

The Diagnosis and Hemodynamic Monitoring of Circulatory Shock: Current and Future Trends

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ABSTRACT

Circulatory shock is a complex clinical syndrome encompassing a group of conditions that can arise from different etiologies and presented by several different hemodynamic patterns. If not corrected, cell dysfunction, irreversible multiple organ insufficiency, and death may occur. The four basic types of shock, hypovolemic, cardiogenic, obstructive and distributive, have features similar to that of hemodynamic shock. It is therefore essential, when monitoring hemodynamic shock, to making accurate clinical assessments which will guide and dictate appropriate management therapy. The European Society of Intensive Care has recently made recommendations for monitoring hemodynamic shock. The present paper discusses the issues raised in the new statements, including individualization of blood pressure targets, prediction of fluid responsiveness, and the use of echocardiography as the first means during the initial evaluation of circulatory shock. Also, the place of more invasive hemodynamic monitoring techniques and future trends in hemodynamic and metabolic monitoring in circulatory shock, will be debated.

Keywords: circulatory shock, hemodynamic shock, transesophageal echocardiography, new statements, future trends

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INTRODUCTION

In 2006, a task force of twenty-five experts, and a eleven individuals representing The American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), Society of Critical Care Medicine (SCCM), and Société de Réanimation de Langue Française (SRLF), published basic guidelines dedicated to the hemodynamic management and treatment of patients with shock [1]. ESICM formed another task force of twelve experts, some of whom had been involved in formulating the 2006 guidelines, with the objective of updating the "Paris Consensus" by taking into account newer published evidence. Because such an exhaustive paper [2], is not published every year, some of its authors, together with other specialists in the field, release every two to three years, clinical reviews to update knowledge [3,4].

The ESICM asked the experts to answer five questions also addressed by the 2006 committee.

- What are the epidemiologic and pathophysiologic features of shock in an intensive care unit (ICU)?
- Should we monitor preload and fluid responsiveness in shock?
- How and when should we monitor stroke volume or cardiac output in shock?
- What markers of the regional and microcirculation can be monitored, and how can cellular function be assessed in shock?
- What is the evidence for using hemodynamic monitoring to direct therapy in shock?

DEFINITION AND PATHOPHYSIOLOGICAL FEATURES OF SHOCK IN THE ICU

According to ESICM (ESICMc-2014), circulatory shock is defined as an acute clinical life-threatening and generalized syndrome of acute circulatory failure associated with inadequate oxygen utilization by the

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cells [2]. Shock states are initiated by inadequate tissue perfusion resulting, in severe dysfunction of vital organs, a condition, which arises when the oxygen supply to the mitochondria is impaired. The result of all types of shock states is cellular dysoxia associated with elevated blood lactate levels. ESICMc-2014 indicated that the occurrence of hypotension is no longer mandatory in defining a shock state. Shock can occur following either hypoperfusion or inadequate perfusion of end organs leading to the loss of the physiological balance between oxygen delivery (DO₂) and oxygen consumption (VO₂) as well as being associated with elevated blood lactate values.

Four types of hemodynamic shock are recognized [5].

Hypovolemic shock: A direct loss of effective circulating blood volume (internal and/or external) which primarily leads to decreased cardiac preload, stroke volume and consequently impaired end-organ perfusion.

Cardiogenic shock: A decreased systemic circulatory blood flow due to an intrinsic defect in cardiac function either the heart muscle and/or valvular dysfunction.

Obstructive shock: Intra-cardiac or extra-cardiac mechanical obstruction to cardiac filling that decreases the cardiac output and consequently decreases end-organ perfusion.

Distributive shock: A peripheral vascular dilatation causing a decreased systemic vascular resistance (SVR) associated with increased cardiac output and compromised perfusion of vital organs.

However many patients with circulatory failure have a combination of more than one form of shock as is seen in cases of septic shock.

Sepsis previously was defined as a systemic inflammatory response syndrome (SIRS) in response to an infectious process, while septic shock is severe sepsis with persistent signs of end organ damage, hypotension (systolic blood pressure <90mmHg) and elevated serum lactate (>4mmol/l) [6].

Considering that there was a need to re-examine the classical definition of sepsis to distinguish sepsis from uncomplicated infection, ESICM and the Society of Critical Care Medicine (USA) published in February 2016, "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [6-8].

They redefined sepsis as "a life-threatening organ dysfunction caused by a dysregulated host response to infection". Hence, they advocated a change in the way sepsis and septic shock is approached, away from a focus on the

reaction to a systemic inflammation and towards a consideration of organ dysfunction,. The latter can be identified in ICU patients as an acute change in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score>2 points, subsequent to the infection [6-8].

According to Sepsis-3, septic shock is a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone (>40 % versus >10 %). The Sepsis-3 definition for the septic shock in adult patients is based on cumulative criteria: sepsis plus hypotension requiring the use of vasopressors to maintain MAP $\geq$ 65 mm Hg, plus elevated blood lactate levels > 2 mmol/L, persisting after adequate fluid resuscitation. Therefore, currently, septic shock is the only form of circulatory shock, which still requires the mandatory presence of hypotension as a definition criterion.

■ EPIDEMIOLOGICAL FEATURES OF SHOCK IN THE ICU

Shock affects about one third of patients admitted to an ICU [9]. According to a pan-European study which included 1,679 acutely ill patients (SOAP II), septic shock was the most frequent cause of shock, accounting for 62 % of cases, followed by cardiogenic shock 17 % and hypovolemia 16% [10]. In Septic shock, the reported mortality ranged between 40–50 %, and in some severe cases, the death rate was as high as 80% [11]. Septic shock is considered to be the tenth leading cause of death in the USA, estimated to claim 90,000 lives per year and its reported incidence in ICU patients varies between 6.3 and 14.7% [12]. The mortality rates are around 17.9% for sepsis, 28.6% for severe sepsis and higher than 40 % for septic shock [6,12,13].

Regarding cardiogenic shock, which is estimated to complicate 3-8% of cases of acute myocardial infarction, mortality historically approached 80%, and presently, despite medical advancements, the mortality is still as high as 40-70% [14,15].

Hemorrhagic Shock occurs in about 1 to 2% of trauma cases. Civilian data indicate that approximately 10% of traumatic deaths are preventable, and 16% of preventable deaths are due to hemorrhage [16].

■ DIAGNOSIS OF SHOCK

Patients should be assessed for the etiology of shock by an initial rapid clinical evaluation based on a history

taking, physical examination, and appropriate initial laboratory tests.

1. Clinical signs and bedside observations

In many cases with maintained arterial blood pressure, it is still possible to find markers of inadequate tissue perfusion such as increased blood lactate levels, low mixed venous oxygen saturation (SvO₂) or low central venous oxygen saturation (ScvO₂) values [17,18]. For this reason, hypotension was excluded from the mandatory definition of shock states, with the notable exception of septic shock [2,6-8]. On the other hand, some early clinical findings such as skin colour and skin temperature disturbances, heart rate, rhythm, electrocardiogram (ECG), capillary re-fill test, urine output, mental status, the effect of body position on the blood pressure, remain valuable signs of hemodynamic shock and pre-shock phases. Clinicians should always check for clinical signs of ineffective tissue perfusion take into account the three “windows” (1) skin (cutaneous perfusion) (2) kidney (urine output) and (3) brain (mental status)[2].

2. Metabolic markers of regional and microcirculation and the assessment of cellular function in shock

A shock state should be suspected if some of the above described clinical findings for shock are identified. The next recommended step is to measure arterial or venous blood lactate levels [2].

Hyperlactatemia: It has been known for more than 40 years, that a close relationship exists between hyperlactatemia and higher mortality and morbidity rates in shock patients. Hyperlactatemia is a marker of the imbalance between the oxygen consumption (VO₂) and oxygen delivery (DO₂) in acute circulatory failure states such as septic shock, obstructive shock, hypovolemic shock, and hypoxemia. It is a much more precise indicator of ineffective perfusion than a base deficit or metabolic acidosis, despite the fact that all of these parameters occur during the transition from aerobic to anaerobic metabolism[19]. In shock patients, hyperventilation and the administration of un-buffered or buffered electrolyte solutions, independently influence base deficit and therefore minimize changes in blood pH [14].

The new ESICMc-2014 report underlines the fact that blood lactate levels > 2mEq/L should be considered the hallmark of an existing shock syndrome [2,20]. Also, previous trials showed that the concomitant pres-

ence of hemodynamic shock plus hyperlactatemia > 4.0 mmol/L is associated with a mortality of 30% to 45% [12,19]. In ICU patients, in the absence of physical exertion, a blood lactate level > 6 mmol/l for more than four hours, confirms the diagnosis of ineffective perfusion and predicts a mortality range between 80% and 90% [18].

Obviously, the other circumstances associated with high lactate levels, are not all driven by ineffective global perfusion and such factors as local ineffective perfusion, drug effects, liver failure, malignancy, thiamine deficiency, seizures, or patients in bed struggling against restraints or shivering, have to be excluded.

Apart from blood lactate, SvO₂ or ScvO₂ values can offer valid information about the balance between DO₂ and VO₂. Low values, especially associated with hyperlactatemia, confirm inadequate oxygen transport [2]. Improvement in their values is used to indicate early therapy protocols but with non-uniform results [21]. In shock states associated with hyperlactatemia, because venous oxygen saturations do not correspond with local ineffective perfusion, high SvO₂ / ScvO₂ values are poor indicators as to whether or not DO₂ is adequate. The veno-arterial carbon dioxide difference ($\Delta v-a$ PCO₂) is another important metabolic marker, which relates to the adequacy of the blood flow and values > 6 mmHg suggest inadequate tissue perfusion [2].

■ THE HEMODYNAMIC MONITORING TECHNIQUES IN SHOCK

There are three main reasons for hemodynamic monitoring in shock patients:

1. To identify the type of shock
2. To select the most appropriate therapy
3. To evaluate the response to that therapy

■ WHAT INDICATORS CAN HEMODYNAMIC MONITORING PROVIDE TO IDENTIFY THE TYPE OF SHOCK?

In most cases of circulatory shock, invasive blood pressure measurement is required to measure both continuous arterial pressure and blood gas samples. The target value of mean arterial blood pressure (MAP) is at least 65mmHg and should be individualized, lower in uncontrolled bleeding source and higher in hypertensive patients or patients with clinical improvement under

these higher pressures [22]. A central venous catheter (CVC) is usually used for CVP measurement, ScvO₂ measurements, vasopressor and/or inotrope therapy administration. Evaluation of CO, cardiac function and preload is essential to identify the type of shock and can be obtained using different techniques and different monitoring devices.

Hemodynamic monitoring techniques have evolved enormously during the last twenty years due to a growing interest in the utilization of less invasive devices that could be substituted for pulmonary arterial catheterization (PAC). In comparison to PAC, some of those new minimally invasive technologies provide static volumetric parameters related to preload and intra-thoracic blood volume (ITBV) parameters related to flow; CO and SV, parameters related to organ function; cardiac power output (CPO), extravascular lung water (EVLW) and pulmonary vascular permeability index (PVPI), dynamic (functional) parameters related to fluid responsiveness; stroke volume variation (SVV) and pulse pressure variation (PPV).

Echocardiography uniquely offers essential information, about cardiac function and structure, in real time. It helps differentiate between different types of shock, and can be used to assess preload, fluid responsiveness, systolic, and cardiac diastolic function. It is the golden standard in the initial hemodynamic assessment of patients in circulatory shock and should be used as a complementary tool in invasively monitored patients [2-4].

■ HOW DO THE PARAMETERS PROVIDED BY HEMODYNAMIC MONITORING HELP TO SELECT AND EVALUATE THE THERAPY?

Treating the underlying cause of circulatory shock is the primary treatment objective. Fluid administration and pharmacological therapy with vasopressor or inotropes are used to maintain CO and improve organ perfusion while the underlying cause is corrected. ESICMc-2014 answered the following two important questions:

- How and when should we monitor SV or CO in shock?
- Should we monitor the preload and fluid responsiveness in shock?

The routine measurement of CO is recommended only in shock patients that do not respond to initial treatment because there is a need to evaluate, in a very

accurate manner, the response to fluid or inotropes [23]. Previous approaches were based mainly on the measurements of cardiac filling pressures (CVP, PCWP) and CO but these parameters cannot always discriminate with enough power, between different types of shock or certain combinations.

However, in non-responders to initial resuscitation, advanced hemodynamic techniques, such as PAC or trans-pulmonary thermodilution-TPTD, should be used to determine the type of shock. PAC does not only calculates CO through PTD but also measures the pressure values inside the right heart and pulmonary artery which make it useful especially in shock patients with pulmonary hypertension, ARDS or right ventricular failure.

TPTD techniques include PiCCO technology (Pulsion Medical Systems - Germany) and EV1000/volume view technology (Edwards Life sciences - USA). Both methods consist of an initial calibration by the TPTD method. The SV then is measured beat by beat, using a pulse contour analysis, through a thermistor tipped catheter inserted into a peripheral artery. The SV, CI, and CO measured by the two types of calibrated pulse contour technologies were shown to agree well with the values obtained with PAC [19-20]. Moreover, TPTD itself offers other critical volumetric parameters (GEDV, ITBV) and organ function parameters (EVLW, PVPI, and CPO). EVLW and PVI may be of extreme importance in pointing to correct fluid therapy in septic shock patients, ARDS and cardiogenic pulmonary edema [11,24]. Those systems are able to measure continuously relevant dynamic parameters of fluid responsiveness: SVV and PPV.

Studies in different patient population, investigating the hemodynamic parameters provided by those technologies as a means of influencing treatment therapy, showed promising outcomes [25-29]. Studies using those technologies in other types of shock are lacking.

Regarding the second question as to whether or not monitoring of the preload and fluid responsiveness in shock, should be undertaken, the new, guidelines recommended the usage of the dynamic parameters of fluid responsiveness (SVV, PPV, etc.) rather than the old static parameters of CVP, PCWP, GEDV, ITBV and left ventricular end-diastolic area measured by echocardiography (LVEDA), during attempts to predict CO response to fluid administration. In comparison with the European intensivists, American nephrologists adopted and recommended a much earlier use of dynamic

(functional) parameters to predict fluid responsiveness in patients at risk [30].

Today, there is evidence that both hypovolemia and hypervolemia are harmful [31-32]. Meantime, the only reason to administer fluid to a shock patient is to attempt to improve the patient's perfusion, namely to increase significantly SV or CO (> 10- 15 %) [32].

Until fifteen years ago most physicians thought the static pressure or volumetric parameters were reliable predictors of fluid responsiveness in patients. However, this approach neglected the reality that no static parameter can predict, with accuracy, the CO response to fluid load [33,34].

Many studies have proven that the approaches to fluid resuscitation, based on static parameters, lack a scientific basis and should be abandoned, as there is no threshold for the discrimination between responders and non-responders to volume administration [32,35-37].

In conclusion, if the problem is fluid resuscitation, functional hemodynamic monitoring using dynamic parameters would be the correct option, taking into consideration the limits to which patients should be sedated, paralyzed, mechanically ventilated, with sinus rhythm and closed chest, no severe pulmonary hypertension or severe right ventricular failure [38-41]. In mechanically ventilated patients, as well as in spontaneous breathing patients, other types of dynamic parameters can be employed, namely those obtained during a passive leg raising maneuver (PLR): direct measurements of the SV or CO variations, or measure-

ments of surrogates such as descending aortic blood flow changes [42,43].

In spontaneously breathing patients, beside the PLR technique, the reduction of the right atrial pressure (RAP) by at least one mmHg, during inspiration, also accurately predicts the CO response to fluid administration [44]. The main ten key messages and recommendations regarding the shock states (in authors' opinion) from the ESICMc-2014 and the Sepsis 3 are summarized in Table 1.

■ FUTURE TRENDS IN HEMODYNAMIC MONITORING:

1. Continuous transesophageal echocardiography

Within the past decade, echocardiography has proven to be an excellent alternative to invasive hemodynamic monitoring and ESICMc-2014 concluded that echocardiography is the preferred technique for initial evaluation as well as for sequential follow up. The effectiveness of echocardiography in assisting the hemodynamic management of patients during general anesthesia and its reliability to make a peri-operative diagnosis, is well established [45,46]. Moreover, many scientists consider that the SVC collapsibility index offered by Trans Esophageal Echocardiography (TEE), appears to be "the most reliable index of volume responsiveness" [3,4,47,48]. Unfortunately the relatively invasive nature of conventional TEE, the lack of continuity and the required long training period, have limited TEE use as a

Table 1. The ten most important key messages and recent recommendations regarding the diagnosis and the hemodynamic monitoring in circulatory shock

No.	Key message and recommendations
1.	The hypotension remains a mandatory definition criterion only for septic shock patients (together with the presence of sepsis and serum lactate > 2 mmol/L)
2.	Echocardiography is preferred for initial evaluation and can be used for sequential evaluation.
3.	Even in complex patients echocardiographic examination comes first, then PAC or TPTD to determine the type of shock.
4.	Serial measurements of blood lactate and SvO2 / ScvO2 / CO2-gap are recommended.
5.	Static parameters (CVP, PCWP, LVEDA, GEDV, ITBV) alone should not be used to guide fluid resuscitation.
6.	Use dynamic over static variables to predict fluid responsiveness.
7.	No routine use for PAC which should be used only in selected cases.
8.	No routine measuring of CO but in non-responders to the initial therapy, CO or SV should be measured to evaluate response to fluid or inotropes.
9.	It is not recommended to target absolute values of DO2 or absolute values of filling pressure or volume.
10.	Sequential evaluation of the hemodynamic status.

SvO2: mixed venous oxygen saturation, ScvO2: central venous oxygen saturation, CVP: central venous pressure, PCWP: pulmonary capillary wedge pressure, LVEDA: left ventricular end-diastolic area, GEDV: global end-diastolic volume, ITBV: intra thoracic blood volume, PAC: pulmonary artery catheter, TPTD: transpulmonarythermodilution, DO2: oxygen delivery.

hemodynamic monitoring tool [48]. The recent development of a mini-invasive, miniaturized, disposable, 2D monoplane TEE probe (ImaCor-USA), dedicated for continuous long term hemodynamic and cardiac function monitoring, is of interest. The system consists of an optimized ultrasound engine and the miniaturized TEE probe of 5.5 mm diameter, hemodynamic transesophageal echocardiography (hTEE), providing three primary cross-sectional views of the heart, i.e. short axis trans-gastric, mid-esophageal four chambers and superior vena cava views (Figure 1).

The main advantages of this device are its fast operation, easy manipulation, continuity of monitoring and no required extensive training [49,50], at the same time allowing direct visualization of cardiac performance and evaluating of the preload, the contractility, and the volume responsiveness (Table 2).

Several studies evaluated the capabilities of hTEE and its therapeutic impact on critically ill patients. The results showed that a short period of training (6 hours) allowed intensivists who previously had no training in TEE before the use of hTEE, could highlight the same hemodynamic disturbances as a trained cardiologist [48-50]. Regarding clinical use, hTEE usage was proven to have a direct therapeutic bearing in 50 - 66%

of the critically ill studied patients [50,51]. In cardiac surgical patients, hTEE was better able to identify critical circumstances than the classic hemodynamic techniques, in 66 % of cases [51-53].

2. Continuous lactate monitoring:

A new monitoring technology (Eirus – Maquet Germany) for continuous and simultaneous measurement of lactate and glucose at the patient's bed-side, was recently introduced into clinical use. This system uses a micro-dialysis technology that analyses blood samples without drawing blood. The ESICMc-2014 guidelines consider lactate to be the most important marker of ineffective perfusion and existing circulatory shock [2], and recommend serial measurements of blood lactate levels in all cases where shock is suspected, as well as in already documented shock states [2]. Early management of patients with hyperlactatemia, significantly reduces both the length of in-hospital stay and mortality in septic patients [18,54-56].

A lactate optimization strategy, as well as targeting CI, ITBV, EVLW and MAP in burn patients, was shown to avoid unnecessary fluid administration and provide adequate tissue perfusion at the same time [57].

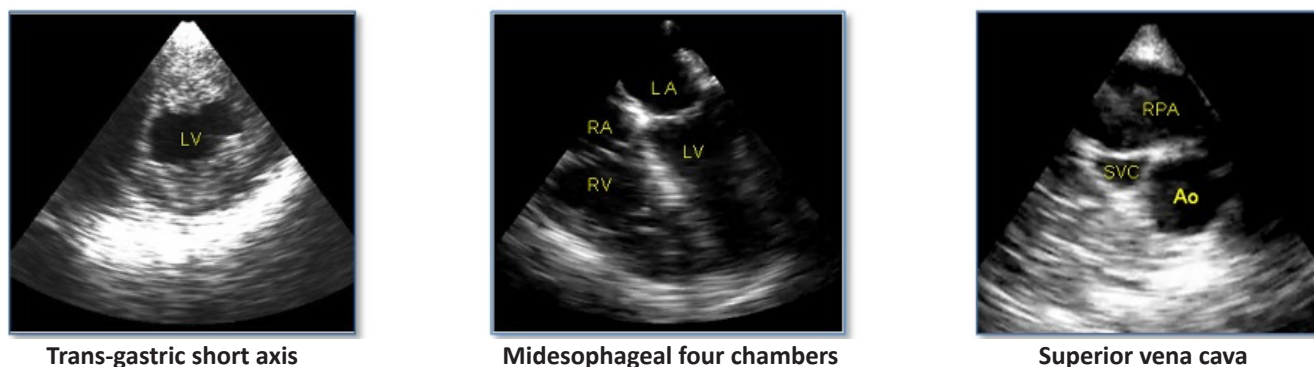


Fig. 1. The three main cross-sectional views with ImaCor – hemodynamic transesophageal echocardiography (h-TEE) probe.

LV: left ventricle, RA: right atrium, LA: left atrium, RV: right ventricle, RPA: right pulmonary artery, SVC: superior vena cava, Ao: aorta (ascending aorta)

Table 2. The hemodynamic assessment with with ImaCor – hemodynamic transesophageal echocardiography (h-TEE) probe

Transgastric short axis view	Midesophageal four chamber view	Superior vena cava view
Evaluates preload and contractility	Evaluates biventricular size and function	Evaluates volume responsiveness
Assess preload using left ventricular size.	Assess relative size of the right ventricle and left ventricle	Assess superior vena cava size and collapsibility
Measure the left ventricular end diastolic area	Right ventricular and left ventricular systolic function	
Assess left ventricular contractility by fractional area change (FAC) %	Shape and kinetics of inter-ventricular septum	

■ CONCLUSIONS

Based on the recommendations of the European Society of Intensive Care Medicine updated guidelines for monitoring hemodynamic shock, the following are considered to be of importance.

1. The superiority of the dynamic over the static parameters to predict fluid responsiveness.
2. Echocardiography is the preferred technical method for the initial diagnosis and follow-up of patient in hemodynamic shock
3. Blood lactate, ScvO₂ and CO₂ A-V gap is an important clinical bed-side biomarker during the follow-up of a patient in circulatory shock.
4. In the future, hemodynamic transesophageal echocardiography and continuous glucose and lactate monitoring may be considered necessary in taking management decisions for patients in hemodynamic shock.

■ CONFLICT OF INTEREST

Nothing to declare.

■ DISCLOSURE

This article is part of the Ph.D. thesis (Perioperative hemodynamic optimization in cardiovascular surgery).

■ REFERENCES

1. Antonelli M, Levy M, Andrews PJ, et al. Hemodynamic monitoring in shock and implications for management. *Intensive Care Med.* 2007;33:575-90.
2. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med.* 2014;40:1795-815.
3. Vincent JL, Rhodes A, Perel A, et al. Clinical review: Update on hemodynamic monitoring - a consensus of 16. *Crit Care.* 2011;15:229.
4. Vincent JL, Pelosi P, Pearse R, et al. Perioperative cardiovascular monitoring of high-risk patients: a consensus of 12. *Crit Care.* 2015;19:224.
5. Herget-Rosenthal S, Saner F, Chawla L S. Approach to hemodynamic shock and vasopressors. *J Am SocNephrol.* 2008;3:546-53.
6. Bone RC, Balk RA, Cerra FB, et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med.* 1992;20:864-74.
7. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315:801-10.
8. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315:775-87.
9. Finfer S, Vincent JL, De Backer D. Circulatory Shock. *N Engl J Med.* 2013;369:1726-34.
10. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis Occurrence in Acutely Ill Patients I. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med.* 2006;34:344-53.
11. Sakka SG, Klein M, Reinhart K, Meier-Hellmann A. Prognostic value of extravascular lung water in critically ill patients. *Chest.* 2002;122:2080-6.
12. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* 2003;348:1546-54.
13. Jawad I, Lukšić I, Rafnsson SB. Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality. *J Glob Health.* 2012;2:010404.
14. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-Year Trends (1975 to 2005) in the Magnitude of, Management of, and Hospital Death Rates Associated With Cardiogenic Shock in Patients With Acute Myocardial Infarction A Population-Based Perspective. *Circulation.* 2009;119:1211-9.
15. Awad HH, Anderson FA Jr, Gore JM, Goodman SG, Goldberg RJ. Cardiogenic shock complicating acute coronary syndromes: insights from the Global Registry of Acute Coronary Events. *Am Heart J.* 2012;163:963-71.
16. Kauvar DS, Wade CE. The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. *Crit Care.* 2005;9:S1-9.
17. Zenati MS, Billiar TR, Townsend RN, Peitzman AB, Harbrecht BG. A brief episode of hypotension increases mortality in critically ill trauma patients. *J Trauma.* 2002;53:232-6.
18. Rivers EP, Kruse JA, Jacobsen G, et al. The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. *Critical Care Medicine.* 2007;35:2016-24.
19. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med.* 2009;37:1670-7.
20. Wacharasint P, Nakada TA, Boyd JH, Russell JA, Walley KR. Normal-range blood lactate concentration in septic shock is prognostic and predictive. *Shock.* 2012;38:4-10.
21. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-77.
22. Rödig G, Prasser C, Keyl C, Liebold A, Hobbhahn J. Continuous cardiac output measurement: pulse contour analysis vs thermodilution technique in cardiac surgical patients. *Br J*

- Anaesth. 1999;82: 525-30.
23. Bendjelid K, Marx G, Kiefer N, et al. Performance of a new pulse contour method for continuous cardiac output monitoring: validation in critically ill patients. *Br J Anaesth*. 2013;aet116.
 24. Chung FT, Lin SM, Lin SY, Lin HC. Impact of extravascular lung water index on outcomes of severe sepsis patients in a medical intensive care unit. *Respir Med*. 2008;102:956-61.
 25. Michard F, Alaya S, Zarka V, Bahloul M, Richard C, Teboul JL. Global end-diastolic volume as an indicator of cardiac preload in patients with septic shock. *Chest*. 2003;124:1900-8.
 26. Spöhr F, Hettrich P, Bauer H, Haas U, Martin E, Böttiger BW. Comparison of two methods for enhanced continuous circulatory monitoring in patients with septic shock. *Intensive care med*. 2007;33:1805-10.
 27. Zhang Z, Xu X, Yao M, Chen H, Ni H, Fan H. Use of the PiCCO system in critically ill patients with septic shock and acute respiratory distress syndrome: a study protocol for a randomized controlled trial. *Trials*. 2013;14:1.
 28. Mirea L, Ungureanu R, Pavelescu D, Grintescu I. Global end-diastolic volume: a better indicator of cardiac preload in patients with septic shock. *Critical Care*. 2015;19:P179.
 29. Madhusudan P, Tirupakuzhi Vijayaraghavan BK, Cove ME. Fluid resuscitation in sepsis: reexamining the Paradigm. *Biomed Res Int*. 2014;2014:984082.
 30. KDIGO (2012) Clinical Practice Guideline for Acute Kidney Injury Section 2: AKI Definition. *Kidney Int Suppl* 2012;2:19–36.
 31. Cannesson M. Arterial pressure variation and goal-directed fluid therapy. *J Cardiothorac Vasc Anesth*. 2010;24:487-97.
 32. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest*. 2002;121:2000-8.
 33. Guyton AC, Jones CE, Coleman TG. *Circulatory physiology: cardiac output and its regulation*. Philadelphia: WB Saunders Company. 1973, pp.135-47.
 34. Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med*. 1998;26:1061-4.
 35. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med*. 2004;32:691-9.
 36. Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med*. 2007;35:64-8.
 37. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med*. 2013;41:1774-81.
 38. Perel A. Assessing fluid responsiveness by the systolic pressure variation in mechanically ventilated patients. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology*. 1998;89:1309-10.
 39. Berkenstadt H, Margalit N, Hadan M, et al. Stroke Volume Variation as a Predictor of Fluid Responsiveness in Patients Undergoing Brain Surgery. *Anesth Analg*. 2001;92:984-9.
 40. Preisman S, Kogan S, Berkenstadt H, Perel A. Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the Respiratory Systolic Variation Test and static preload indicators. *Br J Anaesth*. 2005;95:746-55.
 41. Biais M, Ehrmann S, Mari A, et al. Clinical relevance of pulse pressure variations for predicting fluid responsiveness in mechanically ventilated intensive care unit patients: the grey zone approach. *Crit Care*. 2014;18:587.
 42. Monnet X, Teboul JL. Passive leg rising. *Intensive Care Med*. 2008;34:659-63.
 43. Teboul JL, Monnet X. Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. *Curr Opin Crit Care*. 2008;14:334-9.
 44. Magder S, Georgiadis G, Cheong T. Respiratory variations in right atrial pressure predict the response to fluid challenge. *J Crit Care*. 1992;7:76-85.
 45. Reeves ST, Finley AC, Skubas NJ, et al. Basic perioperative transesophageal echocardiography examination: a consensus statement of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. *J Am Soc Echocardiogr*. 2013;26:443-56.
 46. Perrino ACJR, Harris SN, Luther MA. Intraoperative determination of cardiac output using multiplane transesophageal echocardiography: a comparison to thermodilution. *Anesthesiology*. 1998;89:350-7.
 47. Vieillard-Baron A, Chergui K, Rabiller A, et al. Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. *Intensive Care Med*. 2004;30:1734-9.
 48. Charron C, Caille V, Jardin F, Vieillard-Baron A. Echocardiographic measurement of fluid responsiveness. *Curr Opin Crit Care*. 2006;12:249-54.
 49. Cioccarl L, Baur HR, Berger D, Wiegand J, Takala J, Merz TM. Hemodynamic assessment of critically ill patients using a miniaturized transesophageal echocardiography probe. *Crit Care*. 2013;17:R121.
 50. Vieillard-Baron A, Slama M, Mayo P, et al. A pilot study on safety and clinical utility of a single-use 72-hour indwelling transesophageal echocardiography probe. *Intensive Care Med*. 2013;39:629-35.
 51. Cavarocchi NC, Pitcher HT, Yang Q, et al. Weaning of extracorporeal membrane oxygenation using continuous hemodynamic transesophageal echocardiography. *J Thorac Cardiovasc Surg*. 2013;146:1474-9.
 52. Maltais S, Costello WT, Billings FT, et al. Episodic monoplane transesophageal echocardiography impacts postoperative management of the cardiac surgery patient. *J Cardiothorac Vasc Anesth*. 2013;27:665-9.
 53. Krishnan S, Ngai J, Schlame M, Rabinowitz L. 276: Comparison of Htee and Swan-Ganz Catheter for the Evaluation of Volume Status in Patients Status Post AVR. *Crit Care Med*. 2012;40:1-328.
 54. Puskarich MA, Trzeciak S, Shapiro NI, et al. Whole blood lactate

- kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. *Chest*. 2013;143:1548-53.
55. Pölönen P, Ruokonen E, Hippeläinen M, Pöyhönen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesth Analg*. 2000;90:1052-9.
56. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303:739-46.
57. Sánchez M, García-de-Lorenzo A, Herrero E, et al. A protocol for resuscitation of severe burn patients guided by transpulmonarythermodilution and lactate levels: a 3-year prospective cohort study. *Crit Care*. 2013;17:R176.