to changes in LV SV [17], so that PPV has been used to predict fluid responsiveness. Michard *et al*. [18] showed that a cut-off value of 13% was able to discriminate between responders and nonresponders with a sensitivity and specificity of 94% and 96%, respectively. Moreover, the baseline value of PPV was related to changes in CO after fluid administration. Marik *et al*. [19] showed an AUC ROC of 0.94 and 0.84 for PPV and SVV, respectively. A recent meta-analysis performed by Yang and Du [20▪] including 22 studies confirms that PPV is a good predictor of fluid responsiveness in mechanically ventilated critically ill patients with sensitivity of 88% (95% CI: 81–92%), specificity of 89% (95% CI: 84–92%) and AUC ROC of 0.94 (95% CI: 0.91–0.95).

Recently, a 'grey zone approach' has been introduced, based on the overlap of PPV values between responders and nonresponders when a single cut-off of 13% is used [21,22▪]. The grey zone approach proposes a low cut-off value that excludes fluid responsiveness in 90% of patients (favouring negative predictive value), whereas a high cut-off value predicts fluid responsiveness in 90% of cases (favouring positive predictive value). Between these two cut-off values, no decision can actually be taken. Biais *et al*. [22▪] reported that PPV cannot reliably guide fluid loading for values between 4 and 17%, which occurred in 62% of patients enrolled from nine French ICUs.

All these dynamic parameters have several limitations. First, the patients need to be mechanically ventilated without spontaneous breathing efforts, and tidal volume should be enough to promote adequate preload variations. More than 8 ml/kg is usually required for adequate interpretation of dynamic parameters [23], and this condition

precludes their use during protective lung ventilation such as in patients with acute respiratory distress syndrome (ARDS) [24]. Second, a ratio between heart rate and respiratory rate less than 3.6 is required [25]. Third, conditions under which one of the two ventricles is preload independent, such as RV failure [26] or elevated LV filling pressures [27], preclude the usefulness of dynamic parameters. Finally, arrhythmias are the last exclusion criterion for the use of dynamic variables. Two recent studies have shown that the percentage of patients admitted to the ICU suitable to be assessed using PPV was between 1.3 and 2% [28▪,29]. In these situations, clinicians cannot use dynamic variables based on heart–lung interaction and need other parameters able to predict fluid responsiveness.

END-EXPIRATORY OCCLUSION TEST

As previously stated, the increase in intrathoracic pressure during mechanical ventilation reduces venous return and consequently SV. Thus, a short end-expiratory occlusion (EEO) may prevent the cyclic impediment in left cardiac preload and may act like a fluid challenge. This could serve as a functional test for fluid responsiveness. Because its duration encompasses several cardiac cycles, the prediction of fluid responsiveness could be independent of cardiac arrhythmias. The test could also be used in patients with a spontaneous breathing activity. Nevertheless, as the EEO test consists of interrupting mechanical ventilation at end expiration, its hemodynamic effects, and thus its reliability in predicting fluid responsiveness, could depend upon the positive end-expiratory pressure. Monnet *et al.* [30] performed a 15-s EEO test in 34 patients with shock, and fluid responsiveness was predicted by an increase in cardiac index more than 5% during the EEO with a sensitivity and a specificity of 91 and 100%, respectively. Good results were obtained also in patients affected by ARDS with low-respiratory compliance, a condition that precludes the use of PPV and SVV [31,32].

ECHOCARDIOGRAPHIC INDICES

Echocardiography is a noninvasive technique widely used in intensive care medicine to assess the cardiac function of critically ill patients. Static echocardiographic parameters of cardiac preload, such as volumes and estimated filling pressures, exhibit the same limitations as those reported for invasive cardiac filling pressures. Dynamic evaluation of echocardiographic variables during respiratory cycle has, however, assumed a major role in predicting fluid responsiveness [33]. Clinical data suggest that respiratory variation of inferior vena cava (IVC) diameter can be used to predict the preload-dependence status in mechanically ventilated patients [34,35]. Barbier *et al.* [34] calculated the distensibility index for the IVC (dIVC) using transthoracic echocardiography and showed that a threshold of 18% was able to discriminate responders and nonresponders with 90% sensitivity and 90% specificity. A strong correlation ($r = 0.9$) was observed between dIVC at baseline and the cardiac index increase following blood volume expansion. Transesophageal echocardiography has also been used to evaluate collapsibility of superior vena cava with similar results [36,37].

Using pulsed Doppler in the LV outflow track, echocardiography is able to measure LV SV by multiplying the area under the curve of the aortic flow [velocity time integral (VTI)] by the cross-sectional area of the aortic annulus. Because the cross-sectional area of the aortic annulus remains constant during the respiratory cycle, changes in VTI directly reflect changes in LV SV. Therefore, VTI variations have been used as a surrogate of SVV to predict fluid responsiveness [38,39].

PASSIVE LEG RAISING

Passive leg raising (PLR) is a manoeuvre that transiently and reversibly increases venous return by shifting venous blood from the legs to the intrathoracic compartment. If the ventricles are preload dependent, PLR may result in an increase in SV. Therefore PLR can be considered a brief and completely reversible 'self-volume challenge' [40,41▪▪], avoiding the risk of fluid overload. The effect of PLR is time limited, and SV reaches the maximum value approximately 1 min after starting the manoeuvre, returning to the baseline after the procedure [42]. A further advantage of this test is that it remains reliable when parameters based on heart–lung interaction cannot be used. Monnet *et al.* [42] evaluated PLR in 71 mechanically ventilated patients, 31 of them presenting spontaneous breathing activity and/or arrhythmias. They showed that an increase in aortic blood flow of at least 10% by PLR predicted a volume expansion-induced increase in aortic blood flow of at least 15% with a sensitivity of 97% and specificity of 94% and AUC ROC of 0.96 ± 0.02. Moreover, it has been demonstrated that PLR works better than PPV in patients with low-respiratory system compliance ($\leq 30\,ml/cmH_2O$), with AUC ROC of 0.94 ± 0.05 and 0.69 ± 0.10, respectively [31]. This offers an opportunity to test fluid responsiveness also in patients with ARDS, in whom fluid overload is deleterious and a restrictive fluid strategy might be preferred. A meta-analysis performed by

Cavallaro and co-workers confirmed PLR accuracy to predict fluid responsiveness in patients with arrhythmias and spontaneous breathing [43]. PLR is based on recruitment of both splanchnic and leg blood. Because intra-abdominal hypertension reduces venous return, compressing the inferior vena cava, this condition could impair the ability of this manoeuvre to detect fluid responsiveness. In patients with intra-abdominal hypertension, PLR has been associated with a 48% false negative rate, and an intra-abdominal pressure cut-off value of 16 mmHg discriminated between responders and nonresponders to PLR with a sensitivity of 100% (95% CI: 78–100%) and specificity of 86% (95% CI: 61.6–98.1%) [44]. Finally, PLR cannot be performed in patients with traumatic brain injury because of the risk of increasing intracranial pressure.

DYNAMIC ARTERIAL ELASTANCE

During resuscitation of patients in shock, an increase in blood flow is not the only target for clinicians, but a rise in perfusion pressure is also expected. An increase in blood pressure does not automatically follow the increase of SV, since the pressure–volume relation depends on arterial tone [45]. Assessment of dynamic arterial elastance (Eadyn) has been recently proposed to predict the arterial pressure response after volume loading in preload-dependent patients [46,47,48▪]. Arterial elastance is defined as the ratio of changes in pressure to changes in volume. Although PPV and SVV cannot be accurately interpreted as measures of volume responsiveness in patients with atrial fibrillation and spontaneous breathing, their ratio always defines Eadyn, as the impact of irregular variations in intrathoracic pressure should influence both components to the same degree. Monge García *et al*. [46] showed that a baseline Eadyn value greater than 0.89 predicted a mean arterial pressure increase after fluid administration with a sensitivity of 94% (95% CI: 70–100%) and a specificity of 100% (95% CI: 66.4–100%), in patients under mechanical ventilation. Recently, Cecconi *et al*. [48▪] confirmed this result also in spontaneously breathing patients. Although fluid administration remains the first recommended therapy to treat shocked patients, low arterial blood pressure could be related not only to inadequate blood flow but also to a loss of arterial tone. In this regard, the assessment of Eadyn could help to discriminate those preload-dependent patients in whom arterial blood pressure will improve only with fluids or by using vasopressors. Hypothetically, if a hypotensive patient is not a pressure-responder (low Eadyn), vasopressors should be initiated to improve mean arterial pressure, even if the patient is preload dependent. If the patient is a pressure-responder (high Eadyn), vasopressor therapy should be delayed and intravascular volume administration alone should increase arterial blood pressure.

FROM MACROHAEMODYNAMICS TO MICROCIRCULATION

The microcirculation consists of the smallest blood vessels (<100 μm diameter) and includes arterioles, capillaries and venules [49]. As the capillary network is the site of oxygen release to tissue, every therapeutic intervention should aim to improve microvascular flow. Several clinical studies have shown that microvascular alterations are not always associated with classic macrohaemodynamic parameters such as CO in septic patients [50–53]. Impaired microvascular perfusion, in terms of reduced perfused vessels density and heterogeneous microvascular flow [53,54], is responsible for organ failure, although macrohaemodynamic and blood flow have been optimized by clinical interventions. For all these reasons, resuscitation of hypoperfused patients should not be targeted to optimize only macrohaemodynamic parameters, but clinicians need to look at the microvascular level [55,56]. Pranskunas *et al*. [57] evaluated sublingual microcirculatory flow index (MFI) in 50 critically ill patients at baseline and after fluid challenge. At baseline, an altered MFI (defined as <2.6) was present in 66% of the patients. In these patients, MFI increased from a median of 2.3 (interquartile range 2–2.5) to 2.5 (2.1–2.8) after fluid challenge ($P = 0.003$). This was also accompanied by an improvement in organ perfusion. In patients with MFI at least 2.6 at baseline, MFI and clinical signs did not, however, change significantly. These changes were not restricted to patients with a rise in SV of at least 10%, and there was no difference in the number of responders between the low MFI and high MFI groups. This study showed that microcirculatory response to fluid challenge was not related to the changes of SV and identified a cut-off value for MFI of 2.6 to discriminate responders and nonresponders from a microvascular point of view. As none of the macrohaemodynamic variables at baseline discriminated for MFI less than 2.6, it seems relevant to assess organ perfusion at the level of the microcirculation.

Considering microvascular response to fluid challenge, different organs may present different behaviours. Edul *et al*. [58] showed that an increase in red blood cell velocity in sublingual microcirculation after fluid challenge was not accompanied by the same response as the intestinal microcirculation. Thus, therapeutic approaches aimed at improving systemic haemodynamics may also affect microcirculation in different ways.

CONCLUSION

When clinicians identify an impaired tissue perfusion, they must understand whether their patient will benefit from a fluid infusion or whether other strategies of cardiovascular resuscitation are needed (e.g., inotropic or vasoactive drugs). Echocardiography is a fundamental tool for evaluating patients with cardiovascular impairment, as it is able to give information about preload, afterload and contractility. In addition, several continuous CO monitor systems are now available to evaluate the patients' response to therapy. The decision to give fluids may be difficult in the critical care setting. Clinicians can use many parameters and can perform several tests to assess fluid responsiveness. It is important that a clinician knows the limits of each of them to avoid incorrect interpretation. Probably, different parameters or tests should be considered together to increase their single accuracy to predict the changes of CO after fluid infusion. Finally, we must not forget that the oxygen delivery to tissue can increase only if therapeutic interventions are able to reach the microcirculation. Even if microvascular evaluation is not currently part of routine clinical practice, technologies for the monitoring of the microcirculation are progressing quickly, so that in future a point-of-care tool could be available.

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Conflicts of interest

There are no conflicts of interest.

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