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Hemodynamic monitoring in shock and implications for management

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Abstract *Objective:* Shock is a severe syndrome resulting in multiple organ dysfunction and a high mortality rate. The goal of this consensus statement is to provide recommendations regarding the monitoring and management of the critically ill patient with shock. *Methods:* An international consensus conference was held in April 2006 to develop recommendations for hemodynamic monitoring and implications for management of patients with shock. Evidence-based recommendations were developed, after conferring with experts and reviewing the pertinent literature, by a jury of 11 persons representing five critical care societies. *Data synthesis:* A total of 17 recommendations were developed to provide guidance to intensive care physicians monitoring and caring for the patient with shock. Topics addressed were as follows: (1) What are the epidemiologic and pathophysiologic features of shock in the ICU? (2) Should we monitor preload and fluid responsiveness in shock? (3) How and when should we monitor stroke volume or cardiac output in shock? (4) What markers of the regional and micro-circulation can be monitored, and how can cellular function be assessed in shock? (5) What is the evidence for using hemodynamic monitoring to direct therapy in shock? One of the most important recommendations was that hypotension is *not* required to define shock, and as a result, importance is assigned to the presence of inadequate tissue perfusion on physical examination. Given the current evidence, the only biomarker recommended for diagnosis or staging of shock is blood lactate. The jury also recommended against the routine use of (1) the pulmonary artery catheter in shock and (2) static preload measurements used alone to predict fluid responsiveness. *Conclusions:* This consensus statement provides 17 different recommenda-

tions pertaining to the monitoring and caring of patients with shock. There were some important questions that could not be fully addressed using an evidence-based approach, and areas needing further research were identified.

Keywords Shock · Hemodynamic monitoring · $ScvO_2$ · Lactate · Pulmonary artery catheter · Fluid responsiveness

Introduction

An international consensus conference (ICC) was held in Paris in April 2006 to develop guidelines for the hemodynamic management of patients with shock and implications for management. Developments in understanding of shock and mechanisms of cardiovascular and cellular failure in sepsis and the developments of new monitoring devices and techniques made a case for integration of all these new data and justified the ICC.

A jury of 11 persons representing five critical care societies attended the presentations of 25 experts in the field of shock (name and subjects are available on line as Electronic Supplementary Material). Experts were asked to address several specific questions posed by the conference organizers and scientific advisors. These included: (1) What are the epidemiologic and pathophysiologic features of shock in the intensive care unit (ICU)? (2) Should we monitor preload and fluid responsiveness in shock? (3) How and when should we monitor stroke volume or cardiac output in shock? (4) What markers of the regional and micro-circulation can be monitored, and how can cellular function be assessed in shock? (5) What is the evidence for using hemodynamic monitoring to direct therapy in shock?

Following the formal presentations, the jury met to review the pertinent literature. Jury members addressed and discussed each question, assigned a level recommendation (L1 or L2), and ranked the quality of evidence (QoE) as defined by the GRADE system [1]. The system classifies quality of evidence as high (grade A), moderate (grade B), low (grade C), or very low (grade D) according to factors that include the study methodology, the consistency and precision of the results, and the directness of the evidence. This quality of evidence reflects the confidence in research estimates of the true effects of an intervention. The GRADE system classifies recommendations as strong (L1) or weak (L2), according to the balance among benefits, risks, burden, and cost, and according to the quality of evidence. Keeping those components explicitly separate constitutes a crucial and defining feature of this grading system. One advance of the GRADE system is that it allows for strong recommendations in the setting of lower quality evidence.

This approach provides a framework for structured evaluation and can help to ensure that recommendations are made in a way that can be readily understood by clinicians.

Epidemiology

Septic shock

The majority of epidemiological studies in sepsis have focused on severe sepsis [2], although septic shock has been addressed in some of these studies. In the literature, the reported incidence of septic shock has varied between 6.3% and 14.7% of ICU admissions. The incidence of septic shock appears to be increasing [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14] and the accrued evidence indicates that it is a very common entity in the ICU.

Cardiogenic shock

The incidence of cardiogenic shock has been mostly studied in acute myocardial infarction. Over the past 20 years, the incidence of shock complicating acute myocardial infarction (AMI) has been relatively stable between 6% and 9% [15, 16, 17, 18, 19].

In the SHOCK trial, 18% of patients with cardiogenic shock as an immediate complication of AMI later developed a sepsis as indicated by leukocytosis, a positive culture (74%), or inappropriately low systemic vascular resistance [20]. The conclusion drawn from these data was that abnormal vasodilation – possibly secondary to activation of the proinflammatory cascade – could contribute to the initial clinical picture of shock.

Anaphylactic shock

Anaphylactic shock is considerably rarer and less fatal than either septic shock or cardiogenic shock [21, 22].

Burns, trauma and hemorrhage

The incidence of shock following burns, blunt or penetrating trauma has not been determined with the rigor of septic or cardiogenic shock, most likely because operationalizing definitions is difficult in this population. A study of trauma patients found the incidence of septic shock was 20.2% and shock without sepsis 9.3% [23].

Question 1: What are the epidemiologic and pathophysiologic features of shock in the ICU?

Rationale and evidence

Attempts to define hemodynamic instability in shock commonly mention the presence of specific clinical findings suggesting hypoperfusion [24]. For years, experts have proposed as an initial step in the evaluation of patients with shock a thorough physical examination with the attempt to identify clinical findings such as hypotension, tachycardia, altered mental status, delayed capillary refill, decreased urine output, and cooled skin and extremities. Such clinical findings form an integral part of many of the current definitions for different types of shock. Some of the clinical findings that are most commonly quoted as being useful are the presence of hypotension, delayed capillary refill, and temperature changes in the skin or extremities.

Shock results from poor tissue perfusion and oxygenation, with microcirculatory inadequacy to sustain tissue oxygen needs, leading to cellular dysoxia. This can be defined as ATP flux decreasing in proportion to oxygen availability, with preserved ATP demand.

In critically ill patients, tissue hypoxia is due to inadequate or disordered regional distribution of blood flow both between and within organs. Therefore, therapy in shock should be aimed, at least in part, at restoring an adequate organ perfusion pressure [25, 26]. Inadequate perfusion leads to the generation of lactate and hydrogen ions which spill over into the bloodstream, leading to the biological profile of lactic acidosis. Despite obvious limitations, the plasma level of lactate remains a good surrogate for inadequate tissue perfusion in shock. In particular, the progressive reduction of plasma lactate and correction of acidosis probably reflects the restoration of organ blood flow [27].

While the definition of shock developed through this consensus process is consistent with available data, the jury acknowledges that there is evidence that hypoperfusion or insufficient tissue oxygen delivery alone may not entirely account for the cellular dysfunction observed in septic shock. Mitochondrial dysfunction and other mechanisms may also be present [28, 29].

Is hypotension necessary for the diagnosis of shock?

Since the advent of the sphygmomanometer and the ability to measure blood pressure, low blood pressure has become synonymous with shock.

A systematic evaluation of physical findings in patients with hypovolemia evaluated the diagnostic accuracy for a systolic blood pressure below 95 mmHg in acute blood loss [30]. A random effects model produced a sensitivity of 13% for moderate blood loss and 33% for large blood loss. Therefore, a systolic blood pressure below 95 mmHg is not a sensitive measure for ruling out moderate or significant blood loss.

In septic shock definitions also have required the presence of hypotension for the diagnosis of shock. Rivers et al. demonstrated that aggressive and early goal-directed resuscitation can have a significant impact on patient outcomes [31]. This clinical trial evaluated patients with severe sepsis whose mean systolic blood pressure was above 100 mmHg at baseline, with a blood lactate > 4 mmol/l. Patients in both the control and treatment group had clear evidence of shock as measured by mean saturation of central venous oxygen ($ScvO_2$) of 49% and 48% respectively.

The definition of shock emerging from this consensus conference *does not require* the presence of hypotension. Instead, the definition of shock as "*failure to deliver and/or utilize adequate amounts of oxygen"* may include, but is not limited to, the presence of hypotension.

In this manuscript, shock is defined as circulatory and cellular dysfunction, manifested by markers of hypoperfusion such as elevated blood lactate, decreased $ScvO_2$ or SvO_2, with or without hypotension.

Mechanisms of cell injury due to low perfusion states

The basic mechanisms that underlie the development of cell, tissue and organ damage in shock syndromes depend in part on the duration and the severity of the injury.

The hypoxic cell is compromised in multiple ways [28, 29, 32, 33, 34, 35]. Cell energy metabolism is switched from aerobic to anaerobic glycolysis. This leads to the cellular accumulation of lactate, hydrogen ion and inorganic phosphates. Levels of ATP in the cell are decreased due to diminished synthesis, continued consumption and the actions of ATPase. Protein synthesis is compromised, resulting in mitochondrial damage.

Several injurious factors disrupt mitochondrial function, compromising electron transport and activating apoptosis [36, 37]. Increases in intracellular calcium activate intracellular enzymes which hasten the depletion of ATP stores and damage membrane and cytoskeleton proteins [38].

Jury recommendations

1. We recommend that shock be defined as a life-threatening, generalized maldistribution of blood flow resulting in failure to deliver and/or utilize adequate amounts of oxygen, leading to tissue dysoxia.
Level 1; QoE moderate (B)
2. We recommend that hypotension [SBP < 90 mmHg, SBP decrease of 40 mmHg from baseline, or mean arterial pressure (MAP) < 65 mmHg], while commonly present, should not be required to define shock. Shock

requires evidence of inadequate tissue perfusion on physical examination.
Level 1; QoE moderate (B)

3. In the absence of hypotension, when shock is suggested *by history and physical examination,* we recommend that a marker of inadequate perfusion be measured (decreased $ScvO_2$, SvO_2, increased blood lactate, increased base deficit, perfusion-related low pH).
Level 1; QoE moderate (B)

Systemic inflammatory responses associated with shock states

Shock states are associated with systemic inflammation either due to the primary insult (i.e. infection and septic shock) or as a secondary response to hemorrhage, hypovolemia or severe tissue injury. Leukocytosis, increased acute phase reactants (i.e. C-reactive protein), levels of inflammatory mediators (i.e. cytokines, chemokines) and biomarkers (soluble cytokine receptors, adhesion molecules, calcitonin precursors) can be detected in the blood of all patients in shock, although the magnitude of these responses varies among these shock states. Septic shock has higher levels of inflammatory markers (i.e. TNF, IL-6, calcitonin precursors) than either hemorrhagic or cardiogenic shock and elevated levels of some of the mediators are associated with increased mortality [39, 40, 41]. Traumatic-hemorrhagic shock has less dramatic increases in the levels of inflammatory mediators than septic shock and some are associated with morbidity and mortality [42, 43]. Cardiogenic shock is associated with systemic inflammation with elevated levels of IL-6 but low levels of TNF compared to either septic or hemorrhagic shock [39, 40, 41].

Although there are good animal and human data on the role of mediators in the evolution of shock, current outcome data do not support the routine use of these mediators as bio-markers in the diagnosis and staging of shock.

Jury recommendations

4. Apart from lactate and base deficit, current evidence does not support the routine use of bio-markers for diagnosis or staging of shock.
Level 1; QoE high (A)

Target for blood pressure in the management of shock

Aggressive fluid resuscitation should be avoided and hypotension tolerated in the trauma patients with penetrating injury, until bleeding is surgically stopped [44], whereas there are no guidelines for those with blunt trauma. In cardiogenic shock, no clinical studies have investigated the best level of blood pressure, but guidelines recommend systolic blood pressure at 100 mmHg in the patients with ST elevation [45]. There is evidence that a mean arterial pressure of 65 mmHg is sufficient in most septic shock patients [46, 47]. In conclusion, while the blood pressure is an easy and universal tool for monitoring the patients developing a shock state, there is a lack of data specifying its best level in shock patients.

Jury recommendation

5. We recommend a target blood pressure during initial shock resuscitation of:
For uncontrolled hemorrhage due to trauma: MAP of 40 mmHg until bleeding is surgically controlled.
Level 1; QoE moderate (B)
For traumatic brain injury (TBI) without systemic hemorrhage: MAP of 90 mmHg.
Level 1; QoE low(C)
***For all other shock states*: MAP $>$ 65 mmHg.**
Level 1; QoE moderate (B)

Question 2: Should we monitor preload and fluid responsiveness in shock?

Rationale and evidence

Preload, along with afterload and cardiac contractility, is an important determinant of cardiac output. Preload has been defined as the load present before contraction of the ventricle has started [48]. Ideally, in shock a clinician should be able to use a measure of preload to determine whether a patient requires additional fluids in order to increase cardiac output. Central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) are most commonly used to measure right and left ventricular preloads respectively. End-diastolic ventricular volumes are also used as assessments of preload, most commonly employing echocardiographic assessment. Each of these pressure and volume measurements has limitations.

Dynamic measures of assessing whether a patient requires additional fluid have been proposed in an effort to improve upon accuracy. The principle behind dynamic measures is that pleural pressure swings with ventilation will have an impact on venous return and subsequent cardiac output [49]. Since pleural pressure swings during positive pressure ventilation, the interpretation of dynamic measures will vary depending on the type and degree of ventilation the patient is receiving. For example during a positive pressure breath right ventricular filling might decrease as much as 20%–70% leading to a decrease in stroke volume, that can be amplified in hypovolemic conditions [50]. However, left ventricular output immedi-

ately increases as a result of the positive pressure forcing venous return from the lungs. This leads to an increase in the systolic blood pressure (SBP) termed delta up (Δup). Within moments there is a decrease in the SBP, termed delta down (Δdown), commensurate with the reduced right ventricular output. The sum of the Δup and the Δdown, which is the difference between the maximal and the minimal SBP values during one mechanical breath, is termed the systolic pressure variation (SPV). There are other dynamic measures of fluid responsiveness which take advantage of this physiology including: arterial pulse-pressure variation, respiratory systolic variation test, aortic flow variation, right atrial pressure changes and vena cava collapse or contraction [51, 52].

The need for additional fluid may also be evaluated by observing the response to a fluid challenge [53, 54]. After a rapid bolus of intravenous fluid or a straight-leg lift [55] (akin to a fluid load since venous return increases) cardiac output immediately increases in patients that are fluid responsive.

Despite the fact that current guidelines [56] as well as important clinical trials have used measures of preload to guide fluid resuscitation [57, 58], clinicians should be cautious when using such measures. Importantly, any measure of preload, particularly if it is a one-time measurement, should not be taken out of context of other variables and the overall clinical condition [52]. For example a normal individual with a normal vascular volume may have a very low CVP and not require additional fluid [58]. Likewise, some patients with high measures of preload may benefit from additional fluids. Thus changes in these parameters following interventions may be much more useful than a single measurement [53, 54, 59].

Unfortunately poor correlation between assessments of preload – whether pressures or volumes – and predictions of fluid responsiveness has been widely reported [50, 51]. For example, in normal healthy volunteers both CVP and PAOP are poor predictors of preload, cardiac performance or changes in cardiac performance following fluid loading in comparison to measurements of end-diastolic ventricular volumes [60]. End-diastolic ventricular volumes were also better measures of preload than CVP and PAOP in diverse groups of critically ill patients [61, 62, 63]. Nonetheless there may be clinical settings (such as cardiomyopathy, severe congestive heart failure or hypovolemia) where titration of therapy based on CVP and PAOP may be helpful [64]. In another study involving normal volunteers, improved cardiac output following volume loading did not correlate with changes in end-diastolic ventricular volumes [65]. Notably measurements of ventricular volumes are not always easy to obtain (especially on the right side of the heart), have associated costs, time delays and are operator dependent.

A number of studies have shown that in mechanically ventilated patients dynamic measures of fluid responsiveness are better predictors of fluid responsiveness than static parameters [66, 67, 68, 69, 70]. For example, a Δdown component of more than 5 mmHg was found to indicate that the SV index would increase in response to fluid challenge with positive and negative predictive values of 95% and 93% respectively [67]. Other dynamic parameters such as pulse pressure variation (PPV), stroke volume variation and the respiratory systolic variation test have proven to be good predictors of fluid responsiveness in sedated mechanically ventilated patients without spontaneous inspiratory efforts and in sinus rhythm [68, 71, 72].

Dynamic measures, however, have several limitations. Importantly, patients must be on fully controlled mechanical ventilation without spontaneous efforts, which is seldom the case in the majority of ICU patients. In addition, these parameters are affected by the magnitude of the employed tidal volume and the impact of changes to ventilatory parameters is uncertain. Finally, most of the evaluations involving dynamic measures have included relatively stable patients (post-cardiac surgery patients frequently being evaluated), and the extent to which these measures are useful in other potentially unstable populations is uncertain.

Pleural pressure swings during spontaneous breaths are in the opposite direction to those during positive pressure breathing, and hence proposed dynamic measures of fluid responsiveness are of less value. Notably, few studies evaluating measures of fluid responsiveness have specifically focused on the spontaneously breathing patient. Not surprisingly, the measurement of PPV had no predictive value in the subgroup of patients with spontaneous breathing activity [73]. However, reductions in right atrial pressures by at least 1 mmHg during a spontaneous inspiration (after short disconnection from the ventilator in those receiving mechanical ventilation) were shown to be a reasonable predictor of fluid responsiveness [54, 59].

Straight-leg raising (e.g. 45° elevation for 4 min while maintaining the trunk supine) results in an increase in right and left ventricular preload [73]. Such a test may help in predicting individual fluid responsiveness during spontaneous and positive pressure breaths while avoiding the hazards of unnecessary fluid loading [73, 74, 75].

Jury recommendations

6. We recommend that preload measurement alone not be used to predict fluid responsiveness.
Level 1; QoE moderate (B)

7. We recommend that in shock, low values of commonly used static measures of preload such as CVP, RAP, PAOP (for example less than 4 mmHg) and ventricular volumes, should lead to immediate fluid resuscitation with careful monitoring.
Level 1; QoE low (C)

8. We recommend a fluid challenge to predict fluid responsiveness. A fluid challenge consists of either immediate administration (for example 10–15 minutes) of 250 cc of crystalloid or colloid equivalent (eventually repeatable, if indicated) or a straight-leg raise with a goal of obtaining a rise in CVP of at least 2 mmHg. A positive response includes measures of improved cardiac function and tissue perfusion.
Level 1; QoE low (C)
9. We do not recommend the routine use of dynamic measures of fluid responsiveness (including but not limited to pulse pressure variation, aortic flow changes, systolic pressure variation, respiratory systolic variation test, and collapse of vena cava).
Level 1; QoE high (A)
There may be some advantage to these measurements in highly selected patients
Level 1; QoE moderate (B)

Research questions

1. Well-designed randomized controlled trials are required to compare static and dynamic measures of preload as predictors of fluid responsiveness in applicable populations of critically ill patients. Importantly, these should be tied to goal-directed interventions with clinically meaningful outcomes.

Question 3: How and when should we monitor stroke volume or cardiac output in shock?

Rationale and evidence

While cardiac output (CO) *can* be measured, that does not mean it should be measured routinely. Misuse of CO data may worsen outcomes [75]. Monitoring CO would only be of value *if* it guided therapies to improve patient outcomes.

In most patients, resuscitation commences with physical examination and estimation of CO and, in many, shock can be reversed using simple monitoring (e.g. physical examination, serial blood pressure measurements, urine output) and hypothesis-driven therapies (e.g. fluid loading) *without* need of further measurements or procedures.

In some patients shock persists after the first 30–120 min of resuscitation. In initial non-responders, knowledge of cardiac function *could* be useful to modify the resuscitation. For example, if the heart is adequately filled and heart function is poor, management concentrates on improving cardiac function (i.e. treat reversible lesions, β-agonist medications preferred over pure α-agonists). A second group in whom knowledge of cardiac function may be important is hypoxemic patients with signs of left or right heart failure (when excessive intravascular volume expansion may worsen oxygenation).

Perioperative "optimization" of CO and oxygen delivery may be associated with better outcomes in high-risk patients [76]. Pulmonary artery catheterization (PAC) is *not* associated with reduced mortality in critically ill patients [77]. There are no data to support that knowing or targeting CO affects shock patients' outcomes. Importantly, one study demonstrated higher mortality of patients treated with high doses of inotropes, with the goal of achieving supranormal CO/O_2 delivery [75]. While septic shock patients benefited from *early*, protocolized resuscitation that included augmentation of CO, it was not the target of resuscitation [31]. Thus this study does *not* support directly that knowing or targeting CO improves outcomes. Future studies are required to examine whether *early* CO-targeted management improves outcomes of patients with shock.

While awaiting such data, there may be a justification for measuring cardiac function to clarify mechanisms when shock does not reverse after initial therapies. It is plausible that the studies failed to demonstrate benefit [75, 76] because they focused on all critically ill patients, rather than refractory cases of shock. Lack of benefit could also have related to late initiation of PAC-guided, targeted therapy [79]. Most causes of cardiogenic shock are identified by history and physical examination. In cases that are initially unresponsive to treatment, cardiac dysfunction, either causing or contributing to shock, may require specific therapies that must be administered early, within a particular time after onset of symptoms, to be effective. These include coronary interventions for acute coronary syndrome, drainage of tamponade, and thrombolysis/mechanical extirpation of massive pulmonary embolus. In such cases of cardiogenic shock, knowledge of CO might be diagnostically and therapeutically useful.

Clinical bedside examination using capillary refill times, skin temperature, and pulse pressure have not been sufficiently precise and reproducible to estimate CO [79, 80]. While transthoracic echocardiography does not yet quantify CO precisely, it provides non-invasive qualitative assessment of right and left heart filling, contractility, valvular function, and pericardial disease [81]. When available and performed/interpreted correctly, it can identify cardiac contributions to shock, and allow early therapies. There are no studies to demonstrate that using echocardiography may improve outcome in shock patients. Nonetheless, due to potential benefits and negligible risk, transthoracic echocardiography can be considered when there is clinical evidence of ventricular failure and persistent shock, despite fluid resuscitation.

There are many quantitative methods of measuring CO. Because there is no "gold" reference standard, there are insufficient data to recommend any one method of quantifying CO over the other. The ICC examined studies that included at least some shock patients *and* Bland–Altman plots of newer techniques versus thermodilution (TD-CO) measurement. The operating characteristics of some newer

techniques demonstrate promising results in small numbers of shock patients [82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93]. Importantly, all techniques have limitations preventing use in some conditions and might be operator dependent. Several methods will be described briefly.

Pulmonary TD-CO employs a fluid bolus into the central veins while temperature is measured in the pulmonary artery. Transpulmonary TD-CO employs a fluid bolus into the central veins as temperature is measured in femoral or brachial arteries. These devices calculate CO using temperature–time decay curves.

Thirty-four patients with septic shock were enrolled in a study that compared standard thermodilution with transpulmonary thermodilution [82] and another six patients with septic shock were studied comparing pulmonary DT-CO with transcutaneous measurements of indocyanine green concentration [83]. These studies demonstrated similar operating characteristics (r = 0.97, bias 0.68 l/min, SD 0.62 l/min and r = 0.98, bias 0.73 l/min, SD 1.04 l/min, respectively).

Similar correlations were noted in 60 patients receiving liver transplantation ($R = 0.86$; bias = 0.13 l/min; SD 1.04 l/min) [84]. Nearly continuous TD-CO also demonstrated good correlation with intermittent TD-CO in six patients with septic shock ($R = 0.93$; bias-0.43 l/min, SD 0.71 l/min) [83]. Dye dilution measurement of CO has also correlated well with TD-CO, albeit in small numbers of patients [85, 86].

Arterial pulse *pressure* waveform analysis measures area under the systolic portion of the arterial pulse wave from the end of diastole to the end of systolic ejection. This value is adjusted using a calibration factor for individual impedance derived from transpulmonary TD-CO. In 517 measurements performed in 24 patients with shock, one device yielded CO measures similar to pulmonary TD-CO measures ($R = 0.89$; bias = 0.2 l/min; SD = 1.2 l/min) [87]. Another system using pulse *power* analysis to estimate CO, included some patients with shock, but precision data are not available for the shock sub-cohort [88]. Techniques using pulse pressure or pulse power analysis require frequent recalibration.

Studies of esophageal Doppler measurement of CO have also included some patients with shock (with R values less than 0.6) [89, 90]. A recent analysis of pooled patients, many of whom were not in shock, suggested a mean bias of esophageal Doppler of 0.19 l/min [91]. Esophageal Doppler-measured CO has not been studied well in patients with shock. Fick method CO was compared to TD-CO in 30 patients, some of whom had shock ($R = 0.82$; bias = -0.34; SD = 1.77 l/min) [92]. Electrical bioimpedance measures of CO also show promise, but data are unavailable in large populations with shock [93].

Jury recommendations

10. We do not recommend routine measurement of CO for patients with shock.
Level 1; QoE moderate (B)

11. We suggest considering echocardiography or measurement of CO for diagnosis in patients with clinical evidence of ventricular failure and persistent shock despite adequate fluid resuscitation.
Level 2 (weak); QoE moderate (B)

Research questions:

1. Well-conducted studies are needed to understand whether in patients with shock the management titrated to prespecified COs (e.g. normal), with or without a goal $ScvO_2$, improve outcomes.
2. Investigations are required to define the best methods to measure CO (if knowledge of CO is shown to impact outcomes).

Question 4: What markers of the regional and micro-circulation can be monitored and how can cellular function be assessed in shock?

Rationale and evidence

Conventional physiologic parameters, such as blood pressure and clinical indices of regional organ perfusion may be insensitive indicators of alterations in tissue perfusion and microcirculatory flow. Increased blood lactate concentration in shock is traditionally ascribed to anaerobic glycolysis related to inadequate oxygen delivery. In perfusion-related metabolic acidosis, base deficit reflects the amount of base (mmol) required to titrate 1 l of whole blood to a normal pH, assuming normal physiological values of PaO_2, $PaCO_2$ and temperature. The degree and duration of hyperlactacidemia, perfusion-related low pH, and base deficit have been correlated with the development of organ failure and a poor outcome [94, 95, 96, 97]. However, following restoration of normal arterial blood pressure, patients may still have significant maldistribution of blood flow in vital organs, a condition termed "cryptic shock". Increasing evidence indicates that inhomogeneity in the regional circulation and microcirculation plays a crucial role in the pathogenesis of organ dysfunction. Experimental work has shown that proinflammatory cytokines can induce heterogeneous microcirculatory abnormalities with changes in the activation state and shape of endothelial cells, alterations in vascular smooth muscle tone, activation of the clotting system and changes in red

and white blood cell deformability [98]. Measurements of regional [99, 100, 101] or micro-circulation [102, 103] are good predictors of outcome. Although the initial goal of hemodynamic resuscitation is restoring the macro-circulation, efforts directed at improving regional and micro-circulation might potentially result in improved outcome.

Methods that are currently available to monitor the regional circulation and oxygenation on the macroscopic level include tonometry, sublingual capnometry, laser Doppler flowmetry (mucosal perfusion), indocyanine green clearance and lidocaine metabolism. Techniques that monitor circulation on the microscopic level include orthogonal polarization spectral (OPS) imaging, intravital microscopy and near-infrared spectroscopy (NIRS). However, with the exception of tonometry and capnometry (and perhaps NIRS and OPS), these tools remain experimental and are not routinely used in clinical practice.

Serum lactate level and base deficit are useful measurements in patients with shock.

Lactate levels can be rapidly, and reliably measured using blood gas analyzers or hand held analyzers [104, 105, 106]. In experimental and clinical conditions, serum lactate levels are strongly associated with tissue hypoxia [107, 108]. Other factors related to critical illness may affect lactate levels and should be taken into account in interpreting results [109, 110, 111, 112, 113, 114, 115, 116, 117, 118]. Increased blood lactate levels and their failure to normalize blood lactate levels during treatment of shock have been associated with increased morbidity and mortality and can provide valuable clinical information [119, 120, 121]. Blow et al. found that early identification and aggressive resuscitation aimed at correcting persistent high serum lactate, improved survival and reduced morbidity in severe trauma patients [123]. Similarly, in patients with sepsis, trauma, and hemorrhage, base deficit is a useful guide to severity of illness and response to therapy [31, 97, 124]. However, similar to hyperlactatemia, low pH and base deficit are affected by non-hypoxic causes of metabolic acidosis, including renal and liver dysfunction, drug toxicity (e.g. cocaine), bicarbonate loss, hyperchloremia and hypothermia.

Until now only one randomized controlled single-center trial evaluated treatment intervention directed at correcting elevated lactate levels. This study showed a decrease in morbidity and hospital length of stay in post-cardiac surgery patients targeting oxygen delivery whenever lactate levels were increased or did not normalize [125]. Serial measurements of lactate levels might be useful to monitor response to treatment. To date, however, no randomized study investigated the clinical value of incorporating this parameter or base deficit in a *treatment protocol* of shock patients.

Alterations in regional circulation can be used to predict outcomes and monitor interventions

Several studies have demonstrated the prognostic value of gastric tonometry [99, 126]. Maynard et al. [127] studied 83 critically ill patients and demonstrated that a low gastric intramucosal pH (pHi), as determined by tonometry, predicted outcome with greater accuracy than conventional hemodynamic and metabolic variables. One study reported that gastric intramucosal acidosis in critically ill patients predicted multiple organ failure and death better than did systemic oxygen-derived variables or traditional markers of tissue oxygenation [101]. More recently [128], indocyanine green clearance and gastric tonometry were used to monitor regional perfusion during resuscitation in septic patients. In that study nonsurvivors had a lower indocyanine green clearance and higher gastric mucosal–arterial PCO_2gap than survivors despite normalization of mean arterial pressure, pulmonary artery occlusion pressure and oxygen delivery. Debate exists as to whether or not gastric tonometry requires blockade of H_2 receptors [129, 130]. Enteral feeding can interfere with the CO_2 measurements [131].

Sublingual capnography is a technically simple, noninvasive, inexpensive method that is not affected by changes in gastric pH, and appears to provide potentially useful prognostic information on adequacy of resuscitation. Weil and co-workers investigated the feasibility and predictive value of sublingual PCO_2 measurements as a noninvasive and early indicator of systemic perfusion failure. In a study of patients presenting to the emergency department in a variety of shock states, they found that sublingual capnography was useful in differentiating between patients with circulatory shock and elevated lactate and patients without shock and normal lactate [132]. In critically ill patients, sublingual PCO_2 and the gradient between sublingual and arterial PCO_2 correlate with gastric tonometry findings and are significantly higher in non-survivors [133, 134, 135].

Does manipulation of regional variables improves outcome?

Although monitoring of regional circulations is a useful prognostic indicator, the evidence that therapy guided by these tools may affect outcome is still sparse and limited to gastric tonometry. Gutierrez et al. [136] showed in a large randomized, multicenter study that the maintenance of normal gastric pHi was associated with an improved outcome in the subset of patients whose gastric pHi at baseline was equal to or greater than 7.35, while no effect was observed in patients with a low (< 7.35) gastric pHi at baseline. The majority of other prospective, randomized studies have failed to show a benefit of resuscitation directed by gastric tonometry [137, 138, 139].

Alterations in microcirculation can be used to predict outcomes and monitor interventions

The clinical introduction of new microcirculatory imaging techniques such as OPS and sidestream dark-field imaging [140, 141, 142] have allowed direct observation of the microcirculation at the bedside and given a unique insight to the maldistribution of tissue perfusion associated with shock [141, 142, 143]. De Backer [102], by OPS imaging of sublingual microvascular blood flow, found that the density of all vessels and proportion of perfused small vessels (diameter $\leq 20\,\mu m$) were significantly less in septic patients than in healthy controls or in patients without sepsis. In another series of patients with septic shock, Sakr et al. [103] evaluated longitudinally the microcirculation during shock and observed that capillary perfusion rapidly improved in survivors as opposed to non-survivors, whether they died during acute circulatory failure or from multiple organ failure after the resolution of shock. OPS was applied to the sublingual microcirculation [143], in order to study the distributive defects in septic shock and to evaluate the efficacy of nitroglycerine in recruiting shunted microcirculation. This investigation showed that vasodilatory therapy was effective in correcting microcirculatory shut-down, but pressure-guided resuscitation was not, even though effective in restoring blood pressure.

In summary, these imaging tools have confirmed in humans the existence of microcirculatory defects heretofore observed directly only in animal models. These techniques can be used to identify the response to various therapeutic interventions. However, whether interventions specifically aimed at correcting regional or microcirculatory variables may improve outcome is still not determined.

Jury recommendations:

12. We suggest serial measurements of lactates and/or base deficit as a predictor of outcome.
Level 2; QoE moderate (B)
13. We *do not recommend routine use* of gastric tonometry, sublingual capnography, orthogonal polarization spectral (OPS) imaging and other techniques to assess regional or micro-circulation.
Level 1; QoE (B)

Research questions:

1. Investigations are required to understand if monitoring of regional- and micro-circulation should be incorporated in the randomized studies of treatment intervention in patients with shock.

Question 5: What is the evidence for using hemodynamic monitoring to direct therapy in shock?

Rationale and evidence

Blood pressure

Few studies have explored the accuracy of measuring blood pressure indirectly by auscultation or palpation in patients with shock. Significant differences between direct and indirect blood pressure measurements are evident with systolic blood pressure being higher by direct measurements and when vascular resistance is high [144]. Although cuff blood pressure measurement lacks precision in shock states, it is difficult to argue against checking blood pressure by non-invasive means in the initial evaluation.

Skin temperature

Changes in skin temperature may assist in the assessment of suspected hypoperfusion [145]. The temperature of the great toe is correlated with cardiac index and has prognostic value [146]. In critically ill patients the temperature gradient between the toe and the ambient temperature serves as a predictor of outcome [147]. In cardiogenic shock, the toe–ambient temperature gradient had a stronger correlation with cardiac index, stroke index, and oxygen transport than transcutaneous oxygen tension [148]. Cool skin temperature was found to have a positive predictive value of 39% for hypoperfusion and a negative predictive value of 92% [149]. When combined with low HCO_3, these values increased to 98% and 97% respectively.

Studies have demonstrated that clinicians are poor at determining CO and pulmonary artery wedge pressure from physical examination [80, 150]. The absence of clinical findings consistent with pulmonary congestion in a patient is not sufficient to rule out the diagnosis of cardiogenic shock [151].

In summary, clinical examination is applicable to all patients with shock, is low risk and potentially high yield in information, but its sensitivity and specificity are low, when interpreted in isolation. The favorable risk and cost profile render the physical examination mandatory in all patients suspected of suffering from shock.

Jury recommendation:

14. a) We recommend frequent measurement of blood pressure and physical examination variables (including signs of hypoperfusion, urine output and mental status) in patients with a history and clinical findings suggestive of shock.

b) We recommend invasive blood pressure measurement in refractory shock.
Level 1; QoE very low (D)

PAC versus no PAC

Rationale and evidence

Following its introduction in the 1970s [152] the Pulmonary artery catheter (PAC) found widespread application in the ICU setting, despite the lack of formal evidence for usefulness [153]. Proponents argue that availability of CO and other hemodynamic variables enables improved diagnosis and management of circulatory instability. Critics emphasize complications associated with its use, inaccuracies in measurement and difficulties with data interpretation [154].

The ultimate test of any monitoring technology is whether its use results in improved outcomes for patients. This hypothesis can be tested in two ways by RCTs: by merely providing or not providing results to the clinician or by coupling the monitoring measurements with an explicit management strategy.

In a large prospective cohort study employing a propensity score to account for selection bias, Connors et al. found that patients receiving a PAC had a higher 30-day mortality, a higher mean cost of hospital stay and a longer length of stay in the ICU [154]. Mackirdy et al. reported similar results [155]. In non-cardiac surgery patients, Polanczyk reported a significant increase in cardiac complications in patients with a PAC [156]. Two recent papers refuted these results [157, 158]. In a retrospective cohort of patients with ARDS, Vieillard-Baron showed a higher crude mortality in patients monitored with a PAC, an effect which disappeared on adjustment for vasopressor therapy [159]; this was not a covariate in Connor's analysis [154].

Four recent large RCTs have been performed to analyze the effect of PAC on mortality and morbidity of critically ill patients [160, 161, 162, 163]. Rhodes et al. found no mortality difference, but a greater amount of fluid was administered to patients in the PAC group in the first 24 h and the incidence of acute renal failure and thrombocytopenia was greater at day 3 post-randomization [160]. No major complications were directly attributable to PAC insertion.

In a multi-center randomized trial, 676 patients with shock and/or ARDS were assigned to either receive a PAC or not [161]. The use of a PAC did not affect 28-day mortality or duration of stay in the ICU or hospital, although a trend towards reduced mortality with the use of PAC in larger centers was suggested. A recent randomized clinical trial by Harvey et al. confirmed these findings [162].

In one of the trials by the ARDS network, 1000 patients with ALI/ARDS were randomized to either PAC or CVC monitoring and then, in a factorial design, to a fluid-liberal or fluid-conservative goal-directed strategy [163]. No differences in mortality, time on ventilator, or time in the ICU were found between PAC and CVC.

A meta-analysis of the efficacy and safety of the PAC (13 RCTs; 5,051 patients) [77] included six studies designed in critical care without goal-directed therapy (GDT; three discussed above [160, 161, 162], one older study [164] and two small studies in perioperative patients [165, 166]. This meta-analysis confirmed that PAC per se neither increased overall mortality or days in hospital nor conferred benefit [77].

Jury recommendation:

15. We do not recommend the routine use of the pulmonary artery catheter for patients in shock.
Level 1; QoE high (A)

Early goal-directed therapy

Rationale and evidence

It is reasonable to hypothesize that more detailed monitoring of tissue hypoperfusion and interventions to increase tissue oxygenation might improve outcome.

Rivers et al. demonstrated in patients with severe sepsis or septic shock that early aggressive resuscitation guided by continuous $ScvO_2$, CVP, and MAP monitoring reduced 28-day mortality rates from 46.5% to 30.5% [31]. Patients were randomized to either early GDT or usual care. The early GDT group received more fluids, more frequent dobutamine, and more blood transfusion during the first 6 h. Faster and greater improvement of organ functions occurred in the GDT group.

Jury recommendation

16. We recommend instituting goal-directed therapy without delay, in patients presenting with septic shock (within 6 h or ideally less), particularly where $ScvO_2$ is below 70%
Level 1; QoE moderate (B)

PAC with GDT versus no PAC

Rationale and evidence

In observational cohorts of ICU patients, mortality, duration of ICU stay and cost of treatment were all significantly reduced in patients with 'supranormal' DO_2 values,

leading to the hypothesis that therapy guided by supranormal cardiac index (CI) and DO_2 values would achieve similar benefits.

Three RCTs assessing the effect of perioperative increases in DO_2 in high-risk surgical patients reported positive effects on mortality and morbidity [125, 167, 168, 169].

In critically ill patients, three RCTs comparing PAC with or without GDT to supranormal DO_2 found negative results [75, 76, 77, 78]. Gattinoni et al. randomly assigned 762 critically ill patients with a PAC to one of three groups: normal CI (control), increased CI group, and increased SvO_2 group [78]. At ICU discharge, mortality was 48.4% in the control group, 48.6% in the CI group and 52.1% in the SvO_2 group. The number of dysfunctional organs and the ICU length of stay were similar among survivors in the three groups. Similar results were observed in another study [169].

Potential deleterious effects of aggressive efforts to increase DO_2 were found in a study of 100 patients randomly assigned (when volume expansion failed to increase CI, DO_2 and oxygen consumption) to incremental dobutamine until all goals were achieved or to control group receiving PAC without GDT [75]. The in-hospital mortality was lower in the control group. The study has been criticized for the high dosage of dobutamine used.

The timing of the initiation of GDT in the natural history of shock appears important. Rivers enrolled patients within 1.5 h of their arrival at the emergency department [31]. In contrast, patients in the other studies were enrolled while in the ICU, often after substantial periods of time [75, 169].

No consensus exists for a standard GDT applied to critically ill ICU patients suffering from septic shock and/ or ARDS.

Jury recommendation

17. We *do not* recommend targeting supranormal oxygen delivery in patients with shock.
Level 1; QoE high (A)

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