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EDITORIAL

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Evaluation of fluid responsiveness in ventilated septic patients: back to venous return

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Introduction

Adequate tissue perfusion and oxygen delivery is the primary goal of the therapeutic management of patients with circulatory failure. Cardiac output—a major determinant of oxygen delivery—is the result of the interaction between the cardiac pump and venous return. Since cardiac output must equal the volume of blood entering the heart, an increase in venous return will increase cardiac output, provided that the venous return curve intersects with the ascending limb of the cardiac function curve [1]. This defines the preload dependence of the heart. In contrast, a further increase in preload when the heart operates on the flat portion of its function curve fails to increase cardiac output and results in increased filling pressure with potential deleterious venous congestion. Importantly, there is no fluid responsiveness of the left ventricle (LV) without right ventricular (RV) preload dependence [2]. A pivotal clinical question frequently raised is, therefore, the evaluation of RV ability to increase its output significantly in response to a fluid challenge. Another clinical question even more challenging to address is to determine if the patient *really* needs a higher cardiac output to improve his current condition.

Venous return and mechanical ventilation

Venous return is determined by the pressure gradient between the mean systemic pressure—the forward pressure that drives back the blood to the heart through the venous resistance—and the right atrial (RA) pressure that represents the back-pressure [3]. Accordingly, blood volume expansion increases the venous return as long as the mean systemic pressure increases more than the RA pressure.

When compared to normal breathing, positive-pressure ventilation increases both the pleural and RA pressures. As a result, decreased pressure gradient for venous return is presumed to participate to the decrease of cardiac output frequently observed under tidal ventilation [1]. In addition, changes in intra-abdominal pressure may also alter venous return, since the rise in pleural pressure induced by positive-pressure ventilation is partially transmitted to the abdomen [4]. The cyclic effect of tidal ventilation on venous return is predominantly influenced by the transmural pressure of both the superior (SVC) and inferior vena cava (IVC). Vena cava transmural pressure is determined by the intravascular pressure—that, in turn, depends on the circulating blood volume and RV function—and by the surrounding pressure (i.e., the intrathoracic pressure for SVC and the intra-abdominal pressure for IVC). Accordingly, echocardiographic assessment of respiratory changes in vena cava caliber promises to yield valuable information on venous return in ventilated patients [5, 6]. In this issue of *Intensive Care Medicine*, three clinical studies convincingly demonstrate that the respiratory variation of SVC [7] and IVC diameters [8, 9], measured using M-mode echocardiography, allow the accurate prediction of fluid responsiveness in septic, ventilated patients.

Respiratory variation of superior vena cava diameter

Due to cyclic variations of pleural pressure induced by tidal ventilation, the SVC diameter is minimal during inspiration and maximal at expiration [5]. In 66 ventilated patients with sepsis and circulatory failure, Vieillard-Baron et al. [7] measured the respiratory variation of SVC diameter expressed as a percentage using transesophageal echocardiography (TEE). Interestingly, a large respiratory variation of SVC diameter (>50%) was predominantly observed in the group of responders to a fluid challenge, whereas SVC collapsibility remained below 30% in most of the non-responders. A threshold value of 36% of SVC collapsibility allowed the separation of responders from non-responders with a sensitivity of 90% and a specificity of 100% [7]. Importantly, in the same study population, six false-positive results of pulse pressure variation to predict fluid responsiveness were equally attributed to a marked inspiratory increase in pulse pressure (rather than a decrease during early expiration) and to the presence of an acute cor pulmonale. This lack of specificity is presumably attributable to the frequency of failing ventricles in septic, ventilated patients [10].

In the presence of a congestive LV failure, tidal ventilation not only increases left-sided preload but also may reduce LV afterload, thereby facilitating stroke output [11]. This may increase the respiratory variation of pulse pressure, especially during inspiration, as noted in three patients in the study by Vieillard-Baron et al. [7]. In ventilated patients with severe RV failure, marked expiratory variation of pulse pressure may reflect an augmented inspiratory decrease of RV stroke volume due to transiently increased outflow impedance [12] rather than hypovolemia, as in the patients described with severe acute cor pulmonale [7]. In complex hemodynamic settings such as septic shock, TEE has the unparalleled advantage over other "blind" techniques of allowing an integrated approach of circulatory failure that includes the evaluation of both RV and LV function, as well as accurate estimation of pulmonary artery pressure. In the presence of failing ventricles and resulting high RA pressure, TEE would presumably disclose a low SVC collapsibility consistent with the absence of cardiac preload dependence, as observed in the current study [7].

Respiratory variations of inferior vena cava diameter

In this issue of *Intensive Care Medicine*, two clinical studies sought to evaluate the ability of respiratory changes in IVC diameter to predict fluid responsiveness in ventilated patients with severe sepsis or septic shock [8, 9]. Both studies showed that a marked inspiratory increase in IVC diameter, measured using M-mode imaging from the subcostal view, was consistent with a preload dependence of the heart. Feissel et al. [8] observed that respiratory variations of IVC diameter of more than 12% allowed differentiation between responders to a fluid challenge and non-responders with positive and negative predictive values of 93% and 92%, respectively. Using a different index of variability, Barbier et al. [9] showed that a threshold value of 18% allowed the prediction of fluid responsiveness with 90% sensitivity and specificity.

The IVC diameter is principally determined by its transmural pressure that, in turn, greatly depends on the level of backward pressure (i.e., RA pressure) and on intra-abdominal pressure [13] rather than pleural pressure, because the intrathoracic segment of this vessel is virtual. Since the cyclic rise in pleural pressure induced by tidal ventilation increases the intramural pressure of both RA and IVC on the one hand, and only a minor proportion of airway pressure is transmitted to the abdomen on the other hand [4], IVC transmural pressure increases at inspiration and the vessel tends to dilate. Although in the current studies respiratory variations of the IVC diameter were amplified in preload-dependent patients [8, 9], they may be reduced, or even abolished, in the presence of elevated RA pressure and fully distended—hence less compliant—IVC as a result of hypervolemia, RV dysfunction or severe pulmonary hypertension. In none of the latter clinical settings, however, would a fluid challenge result in a relevant increase of RV output.

Limitations

The same limitations of the use of respiratory changes in systolic arterial pressure, pulse pressure or LV stroke volume to predict fluid responsiveness [14, 15] apply when measuring the respiratory variation of the vena cava diameter. Firstly, patients must be ventilated in the volume-controlled mode and strictly adapted to the ventilator. Practically, patients should be deeply sedated or paralyzed to preclude any voluntary ventilatory efforts (i.e., inspiratory triggered breaths or active expiratory efforts). Secondly, the volume of tidal breaths influences changes in intrathoracic pressure and associated cyclic hemodynamic variations [16]. One may therefore argue that respiratory variation of the vena cava diameter should be cautiously interpreted when small tidal volumes and high levels of PEEP are used [6]. However, tidal volume also influences fluid responsiveness by shifting the ventricular function curve relative to the venous return curve [1, 17]. In fact, respiratory variation of the vena cava caliber reflects the effects of specific ventilator settings (according to patient condition) on venous return at one point in time. Thirdly, clinical situations associated with increased intra-abdominal pressure (e.g., obesity, abdominal trauma, laparotomized patients) may potentially invalidate the use of respiratory variation in the vena cava (especially IVC) diameter to predict fluid responsiveness. Unfortunately, the intra-abdominal pressure was not measured in all pa-

tients of the current studies [8, 9]. Lastly, all three studies published in the current issue of *Intensive Care Medicine* [7, 8, 9] enrolled septic patients who presumably were in sinus rhythm, a crucial criterion of validity for the use of dynamic indices to evaluate fluid responsiveness in ventilated patients [14]. Whether respiratory variation of the vena cava diameter remains valid in predicting RV preload dependence in patients with arrhythmia (e.g., atrial fibrillation) or with cardiopulmonary diseases deserves further studies. All these limitations highlight the fact that respiratory variation of the vena cava diameter will not be a usable marker of venous return in a significant proportion of ventilated critically ill patients.

Clinical relevance

Before embracing respiratory variation of the vena cava diameter as a definite marker of fluid responsiveness, the promising results herein reported should now be validated prospectively in larger cohorts of patients and in other acute conditions than sepsis. Moreover, their clinical impact remains to be determined. In patients with circulatory failure, objective (i.e., quantitative) criteria of fluid responsiveness may help in guiding therapeutic management because the sole clinical judgment fails to identify hypovolemia accurately in a large proportion (59%) of patients [8]. However, as recently emphasized by Magder [15], the potential fluid responsiveness of a given patient does not mean that he *actually* requires blood volume expansion. In patients with shock, the primary goal of acute care should not be to "normalize" a dynamic index of preload dependence, but rather to optimize oxygen delivery and tissue perfusion in order to meet the metabolic demands of the organism, if necessary by increasing cardiac output with volume loading. Accordingly, respiratory variation of the vena cava diameter should be considered as a promising additional tool in the assessment of hemodynamically unstable patients using echocardiography, rather than a quantitative parameter to alter with volume expansion until a target value is reached. We should keep in mind that the (subjective) clinical evaluation of critically ill patients must not be supplanted by the easier access to quantitative (objective) parameters of fluid responsiveness.

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