



# Prediction of fluid responsiveness in ventilated critically ill patients

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**Abstract:** In critical care, hemodynamic monitoring has been extensively studied over the last decades as an essential tool to improve patients' outcomes. Hemodynamic optimization is the key to provide the supply of oxygen and metabolic substrates to tissues according to their metabolic needs. Obtaining hemodynamic stabilization is particularly challenging in the context of circulatory shock. Distinguishing patients which are going to benefit from fluid resuscitation, from others for which administration of large amounts of fluids is detrimental is of paramount importance. Numerous techniques aimed at demonstrate fluid responsiveness in the critically ill patients have been developed over the years. This paper presents a comprehensive review of the various static and dynamic measurements used to study fluid responsiveness in critically ill patients with cardiocirculatory shock.

**Keywords:** Static measurements; dynamic measurements; stroke volume variation; pulse pressure variation; fluid challenge

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## Introduction

Circulatory shock is a life-threatening condition, it is defined as a poor oxygen utilization by cells due to an acute circulatory failure, it can be distinct in various subgroups: hypovolemic, distributive, cardiogenic and obstructive (1). Reducing tissue hypo-perfusion is the most important purpose to pursue in this critically ill patients, this goal can be obtained with administration of intravenous fluids, correcting hypovolemia increasing venous return, cardiac preload and thus cardiac output (2) In patient with septic shock, the 2018 updated guidelines recommend to start fluid resuscitation with a minimum of 30 mm pro kilo of crystalloids, to be completed no later than 3 hours after diagnosis (3). However, the initial infusion is not always enough to correct tissue hypoxia and neither to control cardiovascular instability, at this point the decision to

continue fluid administration can be challenging for the Intensive Care Physician. Most studies have showed that just part of severely ill patients benefit from this therapy (4), such patients present an increase of cardiac output after a fluid administration and are called “fluid responder” (5), the most common definition of fluid responsiveness being an increase of stroke volume of 10–15% after administration of 500 mL of crystalloids in 10–15 minutes (6). On the other hand, patients that don't respond to fluid administration are more likely to develop a condition of fluid overload (7). Fluid overload can result in many adverse effects, without any hemodynamic benefits, like: tissue edema, delays in weaning from mechanical ventilation, increased length in ICU and hospital stays and it is also a predictor of increased mortality in septic shock, acute distress respiratory syndrome (ARDS), intra-abdominal hypertension and acute kidney injury (1,6-8). This data underlines the importance

of identify sign of fluid responsiveness in critically ill patients, in other words those who are capable to respond to an increase in circulating volume with an improvement in cardiac performance.

### Static measurements

Measurements of fluid responsiveness can be static or dynamic. Static measures have been used for the last decades and are used to estimate preload (venous return). Preload in steady-state conditions is equal to cardiac output. Mathematically, preload is determined by the relationship of venous resistance with systemic filling pressure and right atrial pressure (1); venous capacitance is important because influences venous return and central venous pressure (CVP) (2). CVP is the most important static measurement. Further static measures are pulmonary artery occlusion pressure (PAOP), right atrial pressure (RAP) left-ventricular end-diastolic area (LVEDA), inferior vena cava diameter (IVC), right ventricular end-diastolic volume (RVEDV).

### Central venous pressure

Multiple modern studies showed CVP/ $\Delta$ CVP as imprecise and unreliable to predict fluid responsiveness because of a weak relationship between CVP and blood volume; CVP monitoring requires a catheter placed in superior vena cava near the right atrium junction; furthermore, the evaluation of CVP has not a standard pattern although frequently is determined immediately after the atrial contraction (A wave) and the valve closure (C wave) (3). The CVP correspond to right atrial pressure (RAP). Right ventricular output is commensurate to left-ventricular filling but may not reflect the actual filling pressure (4,5): a low RAP indicate the ascending limb of the Frank-Starling curve; a high RAP suggest that the patient is on the plateau (1), although it varies from one patient to someone else, and in the same patient, between different times (6). Static pressures and fluid responsiveness have a few relationship because of variations in venous tone, intrathoracic pressures, ventricular functions. This determine the few link between CVP and RVEDV. Thusly, a ventricular preload could be associated to the existence of ventricular preload reserve even with healthy heart-function or in absence of ventricular preload reserve (decreased contractility). Although CVP has a low accuracy for predicting fluid responsiveness, it is widely used with other static markers to test preload responsiveness in 1/3 of

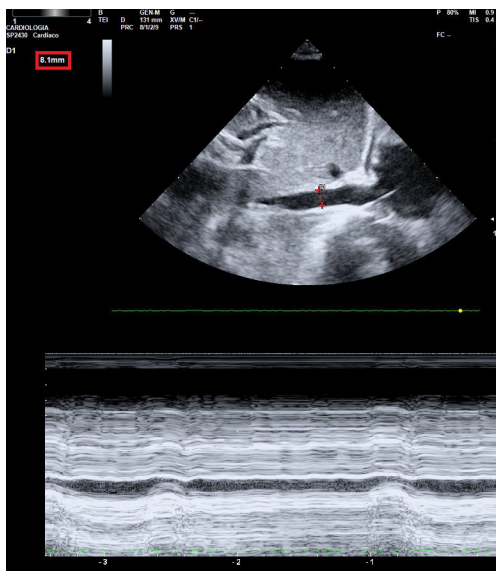
cases, as shown by the FENICE study (7), an observational study operated in intensive care units all over the Earth. In a study about hemodynamic monitoring in patients under high-risk surgery, 73% of American and 84% of European anesthesiologists reported the use of CVP to govern fluid management (8). A systematic review including 803 patients analyzed CVP with measured circulating blood volume and the relationship between CVP/ $\Delta$ CVP following a fluid challenge. The difference in CVP at baseline in responders ( $8.7 \pm 2.32$  mmHg) versus non-responders ( $9.7 \pm 2.2$  mmHg) resulted not statistically significant ( $P=0.3$ ) (4).

### Pulmonary artery occlusion pressure

Pulmonary artery catheters (PACs) measure the PAOP which corresponds to the end-diastolic pressure of the left-ventricular (LVEDP) (1). PAOP could be subject to several valuables: compliance of myocardial tissue alternated (as in septic state or ischemia), pericarditis, increase of pulmonary vascular resistance, right ventricular overload, mitral stenosis and increased intrathoracic pressure due to mechanical ventilation (9). Moreover, to insert a PAC is an invasive operation with risk of arrhythmias, pulmonary infarction, catheter knotting, and rupture of the vessels and its routine use is not recommended in critically ill patients (1). In a study with 96 patients, Osman *et al.* evaluated the relationship between the evaluation of PAOP and patients “fluid responders”: responders had smaller values of PAOP before the infusion than non-responders ( $10 \pm 4$  vs.  $11 \pm 4$  mmHg,  $P=0.05$ ), but they noted a big overlapping of values in different persons. The area under ROC curve misurated was not statistically significant compared to that misurated for CVP: 0.63 (95% CI: 0.55–0.70); the difference between the two under the ROC curves areas was 0.053 (95% CI: 0.01–0.12;  $P=0.12$ ) (10). A study by Michard *et al.* measured PAOP before and after a fluid increase in the two categories of patients: responders and non-responders; they showed a not-significant evidence of measurement of PAOP in seven of nine studies (11).

### Global end-diastolic volume (GEDV)

GEDV and the derived global end-diastolic volume index (GEDI) estimate the blood volume of all the four cardiac chambers with the technique of transpulmonary thermodilution (TPTD). PiCCO<sup>®</sup> (Pulse Contour Cardiac Output) monitor or EV1000 monitor (Vigileo<sup>®</sup>) are employed to obtain these measurements. The monitoring-



**Figure 1** An M-mode image of the subcostal view of the inferior vena cava (IVC) showing changes in its diameter during the respiratory cycle (personal observation).



**Figure 2** An image of a transthoracic cardiac apical 4-chamber view of the left-ventricular end-diastolic area (LVEDA).

system PiCCO utilizes TPTD method through a central venous catheter (CVC) and a thermolulution-tipped arterial catheter; it can measure multiple variables: GEDV/GEDI is an evaluation of preload and of stroke volume because estimates the volume in the four heart-chambers, although the relationship between GEDV-measurement and patients fluid responders is lacking. Venous capacitance and heart chambers compliance are important to identify a change in preload, influenced by different GEDV values (11). Michard *et al.* reported a significant association with stroke volume index (SVI) ( $r=0.72$ ,  $P=0.001$ ) in 36 patients comparing GEDI with SVI before and after a fluid challenge; moreover,

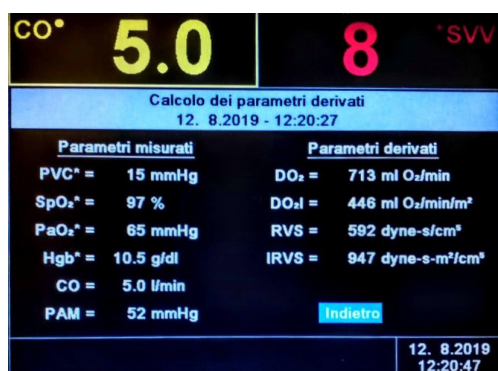
pre-infusion GEDI was smaller in patients fluid responders than in non-responders ( $637\pm134$  vs.  $781\pm161$  mL/m<sup>2</sup>,  $P=0.001$ ) (12). Endo *et al.* found GEDV to be unpredictable in prediction of fluid responsiveness on 93 mechanically ventilated patients (13). Due to the poor data and the heterogeneity of the results about GEDV/GEDI to predict fluid responsiveness, further research is needed.

### *Inferior vena cava diameter*

The diameter of the inferior vena cava (IVC) theoretically changes in relation to preload and its increase should correspond to an increment in preload and right atrial filling pressure. The IVC can be measured through ultrasound at a determined length from the right atrial cavity, during the expiratory time (Figure 1). Its accuracy is operator-dependent and needs image acquiring and analysis. Many components like obesity, lung hyperinflation pneumothorax, abdominal distention or elevated intra-abdominal pressure ( $>12$  mmHg) may cause unsatisfying sonographic windows. The diameter of the IVC is correlated with RAP (14,15). In a multicenter study, in 22% of patients was not possible to obtain the IVCd; in only 29% of the ICU-ventilated patients was possible to predict fluid responsiveness with a specificity of 80%. Even so, a value of end-expiratory IVCd less than 8 mm or more than 28 mm could predict patients fluid responders with a specificity of 95% (16).

### *Left ventricular end-diastolic area (LVEDA)*

LVEDA is estimate with transthoracic echocardiogram (apical 4-chamber view) or transesophageal echocardiography (TEE) (Figure 2) and should increase with fluid expansion in responding subjects. Feissel *et al.* considered LVEDA at end-expiration phase before and after fluid expansion in ICU ill patients with TEE. They found no convincing interaction ( $r^2=0.11$ ,  $P=0.17$ ) between LVEDA index measured at a standard time and the increment in cardiac index in response to fluid expansion (17). Tavernier *et al.* compared different hemodynamic variables and found that LVEDA had a lower area under the ROC curve compared to systolic pressure variation (SPV) (0.77, 95% CI: 0.59–0.92 vs. 0.94, 95% CI: 0.81–0.99) (3,18–21). Michard *et al.* analyzed twelve studies and showed that static indicators of cardiac preload (RAP, PAOP, RVEDV, LVEDA) in patients in ICU, before fluid infusion, were not significantly decreased in responders than in non-responders (11). Not even the CVP (4,10), as well the



**Figure 3** An image of the main hemodynamic parameters estimated by Vigileo® (Edwards Lifesciences®) (personal hemodynamic monitoring).

PAOP (10,22), LVEDA (23,24), the early/late diastolic wave ratio (24), or the B-type natriuretic peptide blood-concentration (25) can contradistinguish responsiveness to fluid therapy in patients because there are many curves that characterize the correlation between stroke volume and ventricular preload, cause of the contractile function of ventricles; moreover a confounding factor is the transmission to the cardiac chambers of the pleural compression.

### *E/e'*

LV diastolic dysfunction can be defined as an increase in myocardial stiffness or a reduction in the rate of relaxation of the heart muscle (26).

This condition can be assessed echocardiographically, with the tissue Doppler, through indices like  $e'$  and  $E/e'$ ; the  $e'$  wave provides information on the maximum speed of movement of the mitral annulus during the rapid ventricular filling phase; the  $E$  wave represents the maximum velocity of the rapid ventricular filling;  $E/e'$  is the ratio between these two values (27,28).

Values of  $e'$  less than  $7 \text{ cm}\cdot\text{s}^{-1}$  for septal and less than  $10 \text{ cm}\cdot\text{s}^{-1}$  for lateral tissue velocity, are considered abnormal. The values of the ratio  $E/e'$  correlate with the LAP (left atrial pressure) and with the capillary Wedge pressure, values below 8 indicate a non-elevated LAP, values above 14 indicate an increase in the filling pressures of the left heart chambers (29).

The alteration of the correct release of LV can lead critically ill patients to heart failure, pulmonary edema and difficulty in weaning from the mechanical ventilator (30). During circulatory failure, fluid administration is often used to increase stroke volume; if we assume that this volume of

liquids, we infuse is able to correct (at least partially) the LVDD, the variables of  $e'$  and  $E/e'$  seems useful and reliable for testing this hypothesis (31-33).

In the study of Mahjoub *et al.* it has been shown that the administration of liquids (500 mL of saline solution) causes an increase in the values of  $e'$  higher in the patients considered responders (SV increased more than 15%) on the other hand the value of  $E/e'$  had increased more markedly in the group of non-responders (34,35).

$E/e'$  ratio proved to be a good predictive value of LV filling pressures in the patient with septic shock. (11). Sanfilippo *et al* found a significant correlation between mortality in critically ill patients and low levels of  $e'$  and high values of  $E/e'$  patients.

The assessment of LVDD in critically ill patients remains difficult and the evaluation of  $E$  and  $E/e'$  is probably the most used tool because it is easy to perform at patients' bedside (36).

### *Dynamic measures of preload responsiveness*

The interactions between heart and lungs are the starting point for almost all tests and dynamic measurements that can be performed in patients subjected to mechanical ventilation. During the respiratory cycle many changes in pressure and load occur in the heart chambers (37). In the inspiratory phase, there is a decrease in preloading of the right atrium due to the transmission of intrathoracic pressure, which increases at this time in the cycle (1,38). Fluid responsiveness has a higher incidence in patients with more pronounced responses in decreasing preload. Patients with higher stroke volume modifications during a respiratory cycle in mechanical ventilation can be more easily preload responsive (37,39).

### **Stroke volume variation**

The first method to be developed for the dynamic valuation of preload responsiveness is the stroke volume variation (SVV) (Figure 3). This parameter goes up during inhalation and goes down during exhalation due to changes in intrathoracic pressure caused by positive pressure ventilation. The rationale can be that, during positive pressure ventilation, insufflation decreases preload of the right ventricle. When end positive pressure is transmitted to the left side, it causes a decrease in preload of the left ventricle (40). If left ventricular stroke volume changes in response to cyclic positive pressure ventilation, this indicates that both ventricles are preload dependent. A larger SVV



variation suggests that the patient will be fluid responsive. Traditionally, the threshold for fluid responsiveness is SVV >13% (1,41-45). Zhang *et al.* showed in their meta-analysis that SVV can predict fluid responsiveness with a diagnostic odds ratio of 18.4 at a sensitivity of 0.81 and specificity of 0.80. One of the main limits of the study is that it has proved to be reliable only in mechanically ventilated patients (1,46). The SVV may not be completely reliable in patients who breathe spontaneously, especially those with respiratory distress, consider the irregularities in the variations of the intrathoracic pressures. Another limit to consider is the need to set the ventilation parameters with a tidal of at least 8–10 mL per kilo. The predictive power of SVV decreases with minor tidal settings (1,47,48) and also in patients with cardiac arrhythmias (1,42,44,49,50).

### Pulse pressure variation (PPV)

The definition of this parameter is given by the differences in pulse pressure during the respiratory phases. We can obtain this parameter by placing a catheter in an arterial vessel and observing the variation of the waveform and calculating the blood pressure modifications during the phases of systole and diastole (1). Patients with septic shock and subjected to mechanical ventilation were studied by Michard *et al.*, their work showed that PPV can predict fluid responsiveness with a threshold of 13% (37,51-53). There are some limitations, this parameter is not reliable in patients with open chest, in those who breathe spontaneously, low tidal volume or high-frequency ventilation, cardiac arrhythmias, intra-abdominal hypertension and in patients with low lung compliance (37,54,55). regarding the latter limitation the cut-of seems to be a compliance less than 30 mL/cmH<sub>2</sub>O, in this case the value of PPV in predicting fluid responsiveness is intensely decreased (1,55). These limitations come into play for intermediate values of PPV (greater than 9% and less than 13%) there are still few reliable data (1,56). A step forward was made by Yang *et al.* who recently proposed a meta-analysis that included patients with tidal volume of less than 8 ml per kilo with interesting results, PPV values have been shown to possess a sensitivity of 0.88 (95% CI: 0.81–0.92), a specificity of 0.89 (95% CI: 0.84–0.92), and AUROC of 0.94 (95% CI: 0.91–0.95) (1,53). Another work regarding this field is the one by Myatra *et al.*, the patients considered had a very low tidal value (6 mL/kg), they put into effect a protocol in which the tidal was increased from 6 to 8 mL per kilo for one minute and the value of

PPV was annotated, significant increases of 3.5% were considered (37,41).

### Systolic pressure variation (SPV)

In both patients who breathe spontaneously and in those subjected to mechanical ventilation, there are physiological fluctuations in systolic blood pressure (1,50). In order to use this parameter, we must define a starting point of the pressure value, generally established after 7–12 seconds after an end expiratory pause. From this baseline the pressure can increase or decrease during the respiratory cycle, the delta Up (dUp) and delta-Down (dDown) values are thus recorded (1,18). The SVP is therefore defined as the difference between the highest and lowest values of the systolic pressure. Many studies observed that dDown can be a reliable predictor of fluid responsiveness (1,18,57). Tavernier *et al.* showed that a value of dDown >5 mmHg can have a positive prediction value of 95% and a negative prediction value of 93% (1,57). The limits of this method are that it is reliable only in mechanical ventilated patients without cardiac arrhythmias, on the other hand it is an inexpensive method (1).

### Aortic velocity time integral (VTI)

This parameter is an echocardiographically obtained measure of the area under the velocimetric curve within the left ventricular outflow tract, or rather the distance travelled by the column of blood cells through the aforementioned tract during ventricular systole, which therefore allows to have a stroke volume measurement. The measurement is performed with transthoracic echocardiography, with 5-chamber apical projection and use of pulsed Doppler, normal values in adult patients at rest are between 18 and 22 cm, lower values are an index of reduced CO. In order to avoid interference related to the respiratory dynamics, it is preferred to carry out this measurement at the end of the exhalation, in this way also the patient's preload status should not significantly interfere (58).

According to various studies in patients in sinus rhythm it is sufficient to perform an average of three measurements while it seems necessary to make at least five measurements in patients with atrial fibrillation (59), an increase in VTI greater than or equal to 15% is considered a positive response to the filling. This parameter seems to be particularly reliable when performed by the same operator (23,24,60-63).

This value is considered equally reliable if the increase is greater than 10% as regards passive leg raising and

mini fluid challenge (100 mL) (24,62,64). This measure is considered fast and easy to obtain and in accordance with numerous studies it is considered accurate and sensitive in predicting fluid responsiveness (65-70).

### Caval index

The ultrasound study of inferior vena cava diameters (IVC) is now considered among the basic examinations in intensive care. One of the possible evaluations we can obtain is the CI, which represents the percentage of the change in vessel diameters during a respiratory cycle (1). These parameters are normally measured with transthoracic echocardiography, the vessel can be studied in a long-axis subcostal longitudinal view in M-mode, about 2 cm apart from right atrium junction and upstream to supra-hepatic vein (37,71,72). Fluid responsiveness can be considered when the CI reaches 12–18% variation in patients subjected to mechanical ventilation and 50% in patients with spontaneous breathing (1,23,72,73). This parameter as others already described previously (PPV and SVV) has some limits in its application due to the complexity of the systems it examines: heart-lung interactions (37,74). The most important limitations are patients not fully adapted to mechanical ventilation and those with increased intra-abdominal pressure, on the other hand this parameter is reliable in patients with cardiac arrhythmias (37).

### Carotid Doppler measurements

The ultrasonographic study of the Doppler pulsed wave can be used to obtain two parameters: the carotid flow time (FTc) and the velocity time integral (VTI). These parameters come from similar studies performed on the aorta with the use of the transesophageal Doppler techniques (3,64,75) but they are easier to achieve and therefore more used. Velocity time integral (VTI) measured the blood flow through the carotid artery during systole. If we multiplied this parameter for the cross-sectional area of the carotid artery, this value assesses the fraction of the stroke volume received by this vessel. FTc measures the amount of time spent in systole per cardiac cycle. A study by Marik *et al.* showed the correlation between two parameters: the SVV and the VTI changes, following the execution of the passive leg raise test with interesting results ( $r=0.59$ ,  $P=0.0003$ ) with a sensitivity of 94% and specificity of 86% (1,76). Jalil *et al.* compared the response to PLR test in both FTc and SVV changes and they observed a prediction in fluid responsiveness with

AUROC of 0.75 with a sensitivity of 60% and specificity of 92% (77,78). These parameters can therefore be used as substitutes to SVV or cardiac output when this is impossible to perform due to the lack of suitable equipment and high costs of this technique.

### End tidal CO<sub>2</sub> variation

The end-tidal carbon dioxide (ETCO<sub>2</sub>) is a measure of the partial pressure of CO<sub>2</sub> at the end of expiration and can be measured with a capnograph. The values of this parameter are determined by changes in cardiac output, therefore, it can be used as its indirect and non-invasive measure. The different values of ETCO<sub>2</sub> registered previously and after a bolus of crystalloid or a simulated volume loading, is termed  $\Delta$ ETCO<sub>2</sub> (1). Toupin *et al.* in their study they compare two parameters: ETCO<sub>2</sub> and cardiac output obtained with the thermodilution technique, before, during and after having performed the passive leg raise test (PLR) (1,78). Patients were considered as fluid responders when an increase in ETCO<sub>2</sub>  $\geq 2$  mmHg values was observed during the test with an odds ratio 7.3; 95% CI: 2.7–20.2;  $P<0.01$ ; sensitivity 75%) and a negative predictive value of 86%.

A recent work Monnet *et al.* confront the values of ETCO<sub>2</sub> and the cardiac index obtained with the PiCCO device, the test was performed on 40 mechanically ventilated patients who underwent PLR tests (1,79). In their publication a 5% increase in ETCO<sub>2</sub> was associated with an increase in cardiac index of 15% after volume loading with a sensitivity of 71% (95% CI: 48–89%) and specificity of 100% (95% CI: 82–100%). This test therefore seems promising and easy to perform on patients in intensive care units and in the operating rooms (1).

### Passive leg raising test (PLR)

Traditionally, passive lifting of the lower limbs has been a first aid maneuver practiced in patients with hypotension and/or cardiovascular shock. This maneuver causes a blood movement from the lower part of the body to thoracic area due to gravitational force, that increases the preload of cardiac chambers (80). It represents a preload test which consists in about 300 mL of blood (81), repeatable and it does not require infusion of fluids or colloids. Numerous studies have analyzed and confirmed the reliability of this maneuver and several meta-analyses have been published (82,83). Monnet *et al.* (83) reported through a meta-analysis in almost 1,000 adult patients and 21 studies included a

pooled sensitivity of 85% and pooled sensibility of 91% of PLR test; the best sensitivity and specificity was found when the maneuver increased cardiac output above an average threshold of 10%. The great reliability of PLR test has allowed its inclusion in the Surviving Sepsis Campaign recommendation (84) and in the European Society of Intensive Care Medicine consensus conference (85). As recently reviewed (86), several aspects about the technique of performing the PLR must be analyzed. The reliability of PLR test cannot be based only in changes of arterial blood pressure and although a very good specificity, the sensitivity remains poor (82,83). Therefore, direct, continuously and real-time measurement of cardiac output is needed. The use of thermodilution in measuring cardiac output may not be sufficient because it is not done continuously. One of the characteristics of the studies in this field is that they have used non-invasive methods to establish the response to the PRL test (82,83). Among the first techniques used we find the esophageal Doppler, which studied changes in the aorta blood flow after the test was performed (87). Recently among the techniques best described in the studies, we find the velocity time integral of the left ventricular outflow tract obtained with echocardiography e measured before and after the PLR test. The modification of cardiac output in response to this test was also evaluated using peak velocity of carotid (76) and femoral (88) arteries and they seem to be good indicators. The argument that still has a conflict of results is bioreactance (76,89). In the ICU and operating rooms, non-invasive techniques such as pulse contour analysis of the arterial curve analyzed with photoplethysmography are in great demand, although for now the evidence on the reliability of this parameter during the test is weak. Another interesting non-invasive method to measure the response to PRL is the measurement of  $\text{ETCO}_2$  (90) variations. However, this method requires stable mechanical ventilation free from artifacts induced by the patient's trigger. Passive lifting of the legs can be considered a safe test for preloading as the effects are completely reversible after the lower limbs return to the supine position (87,91), preventing the risk of overloading fluid and pulmonary edema. Moreover, this technique can mobilize not just the blood of lower limbs, but also blood of splanchnic district, increasing the sensitivity of the test but on the other hand the risk of false negative (92). The main advantages of this maneuver are the possibility of applying it to most critically ill patients, even in spontaneous breathing, low tidal volume, low lung compliance and with arrhythmias (55). However, there are some important

limitations. The maneuver is not applicable in the absence of motorized beds capable of lifting the legs, in traumatized patients, in those with prone position and in patients in the operating room.

### Fluid challenge

The fluid challenge is represented by the administration of an endovenous bolus of fluids (crystalloids or colloids) in a small and predetermined time interval for the purpose of measuring the subsequent hemodynamic response to its administration (93,94). The hemodynamic response to the fluid challenge cannot be reliably measured by monitoring only systemic arterial pressure (95,96) and 22% of false negative has been reported using this method alone (95). Therefore, it is now recommended to assess cardiac output and estimate the stroke volume instead of assessing the fluid-induced changes in central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) (97). End-tidal carbon dioxide ( $\text{ETCO}_2$ ) is an alternative and non-invasive surrogate of cardiac output (98), maximal change in cardiac output should be assessed about 1 minute after ending fluid infusion (99). Since its administration is irreversible, classical fluid challenge can bring to fluid overload, particularly if repeated several times a day. To avoid this problem, a "mini" fluid challenge has been proposed for the first time by Muller *et al.* (48) giving 100 mL of colloid over 1 minute. The cardiac output was assessed measuring the outflow tract velocity time integral of left ventricle (measured with echocardiography), before and following the colloid administration. An increase with a threshold above 10% was more like to predict fluid responsiveness with good accuracy. In mechanically ventilated patients without arrhythmias, this method has great accuracy (area under the ROC curve =0.92, 95% CI: 0.78–0.98,  $r=0.81$ ,  $P=0.0001$ ). Other studies used pulse contour-analysis derived cardiac output (100), or changes in SVV (101) to reliably predict fluid responsiveness.

Other authors try to determine how small the bolus of fluids must be to guarantee a reliable fluid challenge by investigating the effects of different doses of intravenous fluids on changes in cardiac output, measured by pulse contour analysis and mean circulating filling pressure. Kim *et al.* (102) state that a bolus of 4 mL/kg over 5 min was the smallest volume that could reliably increase the mean circulating filling pressure and make fluid challenge interpretable in every circumstance. In conclusion, it can be stated that main limitation of a mini fluid challenge is that

the small volume of fluid determines very small variations in cardiac output that require a very precise measurement technique.

### End-expiratory occlusion test

The end-expiratory occlusion (EEO) test was developed by Monnet *et al.* and is performed interrupting mechanical ventilation for 15 seconds at the end of expiration and observing changes in the cardiac output. An increase in arterial pulse pressure or in pulse contour-derived cardiac index by more than 5% make this test positive and predicts a hemodynamic response to a fluid challenge with good accuracy (103). These findings have been confirmed also with a 30-seconds EEO test (104). The premise is that when EEO is performed, the cyclic impediment in venous return caused by each insufflation is interrupted and a duration of interruption of at least 15 seconds is sufficient to the bring the resulting increase in right ventricular stroke volume to cross the pulmonary circulation and increase also the left cardiac preload. The main advantages of this test are the ease of execution and the possibility to be performed in patients with acute respiratory distress syndrome (ARDS), a situation in which PPV and SVV are not reliable because a “lung-protective” ventilation with low tidal-volume and low lung compliance is applied (55,105). Silva *et al.* stated that predictive accuracy of the test is not altered in patients with ARDS and a level of positive end-expiratory pressure (PEEP) varying from 5 to 15 cmH<sub>2</sub>O (106). However, EOC test cannot be used in patients with spontaneous breathing on the ventilator that do not allow an expiratory pause of 15 seconds and, obviously, in patients who are not intubated. Furthermore, due to the short duration of the maneuver it is always necessary to have a precise and accurate monitoring of the hemodynamic response in real-time enough to detect a 5% change in the cardiac output. Jozwiak *et al.* stated that the end-expiratory occlusion test could be used with non-invasive techniques as the echocardiography, showing that changes in velocity-time integral (VTI) measured by echocardiography allow the EEO test to be monitored reliably (107). The diagnostic threshold was an increase VTI of 4%, however the precision of echocardiography was insufficient. For this reason, they added a 15-seconds end-inspiratory occlusion (EIO) which lowered cardiac output more in preload-dependent patients and predicted fluid responsiveness with a reliability similar to the EEO, with a greater diagnostic threshold of 15% (107).

### Conclusions

Considering the Frank–Starling curve, the response to volume infusion is better when the cardiac preload is low than when it is high, however numerous studies have demonstrated that none of the static measures of cardiac preload is able to predict fluid responsiveness accurately. Although static markers of preload cannot be used to predict fluid responsiveness, they can be used to confirm that the fluid administered has actually filled the heart chambers, as well as to monitor fluid administration in order to decide the goal-directed therapy algorithms. Furthermore, they are good markers of cardiac function and structure and determinants of the pressure gradient organ perfusion. Although static measures are important for historical reasons and are widely used in clinical practice studies show that dynamic measures represent progress in the care of critically ill patients. Regarding dynamic measures and maneuvers, they are in general more reliable in predicting fluid responsiveness, but often they can be applied on selected groups of patients for example those subjected to mechanical ventilation with high tidal, they are more difficult to apply and interpret in patients with spontaneous breathing. Among the various tests examined, the PLR seems the most promising since it is applicable in a wider variety of patients, it is easy to perform and has fewer execution risks.

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### Footnote

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