Hemodynamic assessment in the critically ill patient

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Submitted: 09/30/2009
Accepted: 01/19/2010

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Paulo Novis Rocha declares having received financial support from Fundação ABM de Pesquisa e Extensão na Área da Saúde (Fabamed).

Abstract

A growing fraction of the clinical duties of Nephrologists is undertaken inside intensive care units. While assessing patients with acute renal failure in the context of circulatory collapse, which are also edematous and/or with impaired gas exchanges, the Nephrologist must decide between two opposing therapies: 1) remove volume with the aid of dialysis or diuretics to improve the edematous state; 2) volume expand to improve hemodynamics. To minimize the odds of making incorrect choices, the Nephrologist must be familiar with the tools available for determining the adequacy of volume status and for invasive hemodynamic monitoring in the critically ill patient. In this manuscript, we will briefly review the physiology of extra cellular fluid volume regulation and then tackle the issue of volume status assessment, based on clinical and hemodynamic criteria.

Keywords: shock, hemodynamics, intensive care units, kidney failure acute, cardiac output.

[J Bras Nefrol 2010;32(2):201-212]©Elsevier Editora Ltda.

Introduction

Due to the high incidence of acute renal failure (ARF) in critically ill patients, a growing fraction of the clinical activities of nephrologists occurs in intensive care units (ICUs). In the context of circulatory shock, nephrologists are constantly invited to assess ARF patients, who frequently also have impaired gas exchanges or anasarca. That situation generates an important therapeutic dilemma:

- Should volume be removed through dialysis or use of diuretics aiming at improving gas exchanges and/or edema? Or, on the contrary:
- Is the best management to administer volume to improve cardiac performance, circulatory shock, and, consequently, tissue perfusion?

Often, that highly complex problem is not adequately solved, and the attending physicians prefer to use empirical therapeutic tests:

- "Let us remove fluid; if the patient improves, we know that the decision was correct."
- "Let us administer fluid; if the patient improves, we know that the decision was correct."

In other cases, the degree of indecision is so high that the nephrologist is called to start dialysis aiming at removing volume of a shocked patient, who is being actively expanded with crystalloid solutions by the intensivist.

- "I will continue to expand because the patient is shocked, but I need you to dialyze the patient and remove fluid to improve gas exchanges."

Except for the last situation, which makes no sense (although occurring daily in clinical practice), there is nothing intrinsically wrong with therapeutic tests, as long as they follow a rational use and meet certain goals. However, what frequently occurs is that, after deciding for removing or administering volume, that management is maintained for several hours, or even days, without the necessary assessment of the parameters that can indicate if the procedure was – and continues to be – correct.

To minimize the chance of wrong decisions, such as to submit to ultrafiltration a patient who should be expanded, it is

mandatory that the nephrologist knows the tools available for invasive hemodynamic assessment and estimation of adequate blood volume in the critically ill patient. This article briefly reviews the physiology of the regulation of the extracellular fluid volume, and then approaches the diagnosis of blood volume, based on clinical and hemodynamic criteria.

Regulation of the extracellular fluid (ECF) volume

The regulation of the ECF volume is similar to the regulation of arterial blood pressure and is performed through adjustments in sodium metabolism. What is actually perceived is the effective intravascular volume (EIVV), which is coarsely equivalent to the intravascular volume contained in the arterial system, which perfuses tissues and stimulates the baroreceptors located in the aortic arch, carotid sinus, and kidneys (juxtaglomerular apparatus - macula densa). Alterations in the EIVV, perceived by the afferent sensor system of the baroreceptors, activate effector systems that aim at restoring normal blood volume through adjustments in peripheral vascular resistance, cardiac output, and, mainly, sodium renal excretion.

In the presence of EIVV depletion, such as in shock due to digestive hemorrhage, an immediate hemodynamic response occurs, mediated by catecholamines, angiotensin, and vasopressin, aiming at increasing cardiac output and peripheral vascular resistance. A renal response also occurs, mediated mainly by the renin-angiotensin-aldosterone system (RAAS) and by the antidiuretic hormone (ADH), aiming at water and sodium resorption to restore blood volume. On the other hand, in hypervolemia, the renal response is the most important, and the increase in sodium renal excretion is the desired response. This response is mediated by an increase in the glomerular filtration rate, pressure natriuresis, and secretion of natriuretic peptides (Table 1).

Usually, EIVV varies directly with ECF volume. In the above example of the patient with digestive hemorrhage, depletion of the ECF and EIVV occurs. Likewise, when a previously euvolemic patient receives one liter of intravenous saline solution, expansion of the ECF and EIVV occurs. However, there are situations in which the ECF volume is increased, but EIVV is contracted. In clinical wards, the edematous syndromes, such as congestive heart failure, liver cirrhosis, and nephrotic syndrome, are the main examples. In intensive care units (ICUs), a similar situation can be found in patients with unstable hemodynamics, low albumin, and increased capillary permeability, who underwent excessive solution administration. In that complex scenario, ECF volume is evidently increased due to fluid accumulation in a third space, but arterial hypotension coexists, in addition to a great uncertainty regarding the EIVV status, and, thus, the degree of blood volume adequacy.

Table 1 Comparison between osmoregulation and blood volume regulation

	Osmoregulation (water metabolism)	Blood volume regulation (sodium metabolism)
What is assessed?	Serum osmolarity	EIVV
Sensors	Hypothalamic osmoreceptors	Baroreceptors in the aortic arch, carotid sinus, and kidneys
Effectors	High osm: ADH secretion and thirst Reduced osm: ADH and thirst inhibition	EIVV expansion: pressure natriuresis, ANF secretion EIVV depletion: catecholamine and ADH secretion, RAAS activation
Renal response	Water excretion or retention	Sodium excretion or retention
Diagnostic markers	Serum sodium, urea, glucose osmolaridade séricos	History, clinical examination, simple complementary tests, invasive hemodynamic assessment

Osm = osmolarity; ADH = antidiuretic hormone; EIVV = effective intravascular volume; ANF = atrial natriuretic factor; RAAS = renin-angiotensin-aldosterone system.

Clinical diagnosis of blood volume

Diagnosing the osmolar status of a patient is relatively simple, and can be made by using laboratory tests, such as serum sodium, glucose, urea, and osmolarity (Table 1). We can say that a hypernatremic patient is hyperosmolar and almost always dehydrated (except the rare situation of iatrogenic hypernatremia due to the excessive administration of hypertonic sodium, usually evident on clinical history).

On the other hand, the diagnosis of volemia is more challenging, mainly when the EIVV and the ECF volume vary in opposing directions. There is no single finding of history, physical exam, or laboratory test capable of establishing blood volume precisely (Table 2). Consider the urinary sodium as an example. Renal response to alterations in blood volume involves sodium retention or excretion. Thus, a hypovolemic patient should have low urinary sodium (usually < 20 mEq/L). Although frequently true, this may not

Table 2 Clinical data that may help determining blood volume

	Hypovolemia	Hypervolemia
Clinical history	**Underlying disease symptoms** Vomiting Diarrhea Polyuria Hemorrhage **Hypovolemia symptoms** Fatigue, lethargy Thirst Cramps Postural dizziness Oliguria Abdominal pain Thoracic pain **Secondary Symptoms to HEABD** Muscle weakness: K^+ Encephalopathy: Na^+	**Underlying disease symptoms** *Nephropathy:* hematuria, oliguria, foamy urine, facial edema *Cardiopathy:* dyspnea, orthopnea, PND, lower limb edema *Hepatopathy:* jaundice, choluria, ascitis **Hypovolemia symptoms** Edema Weight gain
Physical exam	Hypotension, tachycardia Agitation, confusion Dry skin, tongue, and mucosas Reduced skin turgor Delayed capillary filling flattened neck veins Cold and cyanotic extremities	**Underlying disease signs** *Nephropathy:* hypertension, facial edema *Cardiopathy*: B3, crackles, jugular turgescence, hepatomegaly, ascitis, lower limb edema *Hepatopathy:* hypotension, peripheral signs of hepatopathy, ascitis
Simple complementary tests	Urea/creatinine ratio Uric acid	BNP Chest radiography
	Urinary indexes	PaO_2
	o urinary Na	
	o Na EF	
	o Urea EF	
	o Osmolarity	

HEABD = hydroelectrolytic and acid-base disorders; PND = paroxysmal nocturnal dyspnea; FE = excretion fraction; BNP = brain natriuretic peptide.

Chart 1. Some common clinical examples in which urinary sodium cannot be used to assess blood volume

Low urinary sodium in the ABSENCE of hypovolemia
Drugs causing renal vasoconstriction
NSAIs
Calcineurin inhibitors
Contrast medium
Glomerulonephritis
Stenosis of the renal arteries
High urinary sodium in the PRESENCE of hypovolemia
Acute tubular necrosis
Use of diuretics

NSAI = non steroidal anti-inflammatory drugs.

help in deciding the therapeutic approach. Evidently, a patient with digestive hemorrhage and urinary sodium < 20 mEq/L needs volume expansion. On the other hand, a patient with congestive heart failure (CHF), who has edema and pulmonary edema, needs a diuretic, even when his urinary sodium is < 20 mEq/L, because, in that case, sodium renal retention represents a response to the poor cardiac performance in perfusing tissues and baroreceptors (a reduction in EIVV). Chart 1 shows some examples in which urinary sodium cannot be used to assess blood volume.

Some studies have shown that the clinical diagnosis of volemia is not reliable. A literature review from 1966 to 1988 has shown that, considering the Swan-Ganz catheter gold standard, the sensitivity of the clinical assessment to detect hypervolemia in clinical patients was 73%; in ICU patients, that sensitivity was only 40%.[1] In fact, the careful physician needs to have expertise in different hemodynamic assessment methodologies applicable to critical patients and to integrate to his rationale a wide range of information to establish a more precise diagnosis of the volemic status and, thus, to define the most adequate therapeutic approach.

Hemodynamic assessment at the ICU

Considering the need to establish a precise diagnosis of volemia in ICU patients, mainly those with circulatory shock, and the difficulty to establish that diagnosis based only on clinical assessment, the use of invasive measures is required. Most ICU patients end up requiring a central venous catheter (CVC) for drug administration and sample collection for tests, and an arterial catheter for continuous monitoring of arterial blood pressure and collection of gas analysis. Those catheters are suitable for invasive hemodynamic assessment in most patients. In more controversial cases, a pulmonary artery catheter (Swan-Ganz) can be used, although it has been less and less used in ICUs.

Static measures of preload

Central venous pressure (CVP)

Measuring CVP is relatively simple, but requires the insertion of a CVC at the junction of the superior vena cava with the right atrium, usually through puncture of the jugular or subclavian vein. Central venous pressure is the most commonly used measure for assessing volemia. The guidelines of the Surviving Sepsis Campaign have recommended that, in the early phase of resuscitation of the septic patient, the CVP goals should be 8 to 12 mm Hg for those breathing spontaneously, and 12 to 15 mm Hg for patients on mechanical ventilation (because of the increase in intrathoracic pressure) or with increased intraabdominal pressure.[2]

In healthy individuals, CVP reflects the right atrial pressure, which reflects end-diastolic right ventricular pressure, which finally reflects left ventricular filling pressure. That filling pressure usually relates directly to the filling volume. However, CVP is not a reliable measure of the left ventricular filling volume in the presence of: 1) right ventricular abnormalities; 2) left ventricular abnormalities; 3) pulmonary abnormalities. Unfortunately, part of the patients admitted to ICUs has at least one of those abnormalities, which hinders the use of CVP as a measure for assessing volemia.

Marik, Baram, and Vahid have reviewed five studies comparing CVP with more sophisticated measures for assessing blood volume, such as radiolabeled albumin, in critically ill patients and have shown a very poor correlation (r = 0.16 for all combined studies).[3] Those studies have reported that patients with low CVP might be hypervolemic, and patients with high CVP, hypovolemic. Those same authors have reviewed 19 studies that aimed at determining whether CVP is capable of predicting which patients will respond to a hemodynamic challenge in face of rapid fluid infusion (challenge or volume test). Those studies have shown that, on average, the CVPs of responders and of nonresponders were similar, suggesting that a certain CVP value cannot predict who will respond to the volume test.[3]

Many have argued that CVP can be a good marker of blood volume in young patients with good cardiopulmonary function admitted to ICU due to polytrauma. However, in the studies available in the literature involving a heterogeneous group of ICU patients, CVP could neither determine blood volume nor predict a response to volume expansion.[3]

Pulmonary artery occlusion pressure (PAOP)

Determining PAOP requires the presence of a Swan-Ganz catheter. Inserting (and adequately positioning) that catheter is more complex and some studies have not shown any benefit with its use, and even suggested an increase in mortality.[4] Therefore, the use of the Swan-Ganz catheter, and, thus, of PAOP is decreasing in clinical practice. Similarly to CVP, PAOP has been used to assess the filling pressure of the left heart chambers (as a marker of volume). However, in a recent study, Osman *et al*. have reported a large overlap of PAOP values of responders and nonresponders; thus, which patients would respond to the volume challenge could not be predicted.[5]

Assessment of cardiac output

Because of the inadequacy of the preload static measures for diagnosing blood volume and for predicting response to volume administration, interest in alternative forms of hemodynamic monitoring has increased. A positive response to the volume test can be defined as the capacity of the heart to increase its systolic volume in response to blood volume expansion. This is due to the Frank-Starling mechanism, which predicts that the greater the myocardial distension in the filling phase, the greater the contraction force. In the ICU literature, several authors have defined a positive response to blood volume expansion as an increase greater than or equal to 15% in the cardiac index after a rapid volume challenge. However, when physiological limits are overcome, even greater myocardial distensions do not result in better cardiac performance. It is necessary to check in which part of the Starling curve the patient is, monitoring cardiac output before and after volume infusion.

Swan-Ganz catheter

The gold standard to assess cardiac output in ICU continues to be the thermodilution technique with the Swan-Ganz catheter. In addition to obtaining the preload static measures, the Swan-Ganz catheter can be used in a dynamic form, such as to assess the cardiac index before and after a volume test. Thus, those patients in the ascending phase of the Starling curve, who still can improve cardiac performance in response to increases in preload, are identified. However, as previously mentioned, the method has been less and less used due to the recurring observation that it does not result in prognostic improvement.[6] It is worth noting that the Swan-Ganz catheter is a diagnostic tool, not a therapeutic one. Thus, a positive impact on survival could only be expected if the information obtained with the Swan-Ganz catheter could translate into improvement in patient management. Despite more than 30 years of its clinical use, a consensus has not been reached neither about the diagnostic use of that catheter, nor about the therapeutic strategies to be applied in response to the information obtained.

Due to all controversy involved in the Swan-Ganz catheter utilization, less invasive forms to determine cardiac output in the ICU have been promoted, but they are not still routinely used in most Brazilian ICUs.

Esophageal doppler

Esophageal Doppler is a technique based on measuring the blood flow velocity in descending aorta by use of a transducer located on the distal extremity of a flexible probe. That probe is orally introduced, advanced until its tip is located approximately at the middle level of the thorax, rotated so that the transducer is in front of the aorta, and adjusted to obtain the better signal. Cardiac output can, then, be monitored continuously by using the same principles of conventional Doppler and echocardiography. Some validation studies have suggested that the estimates of cardiac output through esophageal Doppler are clinically useful.[7] Although the insertion and positioning of the device are relatively simple, there are problems of probe displacement over time and of patient's mobilization, which can result in aberrant measurements.

Methods using the fick principle

The first method to estimate cardiac output in human beings was described by Fick in 1870. He postulated that oxygen captured by the lungs is completely transferred to blood. Thus, cardiac

output can be calculated as the reason between oxygen consumption (VO_2) and the arteriovenous oxygen content difference ($AVDO_2$).

Monitors capable of measuring VO_2 can be used to calculate cardiac output. This technique is limited in cases of severe hemodynamic instability and when the inspired oxygen fraction is greater than 60%. In addition, collection of central venous and arterial blood is required to calculate $AVDO_2$.

Measuring cardiac output through oxymetry has been replaced by a thermodilution determination, derived from the Fick principle. In such cases, the catheter has a thermistor in its extremity positioned in the pulmonary artery. Right ventricular cardiac output is obtained through rapid injection, in the proximity of the right atrium, of a known volume of cooled fluid. The calculation is based on the temperature decrease of mixed venous blood, by use of an equation considering the injected volume, temperature difference, and other constants. Modern devices allow quasi-continuous monitoring of cardiac output (every 3 to 6 minutes) through a thermal filament, located close to the right atrium, which sends hot pulses and calculates output through the temperature increment captured by the distal thermistor. However, the system needs calibration at intervals, by use of the technique of cooled fluid injection. A new line of monitors has been developed aiming at estimating cardiac output in a noninvasive way, applying the Fick principle to CO_2. In the literature, there are few studies comparing that new technique with more established methods of cardiac output estimation, such as thermodilution, and those studies have revealed a certain degree of imprecision (± 1.8 liter/minute).[7]

Pulse contour analysis

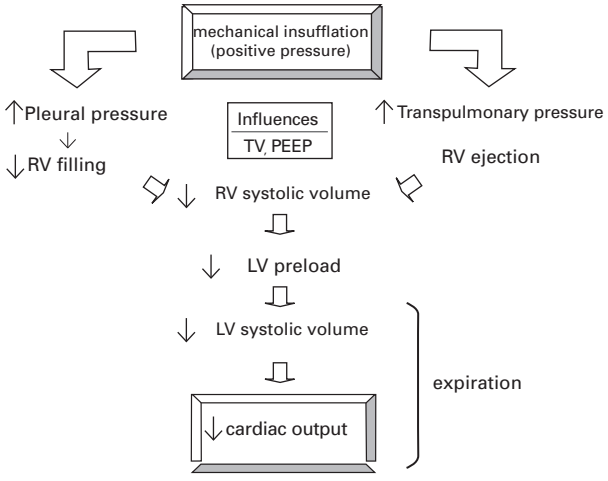
The contour of the arterial curve results from the interaction between systolic volume and the mechanical characteristics of the arterial tree. Berton and Cholley have recently reviewed some models proposed to describe those physical properties of the arterial tree.[7] Monitors have been recently developed to estimate cardiac output based on the contour of the arterial pulse curve and on models of systemic circulation. Two examples are the PiCCO (Pulsion Medical Systems, Munich, Germany) and the PulseCO (LiDCO Ltd., Cambridge, UK). The first uses transpulmonary thermodilution, and the second uses lithium chloride as the dilution technique for calibrating mean cardiac output. Frequent recalibrations (4/4 hours) can be required for accurate measures. Studies comparing that technique with thermodilution have revealed a ± 1.5 liter/minute imprecision, which is common when thermodilution is used as a reference in the comparison with any other technique for estimating cardiac output.[7] Poor quality contours of the arterial curve and cardiac arrhythmia make the use of that technique impossible.

Dynamic markers

The dynamic markers use variations in cardiac output or in blood pressure that occur in response to variations in intrathoracic pressure with mechanical ventilation (Figure 1).

Positive pressure mechanical ventilation causes an increase in intrathoracic pressure during insufflation, which, on its turn, results in a decrease in right ventricular filling and ejection, reducing its performance. The greater the tidal volume and/or positive end-expiratory pressure (PEEP), the more intense the effects of mechanical insufflation on

Figure 1. Cyclic variations in cardiac output during mechanical ventilation



The cyclic variations in cardiac output that occur with mechanical ventilation are influenced by tidal volume (TV) and PEEP, being more marked in hypovolemic patients. Pulse pressure is directly proportional to systolic volume and inversely proportional to aortic elastance. As the latter remains constant between heart beats, pulse pressure can be used as a substitute for systolic volume. Consequently, the variations in pulse pressure that occur during mechanical ventilation reflect variations in cardiac output.

right ventricular performance. The reduction in right ventricular output during insufflation reduces preload, systolic volume, and, thus, left ventricular output in expiration. Therefore, mechanical ventilation causes cyclic alterations in cardiac output: increase in insufflation and decrease in expiration.

The following four dynamic markers have been studied:

- Systolic volume variation (SVV): percentage of change between the maximum and minimum systolic volumes over a predetermined time interval.
- Delta down: drop in systolic blood pressure during expiration.
- Systolic pressure variation (SPV): difference between maximum and minimum systolic pressure over one respiratory cycle.
- Pulse pressure variation (PPV) or DeltaPp: difference between maximum and minimum pulse pressure divided by the mean of the two measures over one respiratory cycle.

To determine the systolic volume variation, a monitor of cardiac output is necessary; the other dynamic markers require only a mean arterial pressure (MAP) catheter to analyze the arterial pulse contour. We will focus on DeltaPp, which is the marker with the best performance in clinical studies.

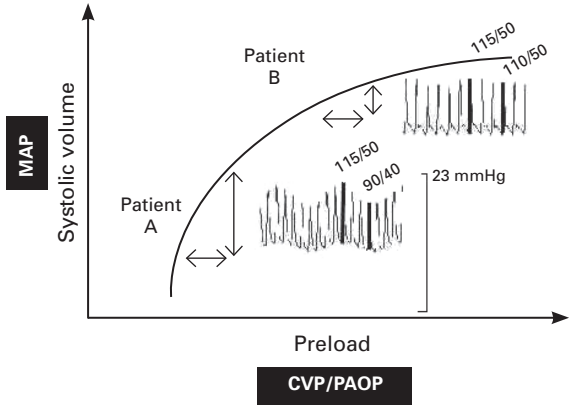
Pulse pressure variation (PPV) or DeltaPp

Pulse pressure is the difference between systolic and diastolic blood pressure. It is directly proportional to systolic volume and inversely proportional to aortic elastance. Because the latter remains constant between one heart beat and another, pulse pressure can be used as an indirect marker of systolic volume. In 1999, Michard *et al*. showed that pulse pressure variation over one respiratory cycle could be used at bedside to predict the adverse hemodynamic effects of PEEP.[8] The formula used to calculate DeltaPp was: DeltaPp % = 100 x {(PPmax - PP min) ÷ [(PPmax + PPmin) ÷2]}.

Those authors showed that the patients with higher values of DeltaPp before applying PEEP were also those who underwent greater reductions in the cardiac index after applying PEEP.[8] In 2000, Michard *et al*. used DeltaPp as a predictor of response to volume in patients in septic shock.[9] Thirty patients underwent a challenge with 500 mL of synthetic colloid in 30 minutes. The response to the volume test was defined as an elevation in the cardiac index greater than or equal to 15%. The DeltaPp of the 16 responders was 24 ± 9% *versus* 7 ± 3% of the nonresponders ($p < 0.001$). When assessing the diagnostic performance of DeltaPp with a ROC curve, the authors have shown that a cutoff point of 13% could discriminate between responders (DeltaPp > 13%) and nonresponders (DeltaPp < 13%), with sensitivity of 94% and specificity of 96%. In addition, DeltaPp proved to be a more reliable indicator of response to volume than SPV, CVP, and PAOP.[9]

According to the studies of Michard *et al*., a DeltaPp value > 13% is a good indicator that the patient will respond to volume challenge. Figure 2 illustrates how the PPV analysis can help in identifying the phase of the Frank-Starling curve where the patient is. However, some conditions need to be satisfied:

Figure 2. Response to volume and DeltaPp



DeltaPp% = 100 x {(PP max - PP min) ÷ [(PP max + PP min) ÷ 2]}

Patient A DeltaPp% = 100 x {(65 - 50) ÷ [(65 + 50) ÷ 2]} = 26%

Patient B DeltaPp% = 100 x {(65 - 60) ÷ [(65 + 60) ÷ 2]} = 8%

Figure 2 shows two patients in circulatory shock in different phases of the Frank-Starling curve. The contours of MAP before volume challenge suggest a greater respiratory variation of pulse pressure in patient A than in patient B. After simultaneous printing of the MAP and airway pressure curves (not shown), DeltaPp can be calculated over a respiratory cycle. It is worth noting that, after challenge with identical volumes (same variation in preload), only patient A shows a significant increase in systolic volume. For patient A, shock should be treated with volume expansion; for patient B, vasoactive drugs are preferred.
PP – pulse pressure; MAP – mean arterial pressure; CVP – central venous pressure; PAOP – pulmonary artery occlusion pressure.

1. Patients need to be on mechanical ventilation, sedated and paralyzed.
2. Mechanical ventilation needs to be in the volume control mode, with tidal volume > 8 mL/kg.
3. There should be no arrhythmia, intracardiac shunt, nor significant valvular disease.
4. The contours of arterial pulse and mechanical ventilation need to be printed in the same sheet, and DeltaPp should be calculated with the previously mentioned formula (without using the "eyeball test"). Alternatively, DeltaPp can be continuously monitored (online) by use of one of the new monitors mentioned above (PiCCO or PulseCO). Recently, Auler *et al.* have developed a technique that allows the automatic calculation of DeltaPp by using a conventional monitor (DX 2020, Dixtal, São Paulo, SP, Brazil), which can help in popularizing the technique.[10]

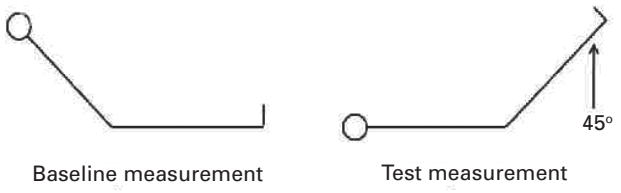
The influence of tidal volume on measuring DeltaPp can be demonstrated in the study by De Backer *et al.*[11] Those authors have reported that, in patients undergoing ventilation with tidal volume lower than 8 mL/kg, the cutoff point of 13% of DeltaPp classified correctly only 51% of the patients. In patients with lower tidal volumes, the reduction in the cutoff point of DeltaPp to 8% improved diagnostic performance, but, even so, classified correctly only 61% of the patients.[11] This does not come as a surprise, because, the greater the tidal volume, the greater the cyclic alterations in cardiac output (and, consequently, in pulse pressure) with respiration.

Recently, Huang *et al.* have assessed the capacity of DeltaPp to predict volume response in patients undergoing ventilation with low tidal volume and high PEEP.[12] Twenty-two patients were ventilated in the pressure control mode. Mean tidal volume was 6.4 ± 0.7 mL/kg, and PEEP, 14 ± 1.4 cm of water. In those patients, the 11.8% cutoff point of DeltaPp could discriminate between responders and nonresponders with a sensitivity of 68% and specificity of 100%. Thus, the low tidal volume is "compensated" by high PEEP, making the cyclic alterations of cardiac output high enough to assess DeltaPp. This is extremely important, because that strategy of ventilation with low tidal volume and high PEEP is frequently used in ICUs in septic patients with adult respiratory distress syndrome.

Passive leg raising test

Passive leg raising (PLR) test at 45° is not exactly a test, but a maneuver applied in association with dynamic assessment tests of volume response, and can be repeated *ad libitum* without the risk of inducing hypervolemia (Figure 3). Like the Trendelenburg position, the PLR test is often used for initially approaching the patient in hypovolemic shock. It is a simple maneuver that, by "autotransfusing" blood from the capacitance veins of the legs to the intrathoracic compartment, mimics temporarily and reversibly a rapid volume infusion. Boulain *et al.* have shown that PLR test for more than four minutes caused hemodynamic alterations and changes in the cardiac output similar to a rapid volume infusion of 300 mL.[13] The maneuver increases preload and, in hypovolemic patients, cardiac output. Initially, PLR test was used in association with Doppler echocardiographic techniques. Lafanechere *et al.* have shown that a positive response to the PLR test, defined as an increase > 8% in the aortic blood flow measured by esophageal Doppler, could predict volume response with sensitivity and specificity similar to a DeltaPp > 12%.[14] The main advantage of the association of PLR test and Doppler echocardiography over DeltaPp is the possibility of its use in patients breathing spontaneously and with cardiac arrhythmia. More recently, the maneuver has been successfully adapted to measure blood flow in the aortic or pulmonary valves with a simplified

Figure 3. Maneuver for the passive leg raising test



Baseline measurement is performed with the patient in the dorsal decubitus position, head of the bed at 45º, and legs in the horizontal position. The head of the bed is then lowered and the legs raised at 45º. After 4 minutes, the measurements are taken.

transthoracic Doppler echocardiographic device, characterizing the method as totally noninvasive.[15] Although that methodology apparently combines great simplicity and sensitivity, further studies and more experience are still required to determine its actual usefulness in clinical practice.

Variation index of the caliber of the superior and inferior vena cava

The simple visual observation of the blood column in the right internal jugular vein is largely used in clinical practice to estimate right atrial pressure. Similarly, the echocardiographic assessment of the vena cava caliber can be used to determine the filling pressures and volume response in critically ill patients. The variations in pleural pressures induced by mechanical ventilation with positive pressure cause cyclic alterations in the vena cava diameter. The superior vena cava (SVC), for example, reaches its minimum diameter in insufflation (because of compression due to the increase in pleural pressure) and its maximum diameter in expiration. Such alterations are more marked in hypovolemic patients. Vieillard-Baron *et al*. have studied 66 patients with septic shock on mechanical ventilation and measured the respiratory variation of the SVC caliber by use of transesophageal echocardiography.[16] Large variations in the SVC diameter (> 50%) were observed only in the group of patients responding to a volume challenge; however, in the nonresponding group, that variation remained usually below 30%. The 36% cutoff point proved to be able to discriminate volume responders from nonresponders with 90% sensitivity and 100% specificity.[16]

The behavior of the inferior vena cava (IVC) is the opposite to that of SVC. The IVC reaches its maximum diameter at the end of mechanical insufflation (because of the resistance to its flow caused by the increase in intrathoracic pressure), and its minimum diameter at the end of expiration. Feissel *et al*. have studied 39 patients on mechanical ventilation with severe sepsis or septic shock, and they have shown that a respiratory variation index of the IVC diameter > 12% could identify responders to a volume challenge (positive predictive value of 93% and negative predictive value of 92%).[17] In a similar study, using different echocardiographic criteria, Barbier *et al*. have shown that the 18% cutoff point for respiratory variation of the IVC diameter could predict volume response with 90% sensitivity and specificity.[18] There are several limitations to the use of those techniques: 1) the patients need to be in the volume-controlled mode of mechanical ventilation, deeply sedated or paralyzed; 2) the technique has not been tested in patients ventilated with low tidal volume and high PEEP; 3) situations that increase the intraabdominal pressure (obesity, trauma, laparotomy) make their use impossible; and 4) no validation in patients with cardiac arrhythmias or severe cardiopulmonary disease.

Tissue perfusion markers

The objective of volume resuscitation of critically ill patients in circulatory shock is to restore perfusion and tissue oxygenation. From the clinical view point, the following should be aimed at: MAP higher than 70 mm Hg; a good level of consciousness; and adequate diuresis (> 0.5 mL/kg/hour). From the biochemical view point, the most used markers are serum lactate and central venous oxygen saturation ($ScvO_2$). The $ScvO_2$ is a marker of oxygen extraction by tissues (normal > 70%) and came into attention with the study by Rivers *et al*.[19] In that study, the authors have compared the in-hospital mortality of 133 patients with severe sepsis or septic shock undergoing standard therapy with that of 130 patients undergoing the goal-oriented therapy protocol. The goals of the protocol were as follows: 1) CVP between 8 and 12 mm Hg; 2) MAP between 65 and 90 mm Hg; 3) $ScvO_2$ > 70%. To reach those goals, the authors used the following: volume resuscitation; vasoactive drugs; inotropic agents; oxygen therapy, to maintain O_2 arterial saturation > 93%; and blood transfusion, to maintain hematocrit > 30%. At the end of the study, in-hospital mortality of patients undergoing standard therapy was 46.5% *versus* 30.5% of those undergoing goal-oriented therapy ($p = 0.009$).[19] That protocol comprises all variables of the oxygen delivery (DO_2) equation, which controls oxygen offer to tissues: cardiac output and oxygen content in blood, which depends on hemoglobin concentration and oxygen saturation.

Blood volume assessment in dialysis

Continuous or intermittent dialysis is frequently used at the ICU to remove volume from hypervolemic patients with acute renal failure (ARF).

Although the new dialysis machines are very precise and remove only the amount of volume prescribed by the physician, that prescription remains fundamentally empirical. In other words, there is no sophisticated calculation that allows the physician to decide precisely the amount of liters that should be ultrafiltrated in a certain time interval. Usually the nephrologist uses only his/her experience and essentially clinical data (described in Table 1) to determine whether ultrafiltration is necessary, and, in that case, its rate. Those same clinical data are reassessed after dialysis to determine if the ultrafiltration volume was adequate or if the losses should be increased or decreased. Because of the complexity of the ARF patient at the ICU and the difficulties described earlier to establish a correct blood volume diagnosis, sometimes the nephrologist only notes that the ultrafiltration rate was miscalculated when the patient develops severe hypotension during dialysis. Therefore, in addition to clinical data, the nephrologist should use measures of preload, cardiac output (before and after volume challenge), and dynamic markers, such as DeltaPp, to improve the accuracy of his/her blood volume diagnosis and to minimize the chances of miscalculating the ultrafiltration rate. Unfortunately, there are no well-conducted studies showing that any strategy of blood volume assessment in the ARF patient is associated with less hypotension during dialysis. In practice, empiricism ends up predominating, and the good nephrologist begins with a more conservative ultrafiltration rate, becoming more aggressive as the patient shows good tolerance to ultrafiltration.

In this context, it would be extremely useful if dialysis machines could precisely determine blood volume, allowing the nephrologist to reduce ultrafiltration before the patient develops hypovolemic shock. Ronco, Bellomo and Ricci published in 2001 their experience with Crit-Line (Hema Metrics, USA), an equipment to monitor blood volume during dialysis. That equipment contains a sensor that detects, through variations in the reflection of a light bundle, minimum alterations in hematocrit. As ultrafiltration develops, an increase in hematocrit occurs (through concentration), allowing the use of hematocrit variation as an estimate of blood volume variation. Those authors assessed 22 patients with CHF and hypervolemia undergoing the following two modalities of ultrafiltration: 2.5 liters in 4 hours (625 mL/hour) and 2.5 liters in 24 hours (104 mL/hour). As already expected, more hemodynamic instability occurred in the group undergoing intermittent ultrafiltration (4 hours). That hemodynamic instability was accompanied by significant decreases in blood volume determined by Crit-Line, which did not occur in the group undergoing continuous ultrafiltration.[20] However, that study did not assess whether the decrease in blood volume determined by Crit-Line preceded hemodynamic instability, in order to avoid it. That question was assessed by Tonelli *et al*. in 2002, by using a similar device (Hemoscan, Gambro).[21] The authors studied 57 consecutive dialytic treatments in 20 ARF patients at the ICU. Hypotension was observed in 30% of the treatments; however, Hemoscan could not show decreases in blood volume before the occurrence of hemodynamic instability. That study has suggested that that strategy cannot reduce hypotension in ARF patients at the ICU undergoing intermittent dialysis.

Conclusions

The aim of determining volemia safely is to identify how to conduct the patient's volume therapy: to offer or remove volume. However, the precise blood volume diagnosis of a critically ill patient is highly challenging. The current trend is to replace the static measures of preload with dynamic markers, emphasizing on the response to volume challenge. It is worth noting that no measure used in isolation is 100% safe. The experienced intensivist thinks based on a combination of data from the patient's history, physical examination, laboratory tests, static and dynamic measures, and tissue perfusion markers. Such cognitive abilities can and should be part of the training of the nephrologist, mainly of those caring for critically ill patients. It is worth emphasizing that in a high-quality medicine environment, nephrologists and intensivists should work together and agree on the definition of goals for suiting blood volume and on their measuring tools. In addition, patients should be often reassessed, not only once a day, because unstable patients can require several changes in goals and hemodynamic management over one single day.

Chart 2. Main messages

Main goal in managing patients with circulatory shock: to improve tissue perfusion and oxygen delivery to tissues.

In isolation, the clinical examination and preload measures are not enough to determine if the patient needs volume expansion to reach that goal.

To observe the clinical response to volume expansion (such as, increase in BP and diuresis, decrease in lactate) is a very used strategy, but, in patients who do not benefit from volume, congestive and edematous findings can get worse, and it may postpone the adequate therapeutic management.

Several strategies have been developed to identify patients who benefit from volume expansion:

a) increase > 15% in cardiac index after rapid volume challenge;

b) DeltaPp > 13%;[9]

c) passive leg raising test: increase > 8% in aortic blood flow;[14]

d) superior vena cava collapse index > 36%;[16]

e) inferior vena cava collapse index > 12%[17] or > 18%.[18]

It is worth noting that there is no evidence in literature that the use of the above strategies can reduce mortality in critically ill patients.

There is evidence that the use of the Rivers protocol19 in the first six hours of hospitalization can reduce the in-hospital mortality of septic patients with hypotension or hyperlactatemia:

a) volume expansion with crystalloid to achieve CVP between 8 and 12 mm Hg;

b) if MAP < 65 mm Hg, despite appropriate preload, use vasopressors; if MAP > 90 mm Hg, use vasodilators;

c) $ScvO_2$ < 70%, transfuse to reach a hematocrit > 30%;

d) if $ScvO_2$ < 70% even after optimization of preload, MAp, and hematocrit, use dobutamine to increase cardiac output;

e) maintain O_2 saturation > 93%.

The above strategy is nothing more than the clinical application of the oxygen delivery formula, whose variables are cardiac output, hemoglobin and O_2 saturation.

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