REVIEWS

Fluid therapy in critically ill patients: perspectives from the right heart

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Abstract

As right heart function can affect outcome in the critically ill patient, a thorough understanding of factors determining right heart performance in health and disease is pivotal for the critical care physician. This review focuses on fluid therapy, which remains controversial in the setting of impending or overt right heart failure. In this context, we will attempt to elucidate which patients are likely to benefit from fluid administration and for which patients fluid therapy would likely be harmful. Following a general discussion of right heart function and failure, we specifically focus on important causes of right heart failure in the critically ill, i.e. sepsis induced myocardial dysfunction, the acute respiratory distress syndrome, acute pulmonary embolism and the effects of positive pressure ventilation. It is argued that fluid therapy should always be cautiously administered with the right heart in mind, which calls for close multimodal monitoring.

Key words: intensive care; fluid therapy, right heart failure

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Intensivists increasingly acknowledge the importance of right heart performance for their patients. This follows the recognition that a wide variety of factors, related to both disease and therapy, affect the right heart in the critically ill [1, 2]. In addition, for patients with severe respiratory dysfunction, right heart failure has proven to be an independent predictor of adverse outcome [3]. Important causes for right heart failure in the critically ill include sepsis-induced myocardial dysfunction, the acute respiratory distress syndrome (ARDS), acute pulmonary embolism (PE) and the effects positive pressure ventilation on the right ventricle. Thus, a thorough understanding of physiological principles governing right heart performance in health and disease is pivotal for managing the critically ill patient. This review focuses on fluid therapy, which remains controversial in the setting of impending or overt right heart failure. In

this context, we will attempt to elucidate the physiological principles in relation to right heart performance and thus determine which patients are likely to benefit from fluid administration and for which patients fluid therapy would likely to be harmful.

DETERMINANTS OF RIGHT HEART PERFORMANCE

The right heart is designed to generate flow against the low impedance of the pulmonary circulation. Thus, right ventricular wall thickness and systolic elastance as a measure of its contractility are low as compared to the left ventricle. Relaxation of the right ventricle occurs late and virtually coincides with atrial contraction. The low-pressure system ensures myocardial perfusion both during diastole and systole [4]. The right heart is connected to the left heart serially and shares with it the interatrial and interventricular

septa and the pericardial space, causing marked ventricular interdependence [5].

Classic theories on cardiovascular physiology continue to be useful in the context of right heart performance [6, 7]. The right heart is responsible for handling the complete systemic venous return. Venous resistance and the pressure gradient between the mean systemic filling pressure (Pmsf) and the right atrium (Pra) determine the rate of venous return. Of course this must match cardiac output (CO), which is the same for the left and right ventricle as are their stroke volumes. Stroke volume itself is determined by contractility, afterload and preload. The latter may be most important for increasing right ventricular stroke volume [8].

PRELOAD AND AFTERLOAD

Preload responsiveness means that stroke volume increases when end diastolic volume increases. The latter is determined by venous return and ventricular compliance. In addition, stroke volume will decrease when afterload increases. Afterload refers to systolic wall tension of the ventricle, itself determined by wall thickness, radius and systolic transmural pressure, i.e. intraventricular pressure minus intrapericardial pressure. During ejection, intraventricular pressure depends on pulmonary artery pressure, which itself depends on CO, pulmonary vascular resistance and compliance [9].

PULMONARY VASCULAR RESISTANCE

Pulmonary vascular resistance (PVR) depends on lung volume [10]. This can be understood by considering the pulmonary vasculature, which consists of alveolar vessels (mainly capillaries), and extra-alveolar vessels, surrounded by lung parenchyma. The latter effectively pulls open these extra-alveolar vessels by radial traction as the lung. When lung volume decreases, the extra-alveolar vessels will contract and ultimately collapse. In contrast, when lung volume increases, the distending alveoli will ultimately cause alveolar vessels to collapse. Both phenomena result in a U shaped curve when pulmonary vascular resistance is plotted against lung volume, with a nadir around functional residual capacity (Fig. 1).

The exact form of the U shaped curve is affected by distribution of the relative magnitude of arteriolar (Pa) and venular (P_v) versus alveolar (P_A) pressures. These determine if an alveolus and its surrounding alveolar vessels are which of the three so called West zones. Major determinants are lung blood volume, alveolar pressure and the gravity induced hydrostatic gradient [11]. In the lower lower areas of the lung, zone 3 conditions are present ($P_a > P_v > P_A$). This implies that there is no resistance from alveolar pressure, nor any collapsed arteries and thus maximum flow. In the topmost areas zone 1 conditions exist ($P_A > P_a > P_v$). Here, distended
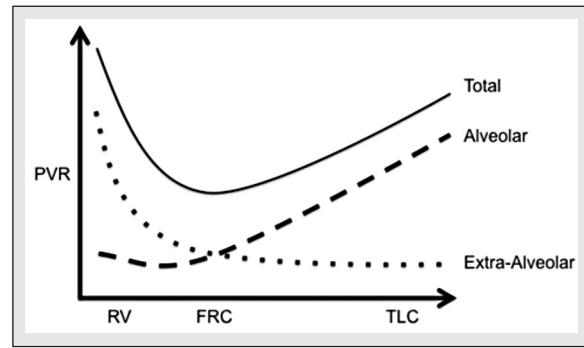

Figure 1. Pulmonary vascular resistance (PVR) is related to lung volume. Resistance from exta-alveolar vessels decreases with increasing lung volume from residual volume (RV) to total lung capacity (TLC), while that of alveolar vessels increases. This results in a nadir of pulmonary vascular resistance around functional residual capacity (FRC). These concepts help explain the effect of mechanical ventilation, positive end expiratory pressure (PEEP) and fluid therapy on PVR

alveoli induce vascular collapse causing flow to stop. Lung areas in between are said to be in zone 2 ($P_a > P_A > P_v$) is intermediate resistance and flow. Thus, pulmonary vascular resistance increases from zone 3 to zone 1 (Fig. 2).

In addition, PVR is also influenced by PaO_2 and $PaCO_2$. Hypoxic pulmonary vasoconstriction causes PVR to rise when PaO_2 decreases and importantly, also when mixed venous PO_2 drops [12]. Both occur frequently in critical care medicine, e.g. in congestive heart failure, pneumonia and ARDS and any cause of insufficient cardiac output. In addition, in some patients, the foramen ovale will open if right atrial pressure exceeds left atrial pressure. Any increase in pulmonary artery pressure may be a cause of this phenomenon, e.g. ARDS, increased cardiac output or PE. This will immediately cause a shunt induced decrease in PaO_2 and thus cause PVR to rise further. PVR also increases, albeit to a lesser extent, when pH decreases, for example when $PaCO_2$ rises [13]. Further, vascular recruitment and distention of pulmonary resistance vessels is known to occur in response to cardiac output increases, which causes PVR to decrease. Finally, hemodilution decreases viscosity and may thus lower PVR, whereas iron deprivation will enhance hypoxic pulmonary vasoconstriction [14].

CONTRACTILITY

The gold standard for determination of contractility is ventricular end systolic elastance (Ees), which has been shown to be load independent [4]. Ees is determined by connecting the end systolic points on pressure volume loops at different levels of preload (Fig. 3), which yields the line of the end systolic pressure volume relationship (ESPVR). Ees is the slope this line and is expressed in mm Hg mL-1. Arterial elastance (Ea) can also be determined
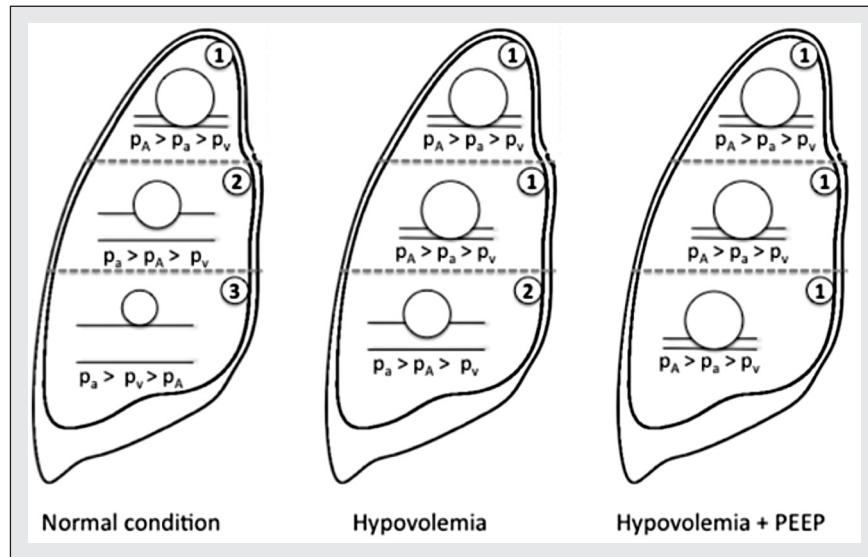
Figure 2. Evolution of West zones during hypovolemia and PEEP. The left panel shows normal West zone distribution. The middle panel represents a patient with hypovolemia where zone 1 conditions ($P_A > P_a > P_v$) expand to zone 2 ($P_a > P_A > P_v$) and zone 2 conditions to zone 3 ($P_a > P_v > P_A$), with pa : arteriolar pressure; P_A :alveolar pressure and P_v venular pressure. The right panel represents the same patient following application of excessive PEEP causing further expansion of zone 1 conditions to zone 3
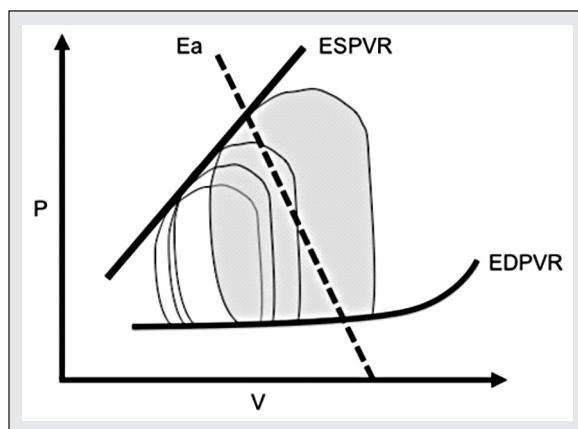

Figure 3. Right ventricular pressure volume loops at different levels of preload. These define the end systolic pressure volume relationship (ESPVR) and the end diastolic pressure volume relationship (EDPVR). The slope of the ESPVR is known as end systolic elastance (Ees), and is a load independent index of ventricular contractility. From the pressure volume loop, the line representing end systolic pressure (Pes) divided by stroke volume (SV) can also be determined. Its slope is pulmonary arterial elastance (Ees). The ratio of Ees/Ea determines ventriculo-arterial coupling

from pressure volume curves and is defined as the systolic pressure divided by stroke volume, again as expressed in mmHg/ml (Fig. 3). The normal heart has been shown to work most efficiently when Ees is about 1.5–2 times Ea, at which ratio ventriculo-arterial coupling is thought to be optimal. Importantly, commonly used indices for contractility are load dependent i.e. they reflect systolic heart function in relation to its load. For example, ejection fraction (EF)

and echographic indices including tissue Doppler derived tricuspid annular systolic velocity and M-mode measurement of tricuspid annular plane systolic excursion (TAPSE) are all load dependent and thus will change when preload or afterload is altered in the patient. These may be thought of as indices of ventriculo-arterial coupling [15]. Thus, while they do not reflect contractility directly, this may actually be advantageous at the bedside, as restoring the Ees/Ea ratio is a prominent therapeutic goal.

RIGHT HEART FAILURE

Right heart failure is defined as a complex clinical syndrome causing inadequate delivery of CO or adequate delivery of CO at the cost of an increased end diastolic volume, increased ventricular muscle mass or contractility [8]. The latter can be viewed as compensated right heart failure. Some of this compensation is immediate and includes sympathetic activation and beat-to-beat heterometric adaptation. The latter results in increased preload and hence stroke volume caused by ventricular dilatation following a rise in afterload. In addition, homeometric adaptation follows within minutes, referred to as the so called Anrep phenomenon. This refers to increases in contractility attributed to the neurohormones [4].

PRINCIPLES OF FLUID THERAPY

Now that we know the various physiological phenomena that determine right heart performance, we can use this theoretical framework to assess in impact of fluid therapy, with a focus on the right heart pathology in the critically ill. Most intensive care patients show at least some degree of

alterations in heart rate, preload, afterload and contractility, causing their right heart performance to be different from normal. These changes are caused both by disease and therapy and may themselves profoundly influence monitoring choices and therapeutic decisions, including fluid therapy.

GENERAL PRINCIPLES

However, it is important to first delineate certain general principles pertaining to fluid therapy, especially regarding indication, timing, type and quantity of fluid administration. Fluid therapy in the current context is related to fluid resuscitation, i.e. the rapid administration of fluids to improve the circulation. Rapid is usually in the range of up to 4 mL kg^{-1} min^{-1}, which sets it apart from replacement and maintenance fluid requirements [16]. By definition, the goal of fluid resuscitation is an improvement in CO, so either this or a surrogate measurement should be measured, such as $S_{(c)v}O_2$ or lactate clearance.

Fluid extravasation may cause edema if its rate exceeds that of lymph drainage. This gives rise to increased oxygen diffusion distances both for uptake and delivery, which may cause organ failure [17]. Therefore, it is important to stop fluid resuscitation if improvements in CO fail to be observed following fluid resuscitation [18]. Despite the added complexity from recent insights from glycocalyx research, the balance between capillary hydrostatic pressure, colloid osmotic pressure, capillary leak remain major parameters governing fluid extravasation. Thus, in capillary leak syndrome, such as in sepsis and ARDS, fluids should be used cautiously, especially considering that depending on fluid composition, only small amount may remain intravascularly.

MICROVASCULAR BACK PRESSURE

As the vascular system is circular, it can also be viewed from the perspective of the microcirculation, which is ultimately responsible for transport of oxygen and nutrients to tissue. Microvascular blood flow is largely determined by the difference between post arteriolar and venular pressure [19]. Therefore, post capillary pressures may be regarded as the back pressure of the microcirculation. These are greatly affected by the pressure further downstream, i.e. pulmonary venous pressure and left atrial pressure for the lung and systemic venous pressure and right atrial pressure for all other organs. If these rise microvascular blood flow may become impaired, in addition to promoting fluid extravasation [17]. Thus, high venous pressures should be avoided if possible. However, this is usually in conflict with the aim of improving CO. This calls for a balanced approach.

FLUID THERAPY WITH THE RIGHT HEART IN MIND

Let us now consider some of the most common conditions encountered in the critically ill that affect right ventric-

ular performance. These include the effects of mechanical ventilation, sepsis induced myocardial dysfunction, acute PE and ARDS. We will use these to integrate our physiological concepts into clinical practice and to answer the question on how to decide whether or not to administer fluid therapy in these cases.

FLUID THERAPY AND POSITIVE PRESSURE VENTILATION

Positive pressure ventilation increases both mean and peak alveolar and intrathoracic pressures. This will at least in part be transmitted to the cardiac chambers. Right atrial pressure will therefore increase, opposing venous return. However, mean systemic filling pressure has been shown to increase as well. This is thought to be caused by a concomitant increase in intra-abdominal pressure because of diaphragm displacement [20]. Still, venous return and therefore preload does in fact markedly decrease. This is attributed to an increase in venous resistance, either in the liver veins because of diaphragmatic pressure and/or in the superior caval vein.

As intrathoracic pressures affect both extraventricular and intraventricular pressure, transmural pressure is relatively unaffected, unlike that of the left ventricle. Thus, the effect of positive pressure ventilation on afterload is mostly related to changes in pulmonary vascular resistance and will thus vary with lung volume. If lung volume is initially reduced, application of PEEP may cause lung recruitment and thus lower pulmonary vascular resistance. As a corollary, hypoxic pulmonary vasoconstriction may be reduced if shunt is decreased because of lung recruitment. However, when overdistention occurs, pulmonary vascular resistance will rise. This is aggravated in condition of hypovolemia, as the same levels positive pressure ventilation will cause a shift towards zone 1 conditions because of easier alveolar distention induced capillary collapse.

Thus the indication for fluid therapy is rational in the setting of initiation of positive pressure ventilation, as this will increase mean systemic filling pressure and thus increase the gradient for venous return, which will increase preload. In addition, if pressure levels are high compared to volume status, afterload will decrease from fluid loading as well in this setting.

FLUID THERAPY IN SEPSIS INDUCED VENTRICULAR CONTRACTILE DYSFUNCTION

Decreased contractility will cause stroke volume to decrease. Heterometric adaptation will cause the ventricle to compensatory dilate. Thus, end diastolic volume increases which will increase stroke volume, essentially moving the working point of the right ventricle towards the horizontal part of the preload versus stroke volume relationship. In

this respect, it is important to consider the end diastolic pressure volume relationship of the right ventricle (Fig. 3). This curve is hyperbolic because pressure will rise as compliance decreases rapidly beyond a critical volume. Thus, in a dilated RV, a small increase in volume will result in a major increase in end diastolic pressure. In addition, a dilated RV implies increased RV wall tension which causes mechanical asynchrony [21], resulting from a prolonged RV systole as compared to LV systole. These processes result in leftward displacement of the interventricular septum in diastole, which will impede left ventricular filling and reduce CO. In addition, pericardial traction will ensue, which also impedes left heart filling as both ventricles compete for the pericardial space. These mechanisms are referred to as ventricular interdependence. Thus, in case of acute right ventricular dysfunction, fluid therapy comes with the risk of not increasing and even reducing CO, in addition to adding to right heart pressures, which may impede organ microvascular flow. However, the ultimate effect of fluid therapy will depend on the magnitude of contractile dysfunction and volume status, which provides a rationale for performing cautious fluid challenges. Of course, causes of acute right ventricular contractile dysfunction also include right sided myocardial infarction and myocarditis.

FLUID THERAPY FOLLOWING PE

Similar considerations apply for acute impending or overt right ventricular failure as a result of PE or other causes of an acute rise in afterload. This could cause shunting across a patent foramen ovale, resulting in a hypoxia induced increase in PVR. Again, heterometric adaptation will result in ventricular dilatation. Depending on volume status and embolism severity, afterload mismatching may be present. This requires fluid therapy to increase stroke volume and cardiac output. Mercat and coworkers showed that fluid infusion in massive PE with circulatory failure — albeit without systemic hypotension — caused an increase in cardiac index [22]. They found an inverse relationship between change in cardiac index and right ventricular end diastolic volume index. Of interest, the Mercat study did not find any relationship between Pra and change in cardiac index. However, their results have never been repeated and should be treated with caution. Therefore, recent guidelines recommend against overzealous fluid loading in the setting of PE [23]. This may vastly increase right ventricular oxygen consumption and cause the right heart to fail and in addition impede left ventricular filling through ventricular interdependence.

FLUID THERAPY FOR ARDS

The right heart is at risk for failure in the adult respiratory distress syndrome, regardless of its many etiologies. Hypoxia and to some degree hypercarbia and acidosis contribute to pulmonary vasoconstriction. Raised right heart pressures could again cause shunting across a patent foramen ovale, resulting in a hypoxia induced increase in PVR. In addition, vascular collapse in consolidated lung areas will contribute to the increased afterload. This can be further aggravated by mechanical ventilation, which is often needed, especially given the concept of the ARDS baby lung, that is prone to creating zone 1 conditions if ventilatory pressures and volumes are not tightly controlled. High plateau pressures were shown to be associated with higher mortality [24] and the protective effect of low tidal volumes and proning, both universally advocated currently, has been attributed to their salutary effects on the right heart. Indeed, using ventilator strategies aimed at limiting the plateau pressure is associated with a reduction of incidence of acute RV failure in ARDS. However, its incidence in ARDS remains 10–25% (3,25) in this setting.

ARDS is frequently accompanied by capillary leak, which provides a strong rationale for withholding fluids whenever possible. However, in case of impending right heart failure, fluid therapy may be useful, as it may increase preload and perhaps surprisingly, also reduce afterload. The latter was shown by Fougères and coworkers who measured cardiac index (CI), PVR and the relation of right ventricular versus left ventricular end diastolic area (RVEDA/LVEDA) in a group of 21 patients with ARDS using different ventilator settings were measured [26]. Starting at low PEEP and tidal volumes (TV) of 6 mL kg^{-1}, they then increased PEEP without no changing TV to reach the maximum allowed Plat of 30 cm H$_2$O. This led to an average PEEP of 13 cm H$_2$O. As expected, a decrease in CI was seen. This was partly explained by an RV afterload effect given the observed increases in PVR and RVEDA/LVEDA. Then a fluid challenge using passive leg raising (PLR) was performed. An increase in CI and a simultaneous decrease in PVR and RVEDA/LVEDA. This confirms a fluid challenge induced decrease in RV afterload. The decrease in PVR may be explained by fluid induced transition of lung areas away from zone 1 and zone 2 conditions, in the direction of zone 3 conditions by increasing Pa and Pv (Fig. 2).

RECOMMENDATIONS

Using physiology as a guide, we have tried to elucidate the principles underlying the response to fluid therapy in critically ill patients from the perspective of the impeding or overtly failing right heart. By illustrating these concepts using commonly encountered clinical scenarios, we have attempted to provide guidance for the critical care physician. This enables rational decision making based on case based estimations of benefit versus harm and can easily be expanded to other scenarios in which the right heart is deemed important.

However, as can be seen from our clinical scenarios, no absolute certainty will exist in any patient on the exact effect of fluid therapy. This calls for prudent administration of fluids, for example by using small volume challenges or better passive leg raising. In addition, it is highly advisable to use multimodal circulatory monitoring that ideally incorporates CO measurements or their surrogates. A case can be made for direct measurement of pulmonary artery pressures in the critically ill. However, as the relation between pressure and volume may not always be straightforward in these patients, intensive care ultrasound may be indispensable as it allows the critical care physician to allow rapid assessment of right heart volume, function and pressures [27, 28]. This may greatly help the decision on fluid therapy and can also directly monitor its effects.

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