The Meaning of Fluid Responsiveness

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Introduction

The management of intravenous fluid infusion in intensive care unit (ICU) patients is complex and often corresponds to the clinical imperative for perfusion and tissue oxygenation [1]. This issue is important because it concerns a large proportion of ICU patients. Indeed, inappropriate volume restriction may cause low cardiac output and/or inappropriate use of vasopressive or inotropic drugs [2]. In contrast, adjusted volume restriction avoids excessive fluid infusion and related complications, which include pulmonary edema, microcirculatory dysfunction and organ failure [3, 4]. Excessive fluid resuscitation may also lead to electrolytic disorders such as hypernatremia and hyperchloremic acidosis [5] and/or coagulation impairments [6].

The understanding of this complex issue and the clinical application of fluid resuscitation involve the integration of different indices of volemia (preload and preload-dependent indices), of which the determinants are arterial and venous circulation, cardiac function, and their interaction with pulmonary mechanics [7, 8]. Ventricular preload indices (static indices) and preload-dependent indices (dynamic indices) can quantify the same hemodynamic status on quite distinct grounds [9]. In a specific hemodynamic status, each value of central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP) or pulse pressure variation (PPV) is determined by the interaction between the two circulations (venous and arterial) and the heart-lung system [10]. Thus, coupling static indices (CVP and PAOP) and dynamic indices [PPV and systolic pressure variation [SPV]] could help to estimate the circulating blood volume and to predict fluid responsiveness [11]. However, in certain clinical situations, combining preload and preload-dependent indices does not facilitate the management of vascular filling in the ICU. This is particularly true in spontaneously breathing patients or mechanically ventilated patients under pressure support (triggering the ventilator), in whom PPV, for example, is not interpretable. In these cases, it is sometimes necessary to transitorily modify the patient's intravascular volume status by performing a passive leg raising maneuver, and to observe the effects on volemia, preload and cardiac output [12]. Here, we review the physiology of circulatory volume, how to optimize intravascular volume status, and the indices allowing prediction of fluid responsiveness.

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Physiology of Circulatory Volume

The concept of preload dependence/independence describes the effect of fluid infusion on cardiac output. An increase in cardiac output of more than a clear percentage value (10 – 15 %) secondary to volume infusion defines the patient as a fluid responder [13]. Conversely, if cardiac output does not increase by more than the present percentage value (10 – 15 %) after volume expansion, the patient is defined as a non-responder. According to experimental studies, preload is defined by the myocardial fiber length before contraction [14]. However, in clinical practice, there is no consensus on the definition of ventricular preload. For each ventricle, the preload can be defined either as the ventricular dimension in diastole (diameter, area, and volume assessed principally by echocardiography), or as the loading conditions of the ventricle in diastole. The relationship between preload and stroke volume is called the Frank–Starling systolic function curve [14] .

The evaluation of preload-dependence and the use of various hemodynamic indices require knowledge of the physiological mechanisms involved in venous return [7, 15, 16]. Parameters which should be considered are: Stressed and unstressed venous volume, the pressure gradient generating venous return (mean systemic pressure minus CVP), cardiac function, and the effective arterial elastance [17] (**Fig. 1**). This systemic return corresponds to drainage by the cardiac pump of the blood volume from the peripheral venous bed towards the intrathoracic central vascular bed through large collapsible veins. When averaged over a period of time, systemic venous return and cardiac output are equal. The pressure gradient of venous return is the difference between the upstream driving pressure prevailing in the venous bed (mean circulatory filling pressure) and the downstream pressure of the venous return, represented by the intravascular right

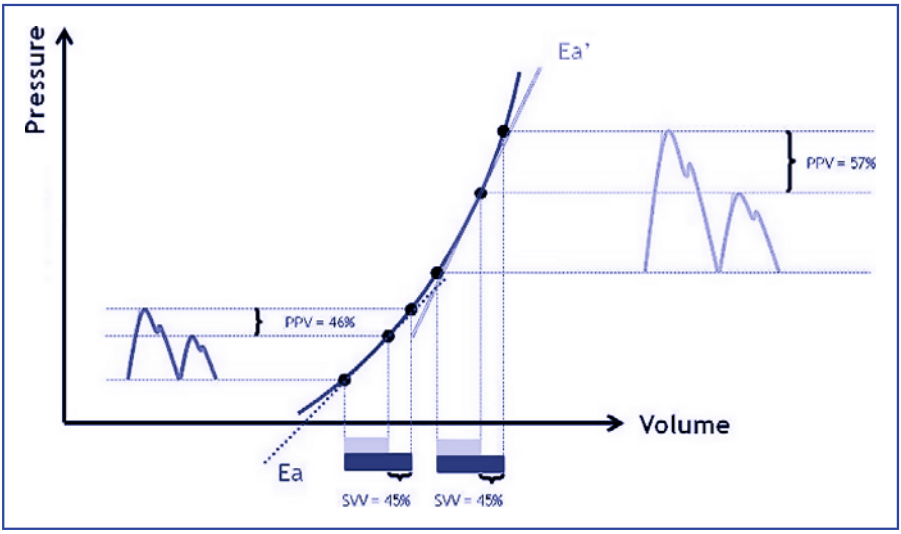

Fig. 1. Model describing the impact of the effective arterial elastance slopes (Ea and Ea') on pulse pressure variation (PPV) values. For a same stroke volume variation (SVV) value = 45 %, PPVs vary from 46 to 57 %.

atrial pressure or CVP [7]. There is also a hemodynamically inactive blood volume that is necessary to maintain the vessels in an open shape, known as the unstressed volume. The ratio between stressed and unstressed volumes within the venous vascular bed depends upon venous tone and/or vasopressor treatment [2].

Volume expansion transiently increases circulating blood volume. Part of this volume may be lost in the case of capillary leakage, as observed in septic patients [18]. Extravascular distribution, which requires a period of equilibration, depends on the vascular permeability coefficient, the properties of the oncotic liquid, and the hydrostatic pressure. It is thus difficult to predict what fraction of the infused solution is contributing to the increase in intravascular volume or is recruited to the cardiac preload. This fraction varies according to time, vascular permeability and the clinical situation. Under stable conditions, an increase in stressed volume can be assessed by measuring the increase in cardiac pressure or ventricular volume [19]. However, stressed volume will increase venous return and cardiac preload only if vascular fillings increase the mean circulatory filling pressure to a greater extent than the CVP [20]. The present statement presupposes that all other determinants of venous return remain stable.

Several parameters can influence the determinants of the pressure gradient of venous return: the intra-abdominal pressure (in turn affected by abdominal compartment syndrome or positive pressure ventilation) [21], the variation of compliance and venous resistance associated with the use of vasoactive substances with venous tropism (e.g., nitroglycerin, norepinephrine), and the intrathoracic and cardiac functions [22]. These pathophysiological states can influence the pressure gradient of venous return, regardless of the stressed volume, and thus limit the effects of volume expansion.

For a given pressure gradient, the venous return generated can also be limited by the flow resistance (venous resistance). The vascular waterfall effect is an adaptive or pathological situation where venous return is impeded when intramural venous vessel pressure becomes lower than extramural pressure. Subsequently, as for example in the vena cava, the venous vessel collapses and flow is interrupted [21, 23]. This phenomenon could be an adaptive protection against an excessive increase in venous return, which would result in right ventricular overload. This is the case when there is an excessive decrease in CVP (during forced inspiration for example) occurring concomitantly with a high stressed volume [23]. In contrast, this mechanism may be harmful in the case of low stressed volume and a pathologically high extramural pressure (high abdominal pressure), where real preload dependence could occur following the collapse of the vena cava [21, 24]. In this case, the appropriate therapeutic approach may consist of not only increasing the circulating vascular volume, but also in reducing the extramural pressure, allowing the stressed volume to reach the cardiac chambers.

Venous Return During Mechanical Ventilation

Under positive pressure ventilation, intrathoracic pressure increases during inspiration. This increase in intrathoracic pressure is partially transmitted to the right atrium, thus reducing the mean circulatory filling pressure–CVP pressure gradient and inducing a decrease in venous return [25]. In a patient with balanced volume status, changes in intrathoracic pressure will have little effect on venous return. However, in cases of hypovolemia, the consequences will be significant.

The effect of positive pressure ventilation on venous return is the main determinant of dynamic indices [25]. The effect of intrathoracic pressure changes on CVP is also dependent on the transmission of this pressure to the abdominal compartment, and its consequences on the inferior vena cava (IVC) [21]. The IVC diameter is mainly determined by the transmural pressure of the vena cava [26], defined as the difference between intramural and extramural pressures. In addition, the impact of positive pressure ventilation on venous return is influenced by the stressed volume and venous compliance [26, 27].

Indications for Fluid Expansion

Four situations may indicate a need to investigate for preload-dependence:

- Systemic hypotension
- A low cardiac output
- Signs of tissue hypoperfusion (lactate, base excess, mixed venous oxygen saturation [SvO_2])
- A pathological but compensated medical state

In some cases, systemic blood pressure can be normalized by sympathetic stimulation, but this can be associated with inadequate tissue perfusion. In this situation, volume expansion may shift the cardiovascular system toward a new state of stability to reduce the often deleterious compensatory mechanisms, such as peripheral vasoconstriction and adrenergic stimulation.

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On What Basis Should Volume Expansion Be Administered?

Static Indices

Although ventricular end-diastolic volume is a good preload marker [8], the relationship between ventricular volume and stroke volume is dependent on cardiac function [11]. For a determined ventricular preload (pressure, volume), preload-dependence can be estimated using the curve of cardiac function [28]. A normal ventricular volume associated with reduced cardiac function could correspond to a zone of preload-independence, while this same volume, in the presence of a hyper-contractile cardiac function, may be associated with a preload-dependent state (**Fig. 2**). Thus, the relationship linking ventricular preload and stroke volume cannot be addressed solely through knowledge of the degree of myocardial fiber stretch [29] (**Fig. 2**).

In clinical practice, in the absence of ventricular volume monitoring, the ventricular pressure measurement is used as a surrogate of preload (CVP, PAOP) [8]. This substitution is limited by two factors. First, the measured pressures represent a component of the transmural pressure; the intramural pressure does not take into account the extramural pressure, which may be important in many situations encountered in the ICU. Second, the relationship between diastolic volume and transmural pressure is determined by ventricular and pericardial elastance, both of which are difficult to assess [30]. Variations in extramural pressure, when measured at the bedside, can cause the intraluminal pressure to vary significantly without being translated into a change in preload [30]. Moreover, under positive pressure ventilation, the change in intrathoracic pressure depends upon the degree of pressure transmission (greater in the presence of increased lung com-

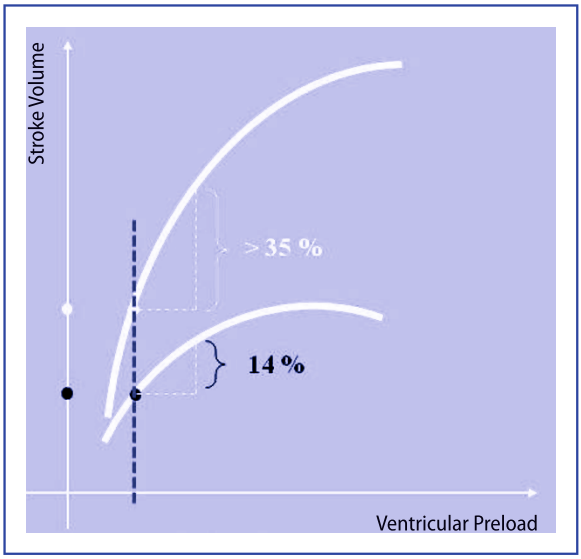

Fig. 2. Model highlighting that the relationship linking ventricular preload and changes in stroke volume (SV) following volume expansion cannot be addressed solely through the knowledge of the preload value. Example: For a same change in ventricular preload, SV increases by 14 % in a failing heart and by 35 % in a normal heart.

pliance). Taking into consideration the multiple pathophysiological concepts mentioned above, it is clear that static indices of cardiac preload cannot predict fluid responsiveness in critically ill patients, and cannot discriminate responders to volume expansion from non-responders [8].

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Dynamic Indices

Over the last decade, pragmatic intensivists were more interested in the fluid responsiveness of the subject than in estimating the ventricular preload [31 – 34]. However, several authors have considered volume therapy in a different way [8, 19, 35, 36], based on the Frank–Starling relationship [14]. Their aim is to predict the response to volume expansion, which distinguishes patients whose cardiac output and blood pressure will increase (responders) from patients whose hemodynamic status is insensitive to volume infusion (non-responders), or in whom the infusion volume may be deleterious [3, 4].

Based on prospective physiological studies directed at understanding and treating circulatory failure, it became clear that assessing cardiac preload does not predict fluid responsiveness [9]. Static indices, based on the measurement of filling pressure, ventricular volumes and surfaces, were shown to be unreliable and of limited use [37] in patients with either spontaneous ventilation or positive pressure ventilation [8, 19, 35, 36]. In contrast, dynamic indices, based on estimation of preload dependence via a disturbance of the circulation by a mechanical breath, proved their utility and reliability for characterizing preload-dependence [8, 19, 35, 36]. These indices are based on heart-lung interactions under positive pressure ventilation in deeply sedated patients with regular heart rhythms, and are now increasingly used to estimate the need for volume expansion and to optimize circulatory status in critically ill patients [8, 35, 36].

Respiratory changes in systemic pulse pressure, stroke volume and systolic arterial pressure during mechanical ventilation reflect changes in left ventricular

preload [35]. These variations in ventricular preload are due to changes in venous return, induced in turn by the cyclic variations of both pleural and transpulmonary pressures [28, 29]. Other dynamic indices, based on the variation of parameters not coupled to the systolic ejection period and stroke volume, have also demonstrated reliability in predicting fluid responsiveness [38–43].

The measurement of cardiac filling pressures and chamber volumes has little value as a predictor of fluid responsiveness. However, these measurements remain important, because they show that the fluid infusion has reached the heart and, therefore, that preload-dependence has been tested [19]. In the intensive care setting, the prevalence of patients presenting with significant capillary leakage (sepsis, acute pancreatitis, ischemia-reperfusion) is very high, and the volume required to load the heart may vary considerably. However, it should be kept in mind that basic conditions are necessary to enable the use of heart-lung interactions and derived dynamic indices. The heart rhythm has to be regular [8], tidal volume breathed through the respirator has to be more than 8 ml/kg [44, 45], and the patient should be deeply sedated and unable to trigger the ventilator [8, 44]. Apart from these specific cases, and in patients with spontaneous ventilation, passive leg raising appears to be the most robust method for predicting fluid responsiveness [12, 46, 47].

Passive Leg Raising

This maneuver mobilizes the blood from the legs and abdomen to the chest compartment and produces the hemodynamic effects of an autotransfusion [47]. The maximum increase in blood flow during this maneuver takes place within the first 20 seconds. Several studies have validated the passive leg raising maneuver as a predictor of fluid responsiveness in patients triggering the ventilator and in those with an arrhythmia [12, 46, 47]. This simple maneuver is easy to perform at the bedside, and can aid in judging whether or not fluid loading is indicated, in all critically ill patients.

Macrocirculation and Microcirculation

The final goal of hemodynamic management is to improve or maintain tissue perfusion. This functional perfusion is provided by the microvascular system. Concerning fluid infusion and after initial resuscitation in a stabilized situation, some considerations must be discussed: First, even if fluid infusion may improve microvascular perfusion, this effect seems to be independent (uncoupled) from the macro-hemodynamic parameters (hemodynamic indices or dynamic markers of preload responsiveness) [48]. Second, the effect of volume expansion on the microcirculation depends on the amount of fluid infused, a quantity which is very difficult to guess [49]. Finally, the effect of fluid infusion may be more effective in particular phases of the disease [48]. Consequently, these specificities of the microvascular response to fluid infusion further increase the complexity of assessing tissue fluid responsiveness. Indeed, vascular fluid responsiveness does not mean tissue fluid responsiveness.

Conclusion

The proposed techniques for monitoring fluid responsiveness should provide the clinician with reliable and reproducible information for deciding whether or not to administer volume expansion to a hypotensive patient, as well as information about how to administer volume expansion safely. Information collected through these indices may allow the intensivist to make more informed treatment decisions, to optimize the patient's hemodynamic status and possibly to improve their prognosis. The benefits of such an approach could result in the optimization of circulatory status, with improved peripheral tissue perfusion and consequent prevention of multiple organ dysfunctions. This reasoned approach, and the practical management of circulating blood volume in critically ill patients, should be based on the pathophysiology of venous return, heart–lung interactions and cardiac function.

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