Assessment of Fluid Responsiveness in Spontaneously Breathing Patients

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■ Introduction

Assessment of volume responsiveness is an important issue in patients with spontaneous breathing activity. The difficulty in predicting the response to fluid infusion in this population of patients is variable and depends on the clinical situation. Three different scenarios must be distinguished:

- The first scenario refers to patients admitted to the emergency room for evident acute blood losses or body fluid losses. The diagnosis of hypovolemia is almost certain and the presence of clinical signs of hemodynamic instability (hypotension, tachycardia, oliguria, mottled skin, altered mental status, etc) strongly suggests that a positive hemodynamic response to volume resuscitation will occur, although these signs lack sensitivity. The degree of hypotension, of tachycardia, and of oliguria is important for estimating the degree of hypovolemia and hence the degree of urgency for initiating volume resuscitation.
- The second scenario refers to patients admitted to the emergency room with a high degree of suspicion of septic shock. In this situation, cardiac preload is always inadequate since relative as well as absolute hypovolemia are always present in the early phase of septic shock. The study by Rivers et al. [1] emphasized the importance of volume resuscitation in the first hours of management in this category of patients. There is no need to search for sophisticated parameters to predict volume responsiveness since a positive hemodynamic response is always present at this stage. Rather, there is a need to define parameters that can indicate whether volume infusion should be either continued or stopped because of no further expected efficacy (see the third scenario). There is also a need to define indicators of lung intolerance; however, this is not the subject of the present chapter.
- The third scenario refers to patients hospitalized in the intensive care unit (ICU) who experience hemodynamic instability that requires urgent therapy. In these patients, volume responsiveness is not guaranteed since they have already been volume resuscitated and continuation of volume infusion carries risks of pulmonary edema. In spontaneously breathing patients either without an endotracheal tube or making inspiratory efforts while receiving mechanical ventilation, prediction of volume responsiveness can be a difficult challenge. In these conditions, indices of volume responsiveness that use heart-lung interaction, such as respiratory variations in arterial pressure or in stroke volume and derived indices, are no longer reliable.

■ Static Markers of Cardiac Preload as Predictors of Volume Responsiveness

From the Frank-Starling relationship (ventricular preload vs stroke volume), the response to volume infusion is more likely to occur when the ventricular preload is low than when it is high. Hence, markers of ventricular preload have been suggested for predicting volume responsiveness. This issue has been extensively discussed in a recent review article by Coudray et al. [2]. Therefore, in the present chapter, we will only give a summary of the main parameters.

Cardiac Filling Pressures

Historically, ventricular filling pressures, namely central venous pressure (CVP) or right atrial pressure (RAP) for the right ventricle, and pulmonary artery occlusion pressure (PAOP) for the left ventricle, have been first proposed as parameters to guide volume resuscitation.

Central venous pressure and right atrial pressure

These two parameters are assumed to reflect the right ventricular (RV) filling pressure. A few studies have addressed the question of whether CVP or RAP can predict volume responsiveness in critically ill patients [3, 4]. In most of these studies, a limited number of patients with spontaneous breathing activity were included. In two studies [5, 6], RAP was lower before volume infusion in patients who responded to fluid infusion (in terms of an increase in cardiac output) than in non-responders. However, a small percentage of patients were studied while breathing spontaneously (6% and 33%, respectively). In addition, the study by Wagner and Leatherman [6], reported a weak correlation between pre-infusion RAP and changes in stroke volume induced by fluid infusion. For example, a fluid-induced increase in stroke volume by 25% was observed for a pre-infusion RAP value of 2 mmHg as well as for a value of 13 mmHg [6]. Conversely, a RAP value of 11 mmHg was associated with a fluid-induced increase in stroke volume ranging from 10 to 45% [6]. In other studies including patients with spontaneous breathing activity, there was no relationship between the initial RAP and the response to volume infusion [7–11]. All these studies, therefore, suggest that RAP is a poor predictor of volume responsiveness for the general population of critically ill patients including those who exhibit spontaneous breathing activity, although the total number of patients included in the available studies is quite low.

Pulmonary artery occlusion pressure

The PAOP is the pressure obtained after inflating the distal balloon of a pulmonary artery catheter in a large branch of the pulmonary artery. Since a static column is created between the inflated balloon and the venous site where the blood flow resumes, PAOP is assumed to reflect the pressure in a large pulmonary vein and, thus, the left atrial pressure and eventually the left ventricular (LV) end diastolic pressure (LVEDP) [12]. Obtaining a meaningful measurement can be a difficult challenge in dyspneic patients who experience large swings in intrathoracic pressure. In order to limit the influence of the intrathoracic pressure on PAOP measurements, it is recommended that PAOP be measured at the end-expiratory period. However, in patients receiving mechanical ventilation who exhibit inspiratory efforts, the end-expiratory period is not always easy to identify [13].

Provided that reliable measurements are obtained, PAOP is considered as a measure of LV preload, although preload is assumed to fit better with end-diastolic volume than with end-diastolic pressure of the ventricle [12]. A few studies have addressed the question of whether PAOP can predict volume responsiveness in critically ill patients [3, 4]. Six studies, in which 16% [14], 24% [8], 33% [5], 36% [9], 54% [7], and 57% [10] of the patients were breathing spontaneously, showed no relationship between the pre-infusion PAOP and the hemodynamic response to fluid. In one study, in which just 6% the patients were breathing spontaneously, the pre-infusion PAOP value was lower in responders but a weak correlation was found between PAOP and the increase in stroke volume induced by volume infusion ($r^2=0.33$); no cut-off value was found to discriminate responders from non-responders [6]. Finally, in one study, the pre-infusion PAOP value was surprisingly higher in the patients who subsequently responded to fluid infusion [15]. No clear explanation was given by the authors of this study, which included only four patients who were breathing spontaneously [15].

In summary, there is no evidence that the pre-infusion PAOP can predict volume responsiveness in critically ill patients, although the total number of patients with spontaneous breathing activity included in the available studies is less than 80.

End-diastolic Ventricular Dimensions

Since ventricular end-diastolic dimensions are considered as better indicators of cardiac preload than filling pressures, measurements of ventricular dimensions have also been proposed for predicting fluid responsiveness.

Right ventricular end-diastolic volume

The RV end-diastolic volume (RVEDV) can be evaluated at the bedside by fast response pulmonary artery catheters. In two studies, in which 16% [14] and 31% [15] of patients were breathing spontaneously, Diebel et al. reported lower values of RVEDV index (RVEDVI) in responder than in non-responder patients and suggested that a beneficial hemodynamic effect of volume expansion was likely when the RVEDVI was below 90 ml/m² and very unlikely when the RVEDVI was greater than 138 ml/m². However, when the RVEDVI ranged between 90 and 138 ml/m², which is probably the most frequent occurrence in critically ill patients who are already resuscitated, no cut-off value could be proposed to discriminate responder and non-responder patients [14, 15]. In two other studies, in which 6% and 24% of patients were breathing spontaneously, no significant difference was observed between responders and non-responders with respect to the baseline value of the RVEDVI [6, 8].

In two older studies, including 54% [7] and 33% [5] of patients breathing spontaneously, RVEDV was calculated after assessing the RV ejection fraction (RVEF) using cardiac scintigraphy and after measuring cardiac output using thermodilution. In these studies, no significant difference was observed between responders and non-responders with respect to the pre-infusion value of RVEDV [5, 7].

Left ventricular end-diastolic dimensions

Cardiac scintigraphy and echocardiography are used to estimate LV end-diastolic volume (LVEDV) and LV end-diastolic area (LVEDA). Two old studies including patients with spontaneous breathing indicated that LVEDV was of poor value for predicting volume responsiveness [5, 7]. To our knowledge, no study has examined

the significance of LVEDV or LVEDA obtained with echocardiography in patients who breathe spontaneously. It should be remembered that in deeply sedated patients receiving mechanical ventilation, the LVEDA was reported to be unreliable for assessing volume responsiveness [16–19].

Global end-diastolic volume

The global end-diastolic volume (GEDV) is obtained by the transpulmonary thermodilution method (PiCCO monitoring system). Regarding the prediction of volume responsiveness, no study using this parameter has been performed in patients breathing spontaneously. It must be remembered that in patients receiving mechanical ventilation, the GEDV was lower in volume responders than in non-responders and that the lower the pre-infusion GEDV, the more likely the positive hemodynamic response [20]. However, GEDV values in responders and non-responders overlapped and no cut-off value could identify responders and non-responders with high sensitivity and specificity values [20].

Why do Static Markers of Preload Fail to Predict Volume Responsiveness?

Markers of preload are not always accurate measures of cardiac preload

This is particularly the case in the following situations:

- In the presence of mitral stenosis or mitral insufficiency, PAOP can be higher than the LVEDP. The value measured just before the 'v' wave upslope must be taken as an estimate of LVEDP in the case of mitral insufficiency.
- In the presence of intrinsic positive end-expiratory pressure (PEEP), PAOP differs from LV filling pressure, even when the measurement is made during the end-expiratory period [21].
- Even when PAOP reflects the LV filling pressure, it can still be a poor marker of LV preload in the case of reduced LV compliance where achieving high filling pressures can be necessary to maintain optimal levels of LV preload [22].
- In the presence of tricuspid regurgitation, thermodilution RVEDV measurements can be erroneous [23].

Assessment of preload is not assessment of preload responsiveness

More generally, there is a physiological reason explaining why even the most accurate static marker of preload will never be a reliable predictor of preload-responsiveness. Indeed, the slope of the Frank-Starling curve depends on the systolic cardiac function. In this regard, a given value of preload can be associated with preload-dependence and hence with volume responsiveness in normal conditions (steep part of the Frank-Starling curve) or with preload-independence and hence with absence of volume responsiveness in the case of decreased cardiac contractility (flat part of the Frank-Starling curve).

Summary

Static markers of preload like CVP, RAP, PAOP, RVEDV, LVEDV, and GEDV are not accurate predictors of volume responsiveness in spontaneously breathing patients as they are in patients receiving mechanical ventilation without exhibiting inspiratory efforts [3, 4, 24]. Importantly, even if an accurate static measure of preload were available, it would not be possible to use it to reliably predict volume responsiveness. However, the following important points should be stressed: First, the available clini-

cal studies that have addressed the issue of volume responsiveness are scarce and did not include a lot of patients with spontaneous breathing activity. In addition, the specific behavior of those patients was not distinguished from the behavior of patients without spontaneous breathing activity. Therefore, the results of these studies must be interpreted with caution. Second, in the available studies, patient selection for fluid challenge and the method used to perform the fluid challenges (volume and type of fluid, duration of the trial, definition of fluid response) were quite heterogeneous. Third, in addition, in these studies, almost all the patients were studied after they had already been resuscitated, such that the values of preload markers were rarely low before the volume challenge was done. Thus, one cannot exclude that low values of CVP and/or PAOP and/or other markers of cardiac preload, potentially measured in non-resuscitated shocked patients, may still be associated with a positive hemodynamic response to volume loading. For example, in the study by Michard et al. [20] (in patients receiving mechanical ventilation), the rate of positive response to fluid was markedly higher (77%) in the subgroup of patients with low GEDV index values ($<610 \text{ ml/m}^2$) compared to the subgroup of patients with intermediate GEDV index values (between 610 and 815 ml/m^2) and the subgroup of patients with high GEDV index values ($>815 \text{ ml/m}^2$) (rates of response: 43% and 23%, respectively). Interestingly, the four patients with a GEDV index $<500 \text{ ml/m}^2$ responded to volume loading while all five patients with a GEDV index $>950 \text{ ml/m}^2$ did not respond to volume loading [20]. Similar findings with RAP as a static measure of preload have been recently reported by Heenen et al. [10]. On the other hand, in the available studies, volume challenges were rarely done in patients with high values of CVP and/or PAOP at baseline, mainly for ethical reasons. Thus, one cannot exclude that high values of markers of preload are associated with the absence of a hemodynamic response to volume loading. For example, in the study by Michard et al. [20], the percentage of positive response to fluid was very low in the subgroup of patients with high GEDV index values ($>850 \text{ ml/m}^2$). Similarly, in the study by Heenen et al., high values of pre-infusion RAP were associated with a low rate of positive response to volume administration [10]. Although the markers of preload do not appear to be good predictors of volume responsiveness, most available studies have shown that these markers did increase after volume challenge in responders as well as in non-responders. This finding suggests that these static indexes are valuable tools to confirm that the volume infused actually reaches the cardiac chambers, and, therefore, that these indexes do inform about changes in cardiac preload [2].

■ Dynamic Parameters

Arterial Pressure and Stroke Volume Respiratory Variation

Numerous studies have demonstrated that dynamic indexes, such as respiratory variation in arterial pressure and in stroke volume, are valuable for predicting volume responsiveness in patients receiving mechanical ventilation, provided that they do not experience any active breathing efforts and/or cardiac arrhythmias and that they do not receive too low a tidal volume [3, 4]. Therefore, the findings of these studies cannot be extrapolated to patients receiving mechanical ventilation while exhibiting inspiratory efforts or to patients who breathe spontaneously without any mechanical support. To our knowledge, only three studies have investigated whether or not arterial pulse pressure variation (PPV) was predictive of volume responsiveness in such

groups of patients. In a study by Monnet et al, a $PPV \geq 12\%$ predicted volume responsiveness with a sensitivity of 88% and a specificity of 93% in the subgroup of deeply sedated patients receiving mechanical ventilation [25]. By contrast, PPV had no predictive value in the subgroup of patients with ventilator triggering [25]. This latter important conclusion has been recently confirmed in the study by Heenen et al. [10]. In a study that included non-intubated patients, a PPV value $>12\%$ was shown to reliably predict a beneficial response to volume infusion in the case of quiet spontaneous breathing [11]. However, that study also showed that PPV was not valuable for predicting volume responsiveness when its baseline value was less than 12% and/or when patients were dyspneic [11].

Inspiratory Decrease in Right Atrial Pressure

During a normal spontaneous inspiration, the intrathoracic pressure decreases and this will eventually result in a decrease in RAP relative to the extrathoracic vessel compartment and, thus, in an increased venous return to the left atrium and an increased RV stroke volume if the right ventricle is preload-dependent. As a result, an increase in LV stroke volume will be expected with a time delay of a few heart beats, provided that the left ventricle is also preload-dependent. Magder et al. [9, 26] hypothesized that when the right ventricle is preload-independent, not only will the right and subsequently the left stroke volume not increase with volume loading, but the RAP will also not decrease during normal inspiration. In their first study, the authors included a heterogeneous population of patients: 36% of them experienced total spontaneous breathing and 64% of them received mechanical ventilation but were able to breathe spontaneously after disconnection from the ventilator [9]. The decrease in RAP was measured during a spontaneous inspiration (after a short disconnection from the ventilator in those receiving mechanical ventilation). An inspiratory decrease in RAP (ΔRAP) of at least 1 mmHg was predictive of a positive response to volume loading with positive predictive values of 77% [26] and 84% [9] and negative values of 81% [26] and 93% [9].

To our knowledge, this index is not widely used in clinical practice. One of the major problems that limits its use is that the patient must generate a sufficiently deep decrease in intrathoracic pressure for a correct interpretation. In the two studies by Magder et al., this was ensured by a decrease in PAOP by at least 2 mmHg during inspiration after postulating that the decrease in PAOP reliably reflects the decrease in intrathoracic pressure [9, 26]. Therefore, the use of ΔRAP requires the insertion of a pulmonary artery catheter, which obviously represents a true limitation.

Contrary to the results of Magder et al. [9, 26], Heenen et al. reported that ΔRAP was not predictive of volume responsiveness in patients with spontaneous breathing activity with or without mechanical support [10]. However, this issue is still a matter of debate [27].

■ Passive Leg Raising

Description and Interpretation

Passive leg raising is a maneuver that transiently and reversibly increases venous return by shifting venous blood from the legs to the intrathoracic compartment [28, 29]. Passive leg raising (45° elevation) results in an increase in right [30] and left

[31] ventricular preload. Passive leg raising can, therefore, mimic the effects of fluid loading and has been proposed for a long time as a first line therapy of hypovolemic shock ('autotransfusion' effect). The way in which passive leg raising alters preload is probably by an increase in the mean systemic pressure, the driving force for venous return, due to the gravitational shift of venous blood from unstressed to stressed volume. This mechanism is probably of major importance during passive leg raising in patients receiving mechanical ventilation because the volume of blood enclosed by the thoracic and splanchnic beds is already stressed by positive airway pressure and these vascular compartments are less compliant than when mechanical ventilation is not used [32]. In these conditions, the increase in mean systemic pressure with passive leg raising is expected to be higher in mechanically ventilated patients than in non-mechanically ventilated patients. However, the effects of passive leg raising on cardiac output are variable [30, 33–35], probably depending on the degree of leg elevation and on the existence of cardiac preload reserve. In this regard, Boulain et al. [36] reported, in deeply sedated patients receiving mechanical ventilation, that the increase in stroke volume induced by passive leg raising occurred only in patients who increased their stroke volume in response to a subsequent 300 ml volume infusion. In patients who did not respond to volume loading, passive leg raising did not change stroke volume despite increases in RAP and PAOP. Thus, passive leg raising, which was able to increase cardiac preload in all the studied patients, increased stroke volume only in those with cardiac preload-dependence. Hence, passive leg raising can be proposed as a test to detect fluid responsiveness in critically patients. It is interesting to note that in the above-mentioned clinical study, the changes in PAOP induced by passive leg raising were immediately and fully reversible when the patients' legs were laid down [36]. This finding suggests that passive leg raising may help in predicting individual fluid responsiveness while avoiding the hazards of unnecessary fluid loading. Since it does not require any analysis of respiratory changes in stroke volume or its surrogates, passive leg raising is potentially usable in patients experiencing spontaneous breathing activity or arrhythmias.

Clinical Use

Changes in arterial pulse pressure

Theoretically, the best marker of the hemodynamic response to passive leg raising as a predictor of the hemodynamic response to fluid loading would be a significant increase in stroke volume. Because arterial pulse pressure is directly proportional to LV stroke volume and assuming that arterial compliance is not altered by passive leg raising, an increase in pulse pressure during passive leg raising should indicate an increase in stroke volume and thus a positive response to fluid infusion. However, in a study by Boulain et al. [36], the correlation between passive leg raising-induced changes in radial pulse pressure and fluid loading-induced changes in stroke volume was only fair. This observation was likely because changes in radial pulse pressure may not reflect changes in aortic pulse pressure owing to the potential occurrence of complex changes in pressure wave propagation and reflection during change in blood flow induced by passive leg raising. In addition, a given change in stroke volume in different patients with different aortic compliance may be reflected by different changes in aortic pulse pressure.

Changes in 'pulse contour' cardiac output

A more direct measurement of stroke volume during passive leg raising should be more relevant to detect volume responsiveness. Because of the short period of this test (less than 1 minute), the thermodilution method is not appropriate even in its automatic and semi-continuous mode. Indeed, this method takes at least 10 minutes to completely detect a given change in cardiac output [37]. A beat-to-beat basis for measuring stroke volume should be a better approach for tracking rapid changes of stroke volume induced by passive leg raising. Technologies using pulse contour analysis – like the PiCCO system – would be appropriate for that purpose. To our knowledge, no study has yet been published on the effects of passive leg raising on PiCCO stroke volume for the prediction of fluid responsiveness. In a preliminary study performed in patients with spontaneous breathing activity and/or arrhythmias, the increase in pulse contour cardiac index induced by passive leg raising correlated nicely with the increase in pulse contour cardiac index induced by subsequent volume loading ($r=0.62$, $p<0.05$) while the passive leg raising-induced increase in pulse pressure correlated only weakly with the fluid-induced increase in pulse pressure ($r=0.40$ $p=0.03$) [38]. An increase in cardiac index $>12\%$ during passive leg raising predicted fluid responsiveness (defined by a fluid-induced increase in cardiac index $\geq 15\%$) with a sensitivity of 70% and a specificity of 92% (Fig. 1), values significantly better than those reported for the prediction of volume responsiveness by passive leg raising-induced increase in pulse pressure (50% and 80%, respectively) [38].

Changes in aortic blood flow

An alternative beat-to-beat based monitoring method is the esophageal Doppler. Recent technologic developments allow continuous measurement of both the descending aortic blood velocity (Doppler method) and the diameter of the descending aorta (time-motion echographic transducer). Therefore, it is now possible to monitor blood flow in the descending aorta.

Fig. 1. Representation of individual values of percent changes in pulse contour cardiac output (CO) in response to passive leg raising (PLR) in responders to volume challenge and in non-responders. Responders to volume challenge were defined as patients who increased their pulse contour cardiac output by more than 15% after receiving fluid infusion. An increase in pulse contour cardiac output by 12% during passive leg-raising was the best cut-off value for discriminating non-responders and responders to volume challenge (see text).

In a study performed in 71 mechanically ventilated patients considered for volume expansion, we hypothesized that the increase in descending aortic blood flow in response to passive leg raising would predict fluid responsiveness [25]. Thirty-one patients had spontaneous breathing activity and/or arrhythmias. In 37 patients (responders), the aortic blood flow increased by $\geq 15\%$ after fluid infusion. A passive leg raising-induced increase in the aortic blood flow $\geq 10\%$ predicted fluid responsiveness with a sensitivity of 97% and a specificity of 94% (area under the receiver operating characteristic [ROC] curve: 0.96 ± 0.02). These excellent predictive values were quite similar in the group of patients with spontaneous breathing activity (area under the ROC curve: 1.00 ± 0.00) and in the group of deeply sedated patients (area under the ROC curve: 0.91 ± 0.06) [25]. Interestingly, a passive leg raising-induced increase in pulse pressure $\geq 12\%$ predicted volume responsiveness with significantly lower sensitivity (60%) and specificity (85%) (area under the ROC curve: 0.75 ± 0.06) [25]. This only fair prediction was similar in the group of spontaneously breathing patients (area under the ROC curve: 0.69 ± 0.13) and in the group of deeply sedated patients (area under the ROC curve: 0.74 ± 0.09) [25]. This study suggests that measuring changes in aortic blood flow rather than pulse pressure during passive leg raising is a more robust indicator of preload-responsiveness in a general population of mechanically ventilated patients including those with spontaneous inspiratory efforts and/or arrhythmias.

■ Conclusion

In spontaneously breathing patients (with or without mechanical ventilation), the prediction of volume responsiveness can be a difficult challenge, in particular in those who have already been resuscitated in the preceding hours or days and in whom continuation of fluid infusion carries risks of pulmonary edema. In these cases, static markers of cardiac preload are generally in the normal range and are rarely helpful for determination of volume responsiveness. Since absolute measures of preload cannot be used effectively to assess volume responsiveness, more dynamic tests need to be employed to improve the utility of these measures [39]. Because of the presence of spontaneous breathing, the indices of volume responsiveness that use heart-lung interactions, such as respiratory variation in arterial pressure and in stroke volume are no longer reliable. Careful analysis of the hemodynamic consequences of passive leg raising using real-time aortic blood flow monitoring may be helpful for predicting the beneficial effects of volume administration. In the most difficult cases, a fluid challenge strategy can still be applied provided that clinicians carefully follow the recommended rules in terms of the type of fluid, rate of infusion, clinical end-points, and safety limits in order to minimize the risks of fluid overload [40].

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