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Hemodynamic monitoring devices to predict fluid responsiveness in septic shock: a systematic review

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Resumo

A monitorização hemodinâmica é um dos pilares da Medicina Intensiva que fornece informação útil sobre o estado do sistema cardiovascular do doente. A medição do débito cardíaco de um doente em choque permite a avaliação de outras variáveis importantes como a entrega de oxigénio e a perfusão tecidular. A abordagem inicial do doente em choque séptico consiste, entre outras atitudes, na ressuscitação hemodinâmica com bólus de fluídos. No entanto, nas fases seguintes do tratamento é necessário avaliar a necessidade de expansão de volume.

O objetivo principal desta revisão narrativa é descrever os métodos de monitorização hemodinâmica utilizados atualmente e destacar as principais indicações e limitações de cada aparelho. A base de dados utilizada durante a pesquisa bibliográfica foi o Pubmed, tendo sido selecionados 73 artigos.

Nesta revisão são mencionados vários métodos, incluindo o cateter arterial pulmonar, técnica de termodiluição transpulmonar, ecocardiograma, análise de contorno do pulso arterial, bioimpedância e bioreactância. A capacidade destes aparelhos determinarem a condição fluidorespondedora em doentes com choque séptico é discutida durante todo o trabalho.

Os parâmetros dinâmicos, incluindo a variação da pressão de pulso e a variação do volume sistólico obtidos através da análise de contorno de pulso, são considerados bons preditores da condição fluidorespondedora. Pelo contrário, variáveis estáticas como a pressão venosa central podem ser utilizadas como indicadores da pré-carga, mas não preveem se o débito cardíaco vai aumentar em resposta a um bólus de fluídos.

Os médicos devem conhecer os mecanismos básicos por detrás destes aparelhos, de modo a utilizá-los de forma correta, prevenindo assim possíveis consequências decorrentes da administração excessiva de fluidos. A criação de protocolos sobre métodos de monitorização pode contribuir para uniformizar a abordagem inicial.

Palavras-chave: choque séptico; condição fluidorespondedora; aparelhos de monitorização hemodinâmica; indicações; limitações.

Abstract

Hemodynamic monitoring is one of the cornerstones of Intensive Care that provides useful information regarding the patient's cardiovascular state. Assessment of cardiac output in patients with septic shock allows the evaluation of other important variables like oxygen delivery and tissue perfusion. The initial approach in septic shock involves an initial hemodynamic resuscitation with fluid bolus, among other approaches. However, it's necessary to evaluate the need for fluid expansion during the following phases of treatment.

The main purpose of this narrative review is to describe the currently available hemodynamic monitoring devices and to point out the main indications and limitations of each device. The database used during the literary research was Pubmed, with 73 articles being included in this review.

In this review are mentioned several methods, including the pulmonary artery catheter, transpulmonary thermodilution technique, arterial pulse contour analysis, echocardiogram, bioimpedance and bioreactance. The capacity of these devices in predetermining fluid responsiveness in patients with septic shock is discussed during the course of this review.

Dynamic parameters, including pulse pressure variation and stroke volume variation obtained by pulse contour analysis, are considered good predictors of fluid responsiveness. On the contrary, static variables such as central venous pressure may be used as preload indicators, but cannot predict if cardiac output will increase in response to a fluid bolus.

Clinicians should understand the basic mechanism in which these devices operate in order to correctly use them and prevent possible consequences of fluid overload. The creation of hemodynamic devices protocols could help standardize the initial monitoring approach in septic patients.

Key-words: septic shock; fluid responsiveness; hemodynamic monitoring devices; indications; limitations.

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1. Introduction

Predicting whether a fluid challenge will improve a patient's cardiac output (CO) and therefore its hemodynamic status remains a challenging task that many clinicians face on a daily basis. It's important to understand that volume responsiveness does not necessarily implicate a need for fluids, but it rather identifies the heart's capacity to increase its output in response to volume expansion. [1] In fact, patients with septic shock do not necessarily present with a hypovolemic state, but rather an arterial and venous vasodilation associated with impaired organ function. However, this therapeutic trial has known deleterious and potentially harmful consequences, namely endothelial injury and interstitial edema that can further aggravate any existing organ dysfunction.[2,3] Furthermore, a fluid conservative approach was shown to decrease the mechanical ventilation period in septic patients with acute respiratory distress syndrome (ARDS).[4] For this reason, there is an increasing need to correctly identify patients that will benefit from this intervention after the initial resuscitation phase in the management of septic shock.

The Frank-Starling curve represents the heart capacity to adapt to preload and volume variations. If the patient's heart operates on the ascending part of the curve, then an increase in preload will result in an increase in stroke volume (SV). However, if the preload capacity is located in the plateau part of the curve, then volume expansion will not only have no influence on SV, but it may also have the abovementioned repercussions.[5]

The utility of assessing fluid responsiveness is to predetermine a patient's response to volume expansion before, rather than after the bolus has been administered. Several devices have been developed to provide important information regarding hemodynamic status. Traditionally, static parameters like central venous pressure (CVP) were considered a reliable measure to guide fluid administration, believing that it reflected intravascular volume.[6,7] Dynamic variables, on the other hand, are mostly based on cardiopulmonary interactions that record the patient's hemodynamic response to a provocative stimulus such as positive pressure ventilation.[2] Pulse pressure variation (PPV) and stroke volume variation (SVV) are reliable surrogates of fluid responsiveness.[8]

The main purpose of this review is to assess the applicability and limitations of the most commonly used hemodynamic monitoring devices in Intensive Care Units (ICU), that routinely assist clinicians in predicting a patient's fluid responsiveness.

2. Methods

The aim of this review is to compare the hemodynamic monitoring devices currently available in ICU. Understanding the basis of each technique allows the clinician to correctly use these devices and identify potential situations in which they cannot be applied.

The database used in the bibliographic research for this narrative review was Pubmed. The literature research interval was established between 2010 and the present year, also including relevant studies mentioned in these papers.

Search terms included combinations of "septic shock", "hemodynamic monitoring", "fluid responsiveness" or "volume responsiveness", "fluid management", "cardiac output monitoring", "pulmonary artery catheter", "transpulmonary thermodilution", "pulse contour analysis" or "pulse pressure analysis" or "arterial waveform analysis", "echocardiography", "bioimpedance" and "bioreactante".

We included randomized clinical trials, observational studies, review articles, systematic reviews and meta-analyses. Animal studies and clinical trials including pregnant women and patients under 18 years of age were excluded from this review.

3. Review

3.1. Defining fluid responsiveness

The main goal of fluid therapy in septic patients is to optimize intravascular volume and cardiac output, which improves tissue oxygenation.[9] Fluid responsiveness is defined as an increase of at least 10% in cardiac output after a fluid bolus or a passive leg raising (PLR) test.[5]

3.2. Cardiac output assessment in hemodynamic monitoring devices

Over the last years, there has been a clear preference for less invasive monitoring alternatives like thermodilution techniques, pulse contour analysis, and echocardiography. [7] These methods allow the assessment of volumetric and dynamic parameters. Transpulmonary thermodilution (TPTD), in addition to CO measurement, also quantifies specific volumetric hemodynamic parameters such as global end-diastolic volume (GEDV), a reliable predictor of cardiac preload, and extravascular lung water (EVLW), a feasible indicator of pulmonary edema. [10] Echocardiography is a monitoring device used to assess cardiac function and several anatomic structures. Measuring the variation of blood flow at the outflow tract or aortic root may support the decision to give fluids.[11] The basis of pulse contour analysis is a mathematical analysis of the relationship between stroke volume and the amplitude and shape of the aortic pressure curve. An advantage of pulse wave analysis is the continuous real-time assessment of CO before, during, and after certain interventions. Stroke volume variation (SVV) and pulse pressure variation (PPV) are among the many dynamic variables estimated by this method, that have shown to reflect the patient's fluid responsiveness. [7,12]

Invasive hemodynamic monitoring devices

The pulmonary artery catheter (PAC) is a well-known monitoring device that was until recently considered standard of care in the ICU. This method, also known as Swan-Ganz catheter or right heart catheterization, was originally designed to measure right heart and pulmonary artery pressures, with latter improvements allowing this device to also evaluate CO by thermodilution and mixed venous oxygen saturation.[13] Through the insertion of a catheter in a central vein, most commonly the internal jugular or the subclavia, the device travels along the central venous circulation into the right atria and ventricule. Inflating the balloon helps guide the tip of the catheter into the pulmonary artery by following intracardiac blood flow, where it gets "wedged", allowing the measurement of the pulmonary capillary wedge pressure (PCWP), also called pulmonary artery occlusion pressure (PAOP). The expansion of the balloon transiently stops blood

flow, recording the back pressure from the pulmonary veins, and hence the left cardiac chambers.[14] This variable is considered an indirect measure of the left ventricular end-diastolic pressure (LVEDP). If ventricular compliance is constant, LVEDP remains proportional to LVEDV, which reflects left ventricular preload.[15,16] However, filling pressures are considered poor predictors of fluid responsiveness since septic patients often have altered ventricular compliance.[17]

The presence of a thermostat at the tip of the catheter records the difference in blood temperature after a thermal filament intermittently heats the blood in the superior vena cava or a cold bolus is injected into the circulation.[13,14] The variation rate in blood temperature gives some insight on the patient's cardiac output status: the greater the variation, the faster is the flow rate and therefore, the higher is the cardiac output.[18] However, in certain conditions this pulmonary thermodilution technique may not correctly evaluate right heart function, such as tricuspid regurgitation or intracardiac shunts, in which the absence of an unidirectional flow alters the thermodilution results.[14,19]

Through the extraction of blood samples from the pulmonary artery or by the incorporation of spectrophotometry into the catheter, the mixed venous blood oxygen saturation (S_VO_2) can be obtained.[15] This measurement represents the relationship between arterial oxygen delivery (DO_2) and oxygen consumption (VO_2). Three main factors influence this relationship, namely hemoglobin, arterial blood oxygen saturation (SaO_2) and cardiac output. A decrease in S_VO_2 can suggest an inadequate oxygen delivery due to any of the parameters mentioned before. However, it can also indicate an increasing oxygen consumption, like in high metabolic demand states. On the other hand, high S_VO_2 reflects oxygen extraction defects, often related to mitochondrial dysfunction. One would expect that a low S_VO_2 value could predict volume responsiveness, however patients with septic shock often present high cardiac output and decreased oxygen extraction, and therefore S_VO_2 can be increased.[20] Velissaris and colleagues [21] demonstrated that S_VO_2 cannot predict fluid responsiveness in the case of severe sepsis, nonetheless, it can guide the therapeutic approach by evaluating global tissue oxygenation.[22]

There are nowadays still some indications for the use of the pulmonary artery catheter in the ICU, including right ventricular failure, pulmonary hypertension, mixed shock sates, pulmonary edema leading to acute respiratory failure and patients who require complex fluid management due to risk of progression to renal failure.[14,23] Contraindications for this procedure can be subdivided into absolute contraindications, including right heart endocarditis and masses, and relative contraindications such as severe coagulopathy and thrombocytopenia. [24,25]

The invasiveness, the difficulty in interpretation of the results and the risk of complications led to the disuse of this technique.[14] Among these complications are ventricular arrhythmias and right bundle-branch block, that are easily managed, and some more concerning events including pneumothorax, thrombosis and pulmonary infarction, endocardial and valvular injury, and pulmonary artery rupture.[14,23]

Initially, studies reported that this device increased mortality and hospitalization time. However, following studies demonstrated no difference in these parameters.[13] A Cochrane review in 2013 confirmed that the use of the PAC in ICU does not alter mortality or hospital length of stay.[24] Nevertheless, the pulmonary artery catheter has possible complications, that although rare can be severe, and so, with the development of less invasive hemodynamic devices that provide reliable hemodynamic information, the use of the PAC has been restricted to those specific conditions.[13,18]

Minimally invasive hemodynamic monitoring devices

Transpulmonary thermodilution techniques are based on the principle that if an indicator is injected into the circulation, the area under the curve (AUC) correlates with flow rate and stroke volume, and therefore it's possible to deduce cardiac output.[26]

These invasive devices use similar methods to evaluate CO through the injection of a fluid bolus into the right atria but measure the results in different locations: the PAC transducer is located in the pulmonary artery, while in TPTD technique the thermodilution curve is recorded in a systemic artery, most commonly the femoral artery.[12,27] This method is not as invasive as the PAC given that it may only require a

central venous access.[28] The PiCCO (Pulse index Continuous Cardiac Output) and Volume View are the commercial names of the two most used TPTD devices in intensive care units. Transpulmonary thermodilution combines the intermittent measurement of volumetric parameters with the real-time evaluation of pulse contour analysis of the arterial waveform. The PiCCO monitor quantifies CO by dividing the area under the curve of the arterial waveform by the aortic compliance.[29] It's important to consider that some situations may compromise the accuracy of the results, like valvular regurgitation, intracardiac shunts, extracorporeal circulation, rapid changes in body temperature and the physiological changes that occur in cardiac output with the normal respiratory cycle. [19,28]

Among the additional parameters provided by TPTD are the global end-diastolic volume (GEDV), extravascular lung water (EVLW), intrathoracic blood volume (ITBV), cardiac function index (CFI), global ejection fraction (GEF) and pulmonary vascular permeability index (PVPI).

The distribution of a defined indicator throughout the intrathoracic cavity allows the assessment of certain volume and function parameters that can be useful in the management of the critical patient. [12] The exponential decay time represents the time it takes the indicator to distribute through the largest chamber of the intrathoracic cavity: the pulmonary circulation. It's calculated from the downslope of the thermodilution curve and it's proportional to the volume contained in the pulmonary vasculature. The mean transit time reflects the time taken for half of the indicator to be detected by the transducer integrated in the arterial line. [27] These two concepts serve as basis for the generation of the mentioned volumetric parameters. EVLW quantifies the volume of water outside of the pulmonary vasculature which can help the diagnosis of subclinical pulmonary edema.[28] Nonetheless, the presence of pulmonary embolism, history of lung resection or pleural effusion may influence the accuracy of this parameter. [30] Along with PVPI, these two variables can distinguish hydrostatic from inflammatory pulmonary edema and also guide fluid management. Patients with high values of EVLW and PVPI should receive the minimal fluid bolus necessary, in order to prevent or even aggravate prior volume overload.[27] Cardiac preload can be assessed through the GEDV, that reflects end-diastolic volume, but it does not, however,

differentiate right from left cardiac preload and loses precision in the case of cardiac chamber dilation. Nevertheless, GEDV and ITBV are used to calculate CFI and GEF that characterize the heart's pumping capacity and, therefore, evaluate cardiac systolic function.[12]

The PiCCO algorithm facilitates the recalibration of the pulse contour analysis, calculating systemic vascular resistance and aortic compliance that are later integrated in the estimation of cardiac output. The repeated calibration of the pulse contour analysis is essential to reduce the inaccuracy of the results, especially in septic shock patients in which vasomotor tone can change between measurements. [31,32]

Central venous oxygen saturation ($S_{CV}O_2$) differs from S_VO_2 in a way that the measure is not in the pulmonary artery, but in a central vein. This parameter is available in the PiCCO system and is assumed to mirror the changes in S_VO_2.

Limitations of TPTD include recirculation of the bolus injected, may not be reliable if cardiac output is to low and it only allows an intermittent assessment of hemodynamic status.[12]

Transpulmonary lithium dilution (LiDCO) uses the same principles as the thermodilution techniques already mentioned. A small bolus of isotonic lithium chloride is administered in a central venous catheter and recorded at a peripheral artery through an ion-selective electrode.[31] The obtained concentration-time curve allows the estimation of CO.[33] Due to inherent properties of this device, it should be used carefully in patients under lithium therapy and repeated measurements can result in lithium accumulation.[28]

Non-invasive hemodynamic monitoring devices

Echocardiography in the critically ill patient is a non-invasive, bed-side monitoring device, that provides essential real-time information on the patient's cardiac function.[34] This device allows the assessment of other parameters that evaluate cardiac function and provide useful information on the patient's hemodynamic status, such as ventricular filling pressures and the presence of valvulopathy or tamponade.[11] Left ventricular end-diastolic area index (LVEDAi) is considered a good indicator of left ventricular preload

but not of fluid responsiveness.[35] Like many other volumetric parameters, it cannot establish the patient's position in the Frank-Starling curve since an increase in CO does not rely only on preload.[36]

In patients with septic shock, cardiac output measurement, peak flow velocity and inferior vena cava (IVC) respiratory variation are validated predictors of fluid responsiveness. [37,38]

In a spontaneous breathing patient, the IVC diameter varies with the respiratory cycle: a negative pressure leads to the collapse of the IVC during inspiration (known as IVC collapsibility index), following a proportional increase in the expiratory phase.[39] Positive pressure ventilation induces the contrary response, i.e increases the IVC diameter, the so-called IVC distensibility index. [40] Since the patient's respiratory effort influences the IVC variation, it is only logical that these two indexes have different thresholds and predictive values regarding fluid responsiveness. A IVC respiratory variation of >12-18% in mechanically ventilated patients correctly distinguishes fluid responders from non-responders. A high IVC variation of >40%-42% also predicts volume responsiveness in case of spontaneous breathing, even so a result of <40% does not rule out the need of fluid therapy. [41,42] When interpretating these results the clinical context should be taken into consideration, given that changes in right atrial pressure, venous compliance or intrathoracic pressures also influence IVC variation.[40]

Stroke volume is considered to be directly proportional to aortic blood flow and, thus, this measurement is equally influenced by the respiratory cycle.[43] A peak flow velocity variation (ΔV_{peak}) of at least 12%, measured at the aortic annulus, is an accurate predictor of fluid responsiveness in mechanically ventilated patients with sinus rhythm.[35]

Imagining the left ventricular outflow tract (LVOT) as a cylinder, the volume passing through this segment can be estimated by multiplying the base with the height, more precisely, the cross-sectional area of the LVOT (CSA-LVOT) with velocity-time integral of the same segment (VTI_{LVOT}).[44] Hence, stroke volume can be estimated by multiplying CSA-LVOT with VTI_{LVOT}. From this value it's possible to deduce other important variables including CO, SVI and CI. [45] VTI_{LVOT}, also known as stroke distance, is determined by pulse-

wave Doppler and represents the average distance that blood travels during each contraction at a precise point.[44]

Considering that CSA remains constant, any variation in the SV value implies a change in the blood flow in the LVOT – the VTI_{LVOT}.[45] An VTI_{LVOT} variation of >20% or an increase of >15% in cardiac index, correctly differentiates fluid responders from non-responders in mechanically ventilated patients.[39,46] In a spontaneous breathing patient, a passive leg raising (PLR) test acts as a transient volume challenge that induces an increase in cardiac preload. [44] In this case, an increase of >12,5% is a good predictor of fluid responsiveness. [47]

One of the disadvantages of this method is the potential measurement inaccuracy of CSA-LVOT, since any error will be squared when calculating the area of the LV outflow tract. Limitations for the use of this parameter include LVOT obstruction, (both at valvular or subvalvular level), moderate to severe aortic regurgitation and intracardiac shunt. All these conditions can alter blood flow and increase flow turbulence, which may compromise the results. [44]

The absence of a sinus rhythm may also compromise the precision of the results, since there is a greater variability in VTI measurements. In this situation it's advisable to record several VTI measures to improve accuracy. [45]

Compared to some of the hemodynamic devices already mentioned, echocardiography does not provide a continuous assessment, is operator-dependent and should be repeated if the patient's condition changes. It may also have limited diagnostic capacities in certain conditions like measurement of superior vena cava (SVC) respiratory variation, endocarditis, left atrial mass and acute cor pulmonale. [48]

Esophageal Doppler is considered a minimally invasive monitoring device that also evaluates CO by recording the aortic blood flow velocity in the descending aorta. One of the advantages this device has comparing to TTE is the capacity to perform a continuous measurement and is less operant-dependent. [33] An aortic blood flow variation (ΔABF) greater than 18% has proved to be an accurate predictor of volume responsiveness.[49]

Considering that this device records this parameter in the descending aorta, then the supra-aortic vessels are not included, thus a correction factor has to be applied.[50]

Transesophageal echocardiography (TEE) role in hemodynamic monitoring allows the measurement of the same variables mentioned in TTE, including VTI, CSA, and the assessment of cardiac structures and pressures.[45,50] It can also accurately record the SVC collapsibility index that has demonstrated to be a good predictor for fluid responsiveness. A variability greater than 36% predicted an increase in CO in ventilated patients. [51] However, due to the insertion of a probe in the esophagus, this device is limited to sedated patients. The risk of esophageal or hypopharyngeal injury, and dislocation of the tracheostomy tube are rare, but possible. [48]

Finally, bioreactance and bioimpedance are other examples of non-invasive devices that have shown some evidence regarding their potential use in hemodynamic monitoring. Nevertheless, more studies are needed to confirm the reliability of this technique to predict fluid responsiveness.[52]

These recent monitoring techniques are based on the changes in intrathoracic impedance over a cardiac cycle. [31] Thoracic impedance (Z) is calculated by the ratio of the voltage measured in the electrodes (V) with the frequency of electrical current (I). The main difference between bioimpedance and bioreactance is that the first modulates electrical amplitude while the second regulates frequency and phase-shifts.[53] Bioimpedance is indirectly proportional to the amount of intrathoracic fluid.[50] Accordingly, variation of thoracic bioimpedance correlates with changes in aortic volume, which can later deduce SV.

3.3. Surrogates of fluid responsiveness in hemodynamic monitoring devices: SVV and PPV

Pulse contour analysis (PCA), also called arterial waveform analysis, is obtained by the interpretation of the aortic curve recorded through an arterial line. This method can be associated with external calibration, as mentioned above in the case of the PiCCO

monitor, or it can be uncalibrated which means that the data is acquired entirely from the geometrical characteristics of the arterial waveform and patient-specific features, without further adjustments.[31] Several factors influence the aortic waveform including systolic volume, contractility, aortic impedance, vascular compliance and peripheral vascular resistance.[33]

The FloTrac system incorporates an arterial sensor connected to a Vigileo monitor, based on the principle that aortic pulse pressure is directly related to stroke volume, and inversely proportional to aortic compliance.[54] Beside cardiac output, this device also measures stroke volume (SV), stroke volume index (SVI), stroke volume variation (SVV) and cardiac index (CI). CO can be calculated by multiplying heart rate (HR) with stroke volume (SV), however, this device uses pulse rate (PR) instead of HR, which represents the number of pulsations in 20 seconds. [55] This means that the transducer integrated in the peripheral arterial line only accounts truly perfused beats, explaining why this method is not reliable in the presence of arrhythmia.[56]

For the determination of SV, the algorithm multiplies the standard deviation of the arterial blood pressure (σ_{AP}) with factor *k*. σ_{AP} is proportional to pulse pressure and SV, while factor *k* incorporates the patient's specific demographics like age, sex and body surface area.[54,55] In order to function without the need for external calibration, the FloTrac technology combines these factors with two main principles: skewness and kurtosis. Skewness measures the asymmetry of the distribution of a variable: if the skew value is zero then the obtained curve is symmetrical, on the contrary if the value is different from zero then one of the extremes of the curve differs from the other.[57] This knowledge can be applied to the arterial waveform reflecting changes in vascular tone, such as vasoconstriction. Kurtosis refers to the degree of peakedness of a waveform, for example a decreased kurtosis value may indicate a reduced central tone.[55,57] These two principles allow the continuous rectification of the patient's CO based on the changes of vascular compliance and resistance.

SVV is a dynamic parameter of great interest to determine fluid responsiveness. It's calculated from the difference between the maximal and minimal stroke volume values in three consecutive respiratory cycles.[58] Understanding the normal physiology of heart

lung interaction helps to comprehend how this device predicts volume responsiveness. In a spontaneous breathing patient, the contraction of the respiratory muscles induces a decrease in intrathoracic pressure during inspiration. This leads to an increase in pressure gradient variation and, therefore, transiently augments venous return. [1] Since variations in right ventricular function are only reflected in the left ventricule two to three heart beats later (a response known as the pulmonary transit time) the increase in LV preload is usually recognized in the expiratory phase of the respiratory cycle. As a result, in the course of positive pressure ventilation each insufflation induces a decrease in venous return, and hence, a decrease in stroke volume.[59]

Pulse pressure variation (PPV) is calculated by dividing the difference between the maximal and minimal pulse pressures (P_{max} - P_{min}) with the mean of these two mentioned values (PP_{mean}). Similar to SVV, PPV estimates the patient's position in the Frank-Starling curve.[60]

SVV and PPV are considered functional hemodynamic parameters since they can continuously assess the heart's response to a given stimulus: the bigger the variation of cardiac output with the respiratory cycle, the more likely the patient will respond to fluid therapy.[8] A SVV value of >10%, as well as PPV value of >13% are considered good predictors of volume responsiveness. [8,26,56] Even so, several limitations preclude the use of this technique including low tidal volume (< 8mL/kg), spontaneous breathing, open chest, arrhythmias, severe bradycardia and right heart dysfunction, increased intra-abdominal pressure. [56,61]

A reduced tidal volume is usually seen in patients with acute respiratory distress syndrome (ARDS) who also demonstrate low lung compliance. Low V_T may not be sufficient to induce the heart-lung interaction aforementioned, and so PPV is only considered a feasible predictor of volume responsiveness when tidal volume is at least 8 mL/kg.[61,62] Nevertheless, a recent test called "tidal volume challenge" has demonstrated some potential interest in identifying fluid responders whose tidal volume is low, by inducing a temporary increase in tidal volume.[63]

In the case of spontaneous breathing or partial ventilatory support, the irregularity of the respiratory cycle due to changes in rate or amplitude, may compromise the accuracy

of the results.[56,60] An open chest situation or an increased intra-abdominal pressure significantly affect the intrathoracic pressures and pressure gradient that are the foundation of this technique.[61]

Knowing that right ventricular pressure has an important effect on venous return, situations such as cor pulmonale predictably influence this parameter.[64]

Comparing the two dynamic variables, a systematic review concluded that PPV is a more accurate predictor of fluid responsiveness than SVV.[8]

Cardiac output measurement: comparison between the hemodynamic monitoring devices

In spite of the specific indications and limitations of each device, some authors have questioned the interchangeability between some methods in the assessment of cardiac output. It's important to highlight that the choice of the best CO measurement device may be difficult, since each method has its own advantages and limitations. In 1999, Sakka et al [65] demonstrated that CO measurements by transpulmonary thermodilution techniques were consistent with the values obtained by the pulmonary artery catheter, which was then considered the gold standard. As a result, most of the newly developed hemodynamic monitoring devices are compared with intermittent thermodilution technique.

A prospective observational study assessed the accuracy of CO measurement in septic patients by a continuous-wave Doppler ultrasound and by PiCCO. The results indicated that Ultrasound cardiac output monitoring (USCOM) is a reliable method compared with intermittent thermodilution [66]. Nonetheless, other studies have demonstrated conflicting evidence concerning the correlation level between these two techniques. Current data does not fully support the interchangeability of thermodilution techniques and echocardiography when evaluating cardiac output in hospitalized patients [67].

There is still some uncertainty regarding the need for calibration in non-invasive or minimally invasive monitoring devices. Several studies compared dynamic parameters obtained by PiCCO and various non-invasive, non-calibrated PCA monitoring devices,

such as Flotrac/Vigileo and MostCare. MostCare was compared to PiCCO during an observational clinical study. Since vasomotor changes influence PCA measurements, it's important to compare the results with a calibrated device. The authors concluded that these two devices present a good level of agreement during CO monitoring, even in the presence of vascular tone changes [68]. Monnet et al [32] demonstrated that Flotrac/Vigileo device accurately measured variations in CI after fluid therapy, but not during vasopressor therapy. Other studies have shown good correlation between these two methods, but they were performed mostly in cardiac surgical patients. This interest in non-invasive monitoring devices that rapidly measure variations in CO may be helpful in a goal-oriented fluid strategy since early stages of shock.

A prospective cohort study compared pulse contour analysis with echocardiography as volume responsiveness predictors. In this study, the authors measured ΔIVC through TTE and recorded the SVV and SVI from the Vigileo/Flotrac monitor. Results indicated that ΔIVC seems to be a more feasible predictor of fluid responsiveness and that functional parameters measured by pulse contour analysis needs additional investigation [69]. On the contrary, another study that compared LVOT-VTI obtained by TTE with the Flotrac/Vigileo device found acceptable correlation between these two methods [70].

Due to the some of these contradictory results, large clinical studies are required to correctly compare the available hemodynamic monitoring devices. The heterogeneity of the population included in these studies, which combined ICU patients with different types of shock and perioperative patients, may also contribute to the difficult interpretation and clinical application of the results. A meticulous selection of patients with a specific pathology, such as septic shock, would be the ideal population for a clinical study to determine which device is more suitable to assess cardiac output changes in this setting. It's also important to highlight that the gold-standard method by itself has limitations, as most of the mentioned studies point out and as it was also mentioned in this review.

Device	Level of invasiveness	Basic mechanism	Parameters measured	Specific indications	Limitations
Pulmonary artery catheter (PAC)	Invasive	- Indirect measurement of cardiac pressures - Distribution of an indicator in blood flow	- Direct right heart pressure - Indirect left heart pressures - PAOP	- Right heart disfunction [14] - Mixed shock states	- CI: Right heart endocarditis or presence of masses in right cardiac chambers [24] - Does not predict fluid responsiveness[25]
Transpulmonary thermodilution (TPTD)	Less invasive	Distribution of an indicator in blood flow	- CO - EVLW - PVPI - GEVDI - GEF	- Cardiac output measurement - Volumetric parameters assessment that may help guide fluid therapy (e.g EVLW in ARDS) [27,28]	- Only allows an intermittent assessment [12] - Volumetric parameters may be influenced by pulmonary embolism, pleural effusion or heart chambers dilatation
Pulse Contour Analysis (PCA)	Less invasive	Arterial waveform analysis	- PPV - SVV - SPV	- Allows a continuous evaluation of CO	- Spontaneous breathing [61] - Low V_T [56] - Arrhythmia - RH disfunction - Increased intra-abdominal pressure
Echocardiography	Non-invasive	Visualize heart anatomy and Doppler measurement	- Peak flow - VTI - IVC and SVC respiratory variation	- Cardiac output assessment - Evaluate cardiac function and anatomy	- Operator-dependent [48] - Does not provide a continuous assessment - Possibility of poor image resolution in certain pathologies
Bioimpedance and bioreactance	Non-invasive	Measures the changes in an electrical current crossing the thorax	- SVI - CI	- Continuous CO evaluation - Can be used in the presence of arrhythmias or in spontaneous breathing [53]	- Inconsistent results [52] - Can be affected by movement or temperature

Table 1. Indications and limitations of hemodynamic monitoring devices.

4. Discussion

Hemodynamic monitoring of the critically ill patient allows an early recognition and rapid intervention in potentially harmful situations. Among critically ill patients, only 50% of these patients will respond to fluid therapy.[8] In non-responders, volume expansion may worsen an overlying acute respiratory failure and aggravate tissue perfusion.

In the last decade, there has been a preference for less invasive monitoring devices, based on dynamic and functional parameters, compared to the classic static variables that used to be considered the standard of care in Intensive Care Units.[71] A variety of factors influence the selection of hemodynamic monitoring devices, namely the severity of the condition, right heart dysfunction or the presence of acute respiratory distress syndrome.[33] Even though the devices discussed in this review have been validated for specific conditions, there continues to be some uncertainty among clinicians on which methods are reliable and which should be used in each specific case. Regarding fluid therapy, a prospective observational study published in 2015 (FENICE study) concluded that clinicians still relied on static hemodynamic parameters, such as CVP, to predict fluid responsiveness.[72]

Currently available data suggest that PPV and SVV are the two indicators that present the highest accuracy to predict fluid responsiveness.[8] The extent of the SV variation proportionally reflects the increase in SV after volume expansion. As a result, these functional parameters are able to determine the patient's position in the Frank-Starling curve and estimate their response to fluid therapy.[58] In order to evaluate the patient hemodynamic status, it can be useful to associate echocardiography to the previously mentioned parameters, combining this heart function evaluation with a reliable fluid response predictor like PPV.[71] Furthermore, Doppler echocardiography also allows the assessment of other predictors such as VTI and aortic flow velocity.[46]

It's also important to highlight that, although the use of invasive devices such as the pulmonary artery catheter is gradually decreasing, this technique can be useful in certain patients. Patients with right ventricular dysfunction or mixed shock states may benefit from this technique. Since difficulty in the interpretation of the results is one of the

drawbacks of this device, training of intensivists is important to guarantee a correct use of the PAC.[73]

Besides measuring cardiac output, TPTD also allows the assessment of volumetric parameters, specially EVLW, that may help the clinician to decide whether or not to give fluids. Anticipating potentially harmful consequences of volume expansion, like pulmonary edema in patients with ARDS, can decrease the patient's need of mechanical ventilation and ICU length-of-stay.[28]

Limitations found in this review include that only a very small number of clinical studies comparing these hemodynamic monitoring devices were performed solely in patients with septic shock. Hence, most of the recommendations and studies found in databases are based on surgical patients.

Novel hemodynamic monitoring devices are constantly being invented, with an increasing interest in non-invasive, bed-side and continuous forms of monitoring fluid responsiveness.

The use of hemodynamic monitoring devices since the early phases of septic shock would probably prevent fluid overload that is known to worse the patient's outcome. However, depending on the clinical setting it may not be possible or practical to implement some of the invasive or even minimally invasive techniques mentioned in this review. The use of non-invasive devices in the emergency department could not only help guide fluid management, but also record dynamic parameters since the initial stages of shock. This would allow the assessment of the patient's fluid status evolution and identify any potential errors during the first contact with a hemodynamically unstable patient. For this to be possible, there would have to exist sufficient evidence that these devices can estimate cardiac output with enough accuracy compared to the gold-standard. Eventually, the creation of protocols of how to initially monitor a septic patient could be elaborated by each institution, depending on the available devices.

In conclusion, there is a need for larger and population-specific studies, that compare the accuracy of these hemodynamic monitoring devices exclusively in septic patients, in order for an evidence-based protocol to be designed.

5. Conclusion

Hemodynamic monitoring in septic shock is the starting point to provide the best treatment for each patient. Knowing the basic mechanisms of the available monitoring techniques helps guide the clinician to which devices to use in each specific case. This knowledge also prevents the misuse of devices in conditions in which they cannot be reliable.

Even though multiple studies have demonstrated the potential risks of fluid challenge after the initial phase of shock, this therapeutic trial continues to be applied in patients that often do not benefit from volume expansion. Awareness of clinicians to the use of feasible surrogates of fluid responsiveness may help resolve this issue.

6. References

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