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Assessment of hypovolaemia in the critically ill

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Abstract

Assessment of the intravascular volume status of patients is one of the most challenging tasks for the intensive care clinician. It is also one of the most important skills in intensive care management as both hypervolaemia and hypovolaemia lead to increased morbidity and mortality. The assessment of hypovolaemic patients is aided by several clinical signs, laboratory investigations, and a multitude of haemodynamic monitoring systems. This review aims to outline the definitions, pathophysiology, and various assessment techniques (both old and new) employed by intensivists on the critically ill patient.

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Key words: fluids, therapy, resuscitation, hypovolaemia, monitoring, biomarkers, preload, hydration, underfilling, fluid responsiveness, passive leg raising

Accurate assessment of the intravascular volume status of patients is one of the most challenging tasks for the intensive care clinician. This undertaking is particularly important in critically ill patients since both hypovolaemia and hypervolaemia are associated with increased morbidity and mortality [1, 2]. Currently, although many techniques and devices exist to help with this assessment, it is crucial that the clinician understands the limitations and clinical applicability of the tool. In this article, we discuss the current literature regarding the assessment of hypovolaemia in the intensive care unit (ICU). We will start by listing the definitions and the pathophysiological implications related to hypovolaemia.

DEFINITIONS

HYPOVOLAEMIA

Although the term hypovolaemia refers to a patient with an insufficient intravascular volume, the term does not usually account for total body fluid. Rather, it refers only the intravascular compartment. Total body fluid is approximately 60% of the body weight of men and 50% for women [3]. Blood volume can be calculated by Nadler's equation or estimated according to Gilcher's rule of fives at 70 mL kg^{-1} for men and 65 mL kg^{-1} for women [4]. When someone loses blood, an initial physiological response is to recruit fluid from the distal compartments to the central compartment. The splanchnic mesenteric reserves are the first to provide by means of vasoconstriction [5]. The activation of the renin-angiotensin-aldosterone-system (RAAS) results in water and sodium retention which replenishes the interstitial reserves and maintains the transcapillary perfusion [6]. These compensatory mechanisms ensure that the body can often lose up to 30% of blood volume before hypovolaemia becomes clinically apparent [7]. Therefore, undiagnosed hypovolaemia may be present long before clinical signs and symptoms occur. Moreover, hypovolaemia can occur in oedematous patients, where total body water (TBW) is in increased, but intravascular volume is reduced. Complicating assessment further, is the concept of patients being fluid responsive, but not necessarily hypovolaemic (e.g., in the case of distributive

shock). Therefore, accurate assessment of fluid status is critical in the management of ICU patients.

FLUID BALANCE

Daily fluid balance is the difference between all fluids given to a patient during a 24-hour period and their combined output. As a consequence, daily fluid balance can be negative, neutral or positive. The daily fluid balance does not include unrecordable insensible losses, unless the patient is being cared for on an ICU bed that can weigh the patient [8].

CUMULATIVE FLUID BALANCE

The cumulative fluid balance is the sum of fluid accumulated over a set period. In research, usually the first week of ICU stay is taken into account for prognostication [8].

FLUID LOSS

Fluid loss is defined as a negative fluid balance, with or without associated intravascular hypovolaemia.

DEHYDRATION

Dehydration is defined by an excessive loss of body water. Commonly, diseases of the gastrointestinal tract that cause vomiting or diarrhoea may lead to dehydration. Other causes include heat exposure, prolonged vigorous exercise, kidney disease, and medications (e.g. diuretics). Although one clue to dehydration is a drop in weight, this is, as stated previously, difficult in the ICU. The percentage of fluid loss is defined by dividing the cumulative fluid balance in litres by patient's baseline body weight and multiplying by 100%. Dehydration is defined by a cut-off value of 5% of fluid loss. Dehydration is considered mild (5–7.5%), moderate (7.5–10%), while a loss of over 10% is considered severe [9].

FLUID RESPONSIVENESS

Fluid responsiveness is a test to assess whether or not a patient will respond to a bolus of intravenous fluid. Fluid responsiveness is defined as an increase in the cardiac index by 15% or more [10]. A patient can be fluid responsive regardless of the (intravascular) fluid status (hypovolaemia, euvolaemia, or hypervolaemia).

SHOCK

Vincent *et al.* [11] described *Shock* as the clinical expression of circulatory failure that results in inadequate cellular oxygen utilization [11]. This results in an imbalance between oxygen delivery and oxygen consumption. It can be divided in four distinct categories: hypovolaemic (internal and/or external fluid loss), cardiogenic (i.e., acute coronary syndrome with myocardial infarction, cardiomyopathy), obstructive (i.e., cardiac tamponade, tension pneumothorax, pulmonary embolism) and distributive (i.e., severe sepsis, anaphylaxis) [11]. A detailed overview concerning circulatory shock is beyond the scope of this article.

ETIOLOGY OF HYPOVOLAEMIA

Although hypovolaemia is commonly the result of bleeding, it also occurs frequently in the ICU due to loss of vascular integrity and leakage into the interstitial compartment. Increased loss of fluid (i.e., diarrhoea, vomiting) that exceeds one's replenishment capabilities will inevitably lead to hypovolaemia, and should be remembered in the ICU as stool and vomitus are often not quantified. Sepsis, severe inflammation (e.g., pancreatitis, burns) or anaphylaxis will cause the redistribution of fluids into the interstitial compartment. Decreased intake during fasting for an inability to maintain fluid intake (e.g., during coma) will exhaust fluid reserves until overt hypovolaemia is established.

CONSEQUENCES OF HYPOVOLAEMIA

Intravascular fluids are needed to transport nutrients, the most important of which is oxygen. The failure of this system results in multiple organ failure (MOF). While some organs can maintain a degree of functionality with a reduced oxygen supply, a persistently reduced perfusing pressure due to greater than 30% loss of circulatory blood volume will eventually result in MOF and death [12].

CLINICAL ASSESSMENT

The initial assessment of patients should include history taking and a physical examination. History taking should include enquiry about overt and occult fluid loss (bleeding, vomiting, diarrhoea) or reduced fluid intake. It is also necessary to determine what kind of fluid the patient has been drinking. Coffee, coca-cola and black tea are caffeine-containing drinks that may dehydrate a patient rather than rehydrate. While thirst may indicate dehydration and hypovolaemia, it is not very sensitive nor specific. Many osmotic disturbances (e.g., hyperglycaemia), electrolyte disturbances (e.g., hypernatremia), pathologies (xerostomia, stomatitis, heart failure) or commonly used medications (anticholinergics, tricyclic antidepressants, proton pump inhibitors) can trigger a sensation of thirst [13]. Signs of dehydration should be sought during physical examination. Vital signs such as blood pressure (mean, systolic pressure, diastolic pressure, and pulse pressure), pulse rate, the presence of orthostatic hypotension or tachycardia, are useful indicators aiding clinical judgment. However, they are dependent on the type and amount of fluid loss. Capillary refill time (usually less than 2 seconds), skin turgor, the presence of dry mucosae, the temperature of the extremities and the difference between central and peripheral temperature, together with skin perfusion (colour, mottling) may be useful, although there are often several confounding factors in

the critically ill patient [14]. Weighing patients in the ICU is useful, but not routinely used.

Urine output is rigorously checked in the ICU and, while recognized as a standard of care, depends on many variables. It cannot be used as the only clinical assessment of hypovolaemia because of the many confounding issues complicating critically ill patients [15]. An observation strongly suggestive of hypovolaemia is the abrupt decrease in blood pressure after the initiation of mechanical ventilation [11]. Two main pathophysiological reasons exist for this phenomenon. Firstly, the decrease in venous return is greater in hypovolaemic patients, and secondly, the sedative medication necessary for the induction of the patient exhibits more hypotensive side effects (vasodilatation).

All of these indicators alone cannot diagnose hypovolaemia. They require integration into a broader assessment of fluid status [15].

BIOMARKERS

Laboratory results, although providing useful information, cannot provide independent markers of volume status. A single biomarker for this assessment does not yet exist. Some point of care tests are of a certain value (e.g., arterial blood gas analysis).

ARTERIAL BLOOD GAS

Arterial blood gas (aBG) analysis can be readily obtained and provides a quick estimation of haemoglobin. Although there are currently no published data on the relationship between hypovolaemia and haemoglobin, it is widely accepted that in states of dehydration, haemoglobin levels will be higher than the upper limit of normal due to concentration effects. This process of haemoconcentration is, however, subject to confounders (e.g., anaemia, toxic effects of infection). The use of haematocrit to estimate whether or not a patient is hypovolaemic has been known for decades, and may contribute towards oxygen imbalance and end-organ failure [16].

RENAL FUNCTION

Renal function may be significantly impaired in states of hypovolaemia. The impact of temporary decreased renal perfusion appears to rely predominantly on the pre-existing physiological condition of the kidneys. An elevated serum urea over creatinine ratio, both expressed in mg dL^{-1} above 20–50 L^{-1} may indicate hypovolaemia.

ELECTROLYTES

Plasma sodium is an electrolyte of specific interest in volume regulation. It is easily measured by point-of-care tests (POCT) like aBG and is strongly associated with volume status. When the different baroreceptors of the body sense hypovolaemia, they activate secretion of antidiuretic hormone by the pituitary gland (arginine vasopressin). Antidiuretic hormone will activate the retention of water, resulting in hyponatremia. This hyponatremia is augmented when patients are given hypotonic fluids to replace the losses [17]. Nevertheless, not every patient with hyponatremia will be hypovolaemic, and not every hypovolaemic patient develops hyponatremia. When a net fluid loss is not replaced, sodium will rise. Sodium values are also confounded by medication (e.g., tricyclic antidepressants, diuretics), the type of fluid loss, adrenal activity, and choice of replacement fluid. Appropriate management of these patients requires a detailed history and clinical examination.

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

Renal baroreceptors stimulate the adrenal glands to activate the RAAS (renin–angiotensin–aldosterone system). This results in aldosterone secretion and sodium retention. Thus, even more water and sodium is retained. Plasma renin activity and plasma-aldosterone levels have thus been reported to be tightly linked to volume status [6]. Unfortunately, dosage of the plasma renin enzymatic activity is not routinely available in the laboratory and plasma-aldosterone level testing is a timely process.

PLASMA OSMOLALITY

Plasma osmolality (P_{osm}) is a good reflection of intracellular osmolality as it operates in very narrow ranges (basal value of approximately 287 mOsm/kg in healthy, well-hydrated individuals). It has thus long been promoted as the perfect hydration status marker [18]. In recent years however, support for this hypothesis has dwindled [19, 20]. Acute changes in extra-cellular fluid status will alter P_{osm} rapidly. P_{osm} will increase to a greater or lesser extent depending on the type of fluid that is lost (e.g., diarrhoea, or vomitus, or sweat, etc). When the extra-cellular hypovolaemia persists, maintenance of fluid homeostasis is attempted by recruiting intra-cellular fluid, as explained previously. A new equilibrium will thereby develop, causing the P_{osm} to shift back to its normal value as much as possible. P_{osm}, therefore, does not readily reflect chronic hypovolaemia. Furthermore, P_{osm} is influenced by several confounders, the most important of which is an elevation of the non-soluble fraction of the extra-cellular compartment, namely elevated concentrations of serum lipids or proteins. Many medications (e.g. diuretics, mannitol) influence P_{osm} and should be considered during evaluation.

PLASMA COLLOID ONCOTIC PRESSURE

The plasma colloid oncotic pressure is an important determinant in the appearance of oedema and the regulation of fluid exchange [21]. The normal human plasma

COP averages 20–25 mm Hg. This value tends to decrease with age, is lower in females, and is also lower in patients confined to bed rest. In dehydrated patients, the COP value may increase. COP values are related to left ventricular filling pressures and may help in the differential diagnosis of pulmonary oedema. COP is increased in hydrostatic oedema and associated with increased LVEDP, whereas in hyperpermeability oedema, COP is usually decreased. As such, COP measurement is a clinical tool with a useful contribution to the differential diagnosis of pulmonary oedema.

URINE-ANALYSIS

Urine output decreases when the body is hypovolaemic, largely through water and sodium retention, as discussed above. This decrease is not necessarily a sign of kidney failure, but rather of the maximum physiological reaction (activation of the RAAS) of a normal kidney [22]. When 24-hour urinary sodium excretion during that phase shows urinary sodium < 100 mEq per 24 h, then hypovolaemia should be strongly suspected [22]. A 24-hour urine collection is of little or no use when trying to determine a patient's volume status at the beside and make immediate changes to treatment. Thus urine output measures are very important when trying to evaluate for immediate changes [18]. They are easy to obtain, contain a wealth of information and do not require heavy technical or costly equipment. Urinary excretion of sodium is probably altered much earlier than when clinically significant changes in vital signs are evident [22]. Therefore, when a clinically hypovolaemic patient has decreased urinary sodium excretion, it is most likely an example of adequate aldosterone activity. In such a case, the response of both serum and fractional urinary excretion of sodium to the administration of normal saline (1–2 L day^{-1} for 2 days) provides even more clues. If serum sodium increases by >5 mmol L^{-1} and fractional urinary excretion of sodium increases by < 0.5%, then it is highly suggestive of hypovolaemic hyponatremia [17]. It is important to stress that urine sampling can only be performed a minimum of 6 hours after the last dose of diuretics.

IMAGING

CHEST X-RAY

Many studies have confirmed that the typical signs of volume overload on a chest X-ray (CXR) are highly variable and insensitive. Furthermore, there are no typical radiological signs that suggest hypovolaemia. The absence of hypervolaemia on a CXR does not imply hypovolaemia, nor does it correspond to fluid responsiveness. A CXR is therefore of no use in detecting hypovolaemia in the critically ill in the ICU [23].

ULTRASOUND ASSESSMENT

Ultrasound is a bedside tool that provides the clinician with several advantages. The technology is readily available and easy to use. The results are accurate and reproducible. It gives real-life direct, non-invasive or minimally invasive images of organs, vessels and other clinically relevant structures [24]. M-mode and Doppler can generate dynamic measurements that can guide efficient treatment rapidly. According to Vincent *et al.* [25], these advantages make ultrasound close to the ideal haemodynamic monitoring system. However, it is operator-dependent and measures should be taken to minimize inter-observer variability. Ultrasound has grown to be an important clinical tool for practicing intensivists and emergency physicians [26–29].

VENOUS COLLAPSIBILITY INDEX (VCI)

The inferior vena cava (IVC) is easily accessible with ultrasound. Even clinicians inexperienced in the use of ultrasound can quickly learn to find the IVC and reproduce this image with acceptable accuracy after minimal training [30, 31]. IVC diameter changes with the respiratory cycle. Measuring the change in diameter provides an index that correlates with a patients' volume status [26, 32]. However, IVC measurement also has important limitations, including technical (e.g., limited visualization in surgical and obese patients) and implementation-related (i.e., requirement for new equipment, limited number of trained sonographers, incomplete understanding of relationships to existing invasive haemodynamic monitoring devices) [26, 29, 32]. As with every tool, the physician using it determines its utility. Recent evidence suggests that the IVC is not only valid in spontaneous breathing patients, but also in those receiving mandatory positive pressure ventilation [26]. The effect of positive end-expiratory pressure (PEEP) appears to be negligible. In ventilated patients, the maximum and minimum IVC diameters are measured to calculate the IVC collapsibility index (IVCCI). This is superior to inspiratory and expiratory values. An alternative to measuring the IVC is to use the superior vena cava (SVC) or the subclavian vein which has also been correlated successfully to haemodynamics [32]. However, there is still some controversy regarding the utility of IVC measurement. IVC measurement in combination with passive leg raising (as will be discussed further) has been shown to be a good predictor of fluid responsiveness [25, 33–36].

TRANSTHORACIC CARDIAC ULTRASOUND

Transthoracic echocardiography (TTE) is another useful point-of-care, repeatable, non-invasive examination. Several studies report the value of echocardiography, particularly regarding volume status, ventricular systolic and diastolic function, loading conditions (pre- and afterload), valve

morphology and function, and anatomy of great vessels [37]. This information can be accurately obtained and interpreted by non-cardiologist intensivists. The information can be used immediately to influence management in as much as 40% of patients, and also provided clinically important information to an additional 48% [38]. Although significant experience is required to utilize echocardiography to the fullest, one study reported that non-cardiologists could be trained to estimate left ventricular (LV) function with as little as 6h of training [39]. Transthoracic echocardiography may be difficult in the ICU, particularly on those who have dressings, external devices that cannot be displaced (e.g., left ventricular assist devices, thorax drainage systems), difficult body constitution, limited cooperation, or hyperinflated lungs (COPD, positive pressure ventilation, high PEEP).

TRANSESOPHAGEAL CARDIAC ULTRASOUND

A more invasive alternative to TTE is transesophageal echocardiography (TEE). Well established in cardiac surgery, it is frequently used in the intensive care population as many patients are already sedated and mechanically ventilated. TEE enables better visualization of the heart, particularly posterior structures. This results in a better assessment of the global function, preload, afterload, and fluid responsiveness. Recently, miniature TEE probes have been developed to minimize the risk of trauma associated with the investigation. This micro-TEE expands the utility of TEE in the ICU as it diminishes the need for procedural sedation and analgesia [40]. In a small observational study of 94 mechanically ventilated acute respiratory distress syndrome [ARDS] patients, the micro-TEE could be left in place for up to 72 hours [41]. This provided useful, continuous haemodynamic information that led to direct therapeutic interventions in 68% of patients. The visualization with micro-TEE is not as good as normal TEE, thus even though it is useful for haemodynamic monitoring, it is not as useful for diagnosing structural problems [42].

VOLUMETRIC ASSESSMENT

Volumetric assessment of the heart via echocardiography is often challenging, even in perfectly aligned patients and in ideal, elective circumstances. In the ICU, circumstances are often more difficult [43]. Right ventricular end-diastolic volume (RVEDV), left ventricular end diastolic volume (LVEDV) and global end-diastolic volume (GEDV) are all measurements that can indicate hypovolaemia when low. The latter will be discussed further when reviewing transpulmonary thermodilution techniques. As there is consensus but still with ongoing discussion on normal dimensions, volumetric assessment of the heart through echocardiography often relies on 'eyeballing'. Normal LVEDV is greater than RVEDV and the septum bulges slightly in the right ventricle. Therefore, the right ventricle end-diastolic diameter (RVEDD) is around 0.6 of the LVEDD. If the dimensions are reversed, this supports a diagnosis of fluid overload [43]. It is agreed that normal left ventricular end-diastolic area (LVEDA) is between 10 cm^2 and 20 cm^2. A LVEDA < 10 cm^2 signifies hypovolaemia and an area > 20 cm^2 is suggestive of volume overload.

ESOPHAGEAL DOPPLER MONITORING (EDM)

EDM-probes have a unidirectional echo-Doppler that can be directed to the descending aorta to measure blood flow in real time. EDM showed a decent correlation with pulmonary artery catheter (PAC or Swan-Ganz catheter) and transesophageal echocardiography [44, 45]. The probe is quite large, frequently causing intense discomfort during the procedure and resulting in movement and Doppler signal loss. This is the main limitation of this tool, along with the need for additional sedation and analgesia, operator dependence and the need of frequent probe readjustments [29, 46]. These limitations, the important influence that many pathologies (mainly aortic disease) have on the measurement results, and the availability of modern alternatives, make EDM less popular in the ICU.

BIO-ELECTRICAL IMPEDANCE ANALYSIS (BIA)

BIA uses electrical current to calculate the body composition and volumes. It has to make five assumptions to be able to reproduce reliable measurements. Firstly, it has to see the body as a cylinder. Secondly, that cylinder consists of five smaller cylinders (torso being the central one with 2 arms and 2 legs counting for the other four). Thirdly, the body composition is considered to be homogenous. Fourthly, the composition of the body is not alterable, so the only variables are the volumes. Lastly, environmental changes do not have an influence on the measurements. These assumptions are rarely true in ICU patients (e.g., amputations, local oedema, muscle wasting, etc.) [3, 47–49]. BIA seems promising as it can measure not only TBW, but also extra- and intracellular water, the extracellular water/intracellular water (ECW/ICW) ratio, and the presence of excess fluid volume [3, 50]. Further studies are required before BIA can be recommended as a useful tool in ICU to detect dehydration.

ISOTOPE DILUTION TECHNIQUES

Labelled solutes or isotopes have been used to determine TBW [18]. The most commonly used isotopes are those of hydrogen or oxygen (i.e., D_2O, $3H_2O$). After ingestion or infusion, the tracer distributes itself in all of the different body fluid compartments. After several hours, a balance is measured in the plasma and/or urine. Its concentration allows one to determine TBW content [19, 51]. Specific tracers that get distributed only in extracellular compartments can be used to ECW content. The difference between TBW

and ECW content is an estimation of the ICW compartment. This is an exact and correct measurement but takes time and preparation. Of course, infusion of these tracers carries risks of adverse reactions. Specific technical apparatus and skill is also needed.

BAROMETRIC PRELOAD ASSESSMENT

CENTRAL VENOUS PRESSURE (CVP)

CVP was previously the primary parameter for determining volume status. The argument revolved around fluid administration increasing RVEDV, LVEDV and cardiac output (CO). However, CVP is no longer used for this purpose as CO and fluid responsiveness are not directly correlated with CVP. Stroke volume (SV) will only increase if the heart fibres have the right length, a phenomenon known as the Frank-Starling law [52]. Furthermore, SV and CO are dependent on venous return, right ventricular compliance, peripheral venous tone, underlying pulmonary vascular disease, intra-abdominal pressure and heart disease (valvular, ischemic, structural) [53]. These variables make CVP a weak indicator of volume status and fluid responsiveness. The likelihood that CVP can accurately predict fluid responsiveness is only 56% [54]. It is thus possible to have a low CVP and not be fluid responsive. If there is an intact sympathetic response, the CVP may fall in response to fluid administration due to loss of compensatory venoconstriction [55]. A low CVP will thus not be able to diagnose hypovolaemia, nor accurately predict fluid responsiveness.

PULMONARY ARTERY OCCLUSION PRESSURE (PAOP)

In cardiac surgery, a PAC is sometimes used. Ideally, the PAOP is related to LVEDV (preload) and thus a good parameter to assess volume status. However, many studies have demonstrated a poor correlation between PAOP, volume status, and fluid responsiveness [23, 36, 56, 57]. Some studies have even suggested a negative effect on outcome for patients in which this catheter is placed due to many, possible severe complications during placing and measuring [58]. The PAOP is, therefore, not routinely used in the assessment of volume status in our critically ill patients in the ICU. It is used in some parts of the world to refine treatment in patients with known pulmonary hypertension (PHT) or to diagnose PHT when suspected.

VOLUMETRIC PRELOAD MONITORING

VOLUMETRIC SWAN-GANZ

Besides PAOP, CVP and right atrial pressure (RAP), a PAC can also derive right ventricular ejection fraction (RVEF), RVEDV and its index (RVEDVI) and CO. When hypovolaemia is suspected, such a suspicion can be confirmed by this technique [59]. A low CO and low RVEDV are strongly suggestive for hypovolaemia. The greatest limitation of this technique is its invasive nature [58].

TRANSPULMONARY THERMODILUTION

Transpulmonary thermodilution (TPD) derives CO and its index (CI), global end-diastolic volume (GEDV) and its index (GEDVI), global ejection fraction (GEF), extravascular lung water (EVLW) and its index (EVLWI), as well as pulmonary vascular permeability (PVP). It is a well-validated instrument that is now a standard of care in many intensive care units [60–62]. There are different devices available ($PiCCO_2$, Pulsion Medical Systems, Getinge, Rastatt, Germany or EV1000, Edwards Lifesciences, Irvine, USA) to perform this technique that can diagnose hypovolaemia at the bedside if suspected. A low CI with low GEDV(I)/ EVLW(I) and high pulse pressure variation (PPV) is pathognomonic for hypovolaemia where a high CI with low GEDV(I) is suggestive of a distributive problem requiring fluid administration. In the second case, the EVLW(I) determines the amount and kind of fluid administered and the necessary adjunctive medication (e.g., vasopressor) [59]. The limitations of this technique are the need for invasive procedures (insertion of a central venous line and arterial line) and the fact that no good nomograms exist with normal values in different patient populations [53].

FUNCTIONAL HAEMODYNAMIC VARIABLES

STROKE VOLUME VARIATION (SVV) AND PULSE PRESSURE VARIATION (PPV)

Breathing has effects on intra-thoracic pressure. In spontaneously breathing patients, inspiration will lead to a decrease in systolic pressure, while expiration will lead to an increase. In mechanically ventilated patients, the effect is the opposite. Although intrathoracic positive pressure decreases venous return and thus decreases right ventricular filling (preload), left ventricular preload increases because of an increase in pressure in the pulmonary vascular bed. When we take the maximum systolic pressure, and compare it to the minimal systolic pressure, we can then see a difference. This difference is called the PPV. SVV is calculated through a pulse contour analysis and an area under the curve calculation of the systolic portion of the arterial pressure curve [63]. These variations are more pronounced in the hypovolaemic patients making them sensitive tools to detect hypovolaemia in our ICU-patient population [23, 64].

There are important conditions linked to the use of these tools. The patient needs a normal sinus rhythm, requires mechanical ventilation without spontaneous breathing and with a tidal volume of at least 8 mL kg^{-1}, as well as needing to have a closed chest. Furthermore, PPV and

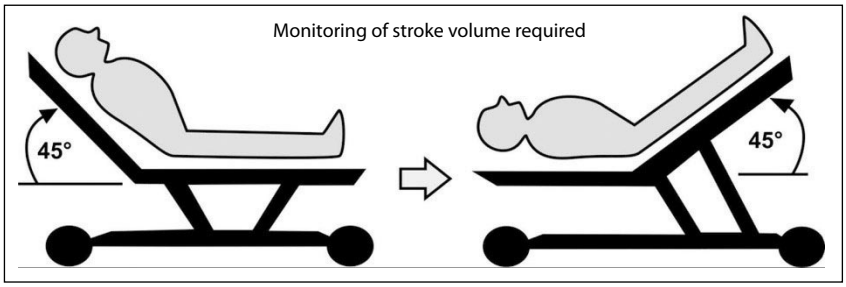

Figure 1. The passive leg raising test. In order to perform a correct PLR test, one must not touch the patient in order to avoid sympathetic activation. The PLR is performed by turning the bed from the starting position (head of bed elevation 30–45°) to the Trendelenburg position. Adapted from Hofer and Cannesson, with permission [74]

SVV are validated to predict fluid-responsiveness rather than sensing hypovolaemia. PPV is more reliable than SVV in this estimation as SVV requires calculation while PPV is measured directly [23, 65].

PASSIVE LEG RAISING TEST (PLR)

The PLR test has been used for many decades to assess a patient's response to an intravenous fluid challenge of 150–200 mL [34, 35]. Correct execution of this procedure is vital. A patient should be in the semi-recumbent position with the head up at 45 degrees. The patient should then be switched to the PLR-position in which the legs are now 45 degrees up (see Fig. 1) [74]. A positive response is defined as an increase in stroke volume of 10–15% [66]. Alternatively, the attending ICU doctor can estimate ("eyeball") the left ventricle on TTE and look at the left-ventricle diastolic area index (LVDAI) . This avoids the need for an invasive blood pressure monitoring system [67]. This technique has limitations. Heart failure (particularly right heart failure) with dilated ventricles will eliminate the desirable rapid filling effect of PLR. Orthosympathetic responses related to blood bolus and/or sudden movement in sedated patients may lead to a false positive PLR result.

END-EXPIRATORY OCCLUSION TEST (EOT)

Monnet *et al.* [68] tested the physiology behind SVV/PPV and whether the EOT could essentially function as a fluid challenge in mechanically ventilated patients, without actually giving fluids. They found that an end-expiratory hold of 15 seconds increased left ventricular preload sufficiently to increase the pulse pressure and CI by > 5%. This predicted fluid responsiveness with an accuracy that was similar to the response of CI to PLR, and was better than that of pulse pressure to PLR. Thus, EOT has proven a useful alternative to techniques already discussed [48]. Fluid responsiveness does not always equate to hypovolaemia (i.e., distributive shock) but can be strongly suggestive. Limitations for the EOT are the same as for the other tests using functional haemodynamics (as described above).

SUBLINGUAL MICRO-CIRCULATION

In recent years, the micro-circulation has attracted more attention [69–71]. The micro-circulation is the collection of the smallest blood vessels in the body. It consists of the arterioles, capillaries, and venules. Various studies have shown the essential role of these vessels, the most important being the delivery of oxygen [72]. Furthermore, in our critically ill patient population, the micro-circulation is nearly always compromised [69, 70]. There are limitations in using the surrogates of inadequate macro-circulation to diagnose hypovolaemia and guide fluid-therapy. Due to several confounding issues, it is possible to administer inappropriate amounts of intravenous fluids and vasoactive drugs which could potentially lead to harm. Monitoring the micro-circulation is possible through the sublingual space [73]. Through these measurements it is possible to estimate the rate of haemodynamic coherence: a parallel improvement of the macro- and micro-circulation. Hypovoalemia may present itself as micro-circulatory failure, now visualized on these novel micro-circulatory devices [69, 73]. Limitations include difficulty in elucidating the cause of the micro-circulatory dysfunction (e.g., hypovolaemia versus obstructive flow versus sepsis), the need for an expensive item of equipment, and inter-observer variability.

CONCLUSIONS

Few tasks are as important, and as difficult for intensivists as the assessment of fluid status in critically ill patients. Various monitoring tools exist and different situations demand variety of tools. To date, no ideal method has been developed to assess and continuously monitor hydration status. Understanding the mechanisms (and inherent limitations) behind each tool is thus essential and makes the physician the most important factor in the assessment, while interpreting the results in the light of the patients' clinical condition. Assessment should always commence with a thorough clinical examination, followed by a careful interpretation of the laboratory results and specific attention to plasma sodium, COP and P_{osm}. A 24h-urine collection and

cumulative fluid balance are useful guides to future fluid therapy, while simple urine indices are readily available and provide instant information. A daily chest X-ray for the purpose of volume assessment is not recommended, whereas daily ultrasound screening (VCI, cardiac ultrasound) by an experienced clinician has shown to directly influence fluid therapy.

When these non-invasive tools are insufficient, invasive monitoring should be implemented. Transpulmonary thermodilution with volumetric monitoring provides additional information in unstable ICU patients while the PAC is helpful in obstructive shock, right heart failure or pulmonary hypertension, but infrequently used. Research will undoubtedly shed new light on approaches to the assessment of volume status.

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2. Conflicts of interest: Manu Malbrain is founding President of WSACS (The Abdominal Compartment Society) and current Treasurer, he is also member of the medical advisory Board of Pulsion Medical Systems (part of Maquet Getinge group) and consults for ConvaTec, Acelity, Spiegelberg and Holtech Medical. Manu Malbrain is co-founder of the International Fluid Academy (IFA). The other authors have no possible conflicts of interest in relation to the content of this review article.

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