Endpoints in resuscitation

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Purpose of review
Shock occurs bsecause of a failure to deliver adequate oxygen to meet the metabolic demands of the body resulting in metabolic acidosis, inflammation, and coagulopathy. Resuscitation is the process of treating shock in an attempt to restore normal physiology. Various hemodynamic, metabolic, and regional endpoints have been described to evaluate the degree of shock and guide resuscitation efforts. We will briefly describe these endpoints, and propose damage control resuscitation as an additional endpoint.

Recent findings
Serum lactate, base deficit, and pH are well established endpoints of resuscitation that provide valuable information when trended over time; however, a single value is inadequate to determine adequacy of resuscitation. Rapid normalization of central venous oxygen concentration has been associated with improved survival, and bedside transthoracic echocardiography can be a reliable assessment of volume status. In hypovolemic/hemorrhagic shock, early hypotensive, or controlled resuscitation strategies have been associated with improved survival, and hemostatic strategies guided by thrombelastography using a balanced transfusion approach result in improved hemostasis.

Summary
Numerous endpoints are available; however, no single endpoint is universally applicable. Damage control resuscitation strategies have demonstrated improved survival, hemostasis, and less early death from exsanguination, suggesting that hemorrhage control should be an additional endpoint in resuscitation.

Keywords
damage control resuscitation, endpoints in resuscitation, hemostatic resuscitation

INTRODUCTION

Our current understanding of shock stems from the work of Alfred Blalock, who concisely defined shock in 1936 as 'The work of recent years has shown that it is dependent on an inadequate supply of blood to the tissues, which may be brought about by the most diverse causes' [1]. Our fundamental understanding has not changed. The shock state can result from numerous insults – hypovolemic, hemorrhagic, cardiogenic, septic, and neurogenic; however, regardless of its cause, the final common pathway of shock is defined by failure to meet the metabolic demands of the body because of inadequate oxygen delivery (DO_2) or utilization [2].

Shock occurs because of inadequate tissue perfusion, and therefore, inadequate DO_2. The goal of resuscitation is to normalize physiology through the restoration of DO_2, most typically accomplished through volume loading to improve preload and cardiac output (CO), but also with medications and optimization of hemoglobin. There are numerous methods to help guide resuscitation efforts in the treatment of shock, known collectively as resuscitation endpoints. Resuscitation endpoints can be divided into three groups – metabolic, hemodynamic, and regional perfusion endpoints. The review will discuss each of these endpoints and the effectiveness of various resuscitation strategies. We also propose a fourth endpoint, damage control resuscitation, and hemostasis, in light of recent evidence.

Compensated versus uncompensated shock

To appreciate the need for well defined endpoints in resuscitation, a distinction between compensated and uncompensated shock is needed. We are typically confronted with hypovolemic/hemorrhagic

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KEY POINTS

- There are numerous hemodynamic, metabolic, and regional resuscitation endpoints available to clinicians; however, no single method is superior and a combination of approaches should be used.
- Damage control resuscitation and hemostasis should be considered a fourth endpoint in resuscitation.
- Additional serum protein markers have been proposed to assess shock.
- Bedside transthoracic echocardiography is a noninvasive adjunct in the assessment of shock and resuscitation.

shock in trauma surgery. The American College of Surgeon Advanced Trauma Life Support (ATLS) manual classifies shock into four stages based on straightforward physiologic parameters, including heart rate, blood pressure, mental status, and urine output [3]. However, their utility in the initial assessment of shock has been questioned [4▪], and these parameters alone are insufficient to define adequate resuscitation. Shock should be considered as a spectrum of physiologic derangements, from initial compensated shock to uncompensated shock. Conventional measures of shock, like those assessed in ATLS, are obviously deranged during uncompensated shock, providing easy targets to measure during the resuscitation process. However, in compensated shock, the cardiovascular system can maintain perfusion adequate to normalize these physiologic parameters. Despite normalization, ongoing tissue hypoxia may occur, leading to persistent acidosis and worsening shock. It is during this phase that improved endpoints must be established to help guide appropriate resuscitation and to prevent over-resuscitation, which is associated with increased mortality and acute lung injury.

HEMODYNAMIC ENDPOINTS

The balance between DO_2 and oxygen consumption (VO_2) dictates tissue oxygenation. The Fick equation defines these physiologic parameters as a function of hemoglobin concentration, cardiac function, arterial (SaO_2), and venous (S_vO_2) oxygen concentrations:

$$DO_2 = CI \times 1.34 \times Hb \times SaO_2$$

$$VO_2 = CI \times 1.34 \times Hb \times (SaO_2 - S_vO_2)$$

Hemodynamic endpoints in resuscitation are based upon this understanding.

Mean arterial pressure

Mean arterial pressure, defined as: [MAP = diastolic pressure + 1/3 (systolic pressure – diastolic pressure)], is a common endpoint used to guide resuscitation. However, the interaction between individual patient characteristics and preexisting disease states with injury is complex. Therefore, despite its widespread use, no uniform MAP goal exists. In traumatic shock, considerable evidence suggests that a delayed, or controlled resuscitation strategy with permissive hypotension may improve mortality. The benefits of hyporesuscitation are thought to be because of prevention of clot disruption of an effective thrombus leading to increased blood loss and fatal secondary hemorrhage. Further, room temperature crystalloid resuscitation leads to worsening hypothermia, acidosis, and coagulopathy [5–12]. Delayed resuscitation was described by Bickell *et al.* [13] who demonstrated a survival advantage in hypotensive penetrating torso trauma patients in whom resuscitation was delayed until hemorrhage, was controlled. In a follow-up, prospective randomized trial, this group demonstrated a reduction in early mortality and trend toward decreased overall mortality in hypotensive patients requiring emergency surgery for hemorrhage control [14]. Medics in the US military use a hypotensive resuscitation strategy for patients without traumatic brain injury. They are trained to administer a fluid bolus only when the radial pulse is absent or mental status is diminished [15]. Two recent studies have supported this approach to resuscitation. In a secondary analysis of the Prospective Observational Multicenter Massive Transfusion study, Hampton *et al.* [16▪] showed that an out-of-hospital crystalloid resuscitation of 700 ml was associated with improved survival compared with no resuscitation. In a prospective randomized trial of civilian trauma patients treated with crystalloid fluid in the prehospital setting, Schreiber *et al.* [17▪▪] demonstrated an early survival advantage among blunt trauma patients who received 250 ml fluid boluses to maintain a radial pulse or systolic blood pressure (SBP) > 70 mmHg compared with those patients who received an initial 2l fluid bolus with additional boluses to maintain a SBP > 110 mmHg.

Central venous pressure, pulmonary artery catheters, and pulse contour wave analysis

The goal of resuscitation is to restore DO_2. Hemoglobin and oxygen concentrations are relatively straightforward to manipulate and monitor; however, CO requires more attention. CO is largely determined by preload, which can be assessed using central venous pressure (CVP). CVP has been used

widely as a resuscitation target, with the 2012 Surviving Sepsis Guidelines recommending a goal CVP of 8–12 mmHg in the first 6 h of resuscitation for septic shock. Despite strong recommendations, CVP does not necessarily correlate well with actual intravascular volume or right ventricular volume, and can be altered in the presence of mechanical ventilation and pulmonary hypertension. Furthermore, recent randomized trials have not demonstrated a mortality benefit of early goal directed therapy in sepsis using specific CVP goals [18▪▪–20▪▪]. In addition, aggressive pursuit of specific CVP goals may actually lead to over-resuscitation and worsened patient outcomes. Therefore, CVP alone cannot be advocated as a global endpoint in resuscitation.

Pulmonary artery catheters (PACs), and the newer volumetric and oximetric PACs were developed to provide dynamic measures of intravascular volume status, cardiac performance, and to diagnose shock. Although these devices provide important data on cardiovascular status, they are associated with significant complications and do not improve survival [21–23]. Consequently, their use has decreased significantly, and it is felt that PACs should not be used routinely [24,25].

Less invasive techniques using the arterial pressure waveform have been developed to monitor CO. Pulse contour wave analysis requires arterial and central venous catheters placed on opposite sides of the diaphragm, and uses the thermodilution technique to measure hemodynamic values. Although these devices avoid the complications of PACs, and may better assess preload than CVP [26], their accuracy in measuring CO among critically ill medical patients has been questioned, and no randomized data exist [27▪].

Mixed and central venous oxygen saturation

Mixed venous oxygenation saturation (S_vO_2) and central venous oxygenation saturation ($S_{cv}O_2$) are representative of oxygenation extraction by tissue. S_vO_2 is measured using a PAC, and most accurately gives total body oxygenation extraction because it is a true mixed venous sample. $S_{cv}O_2$ is measured with a central line catheter, avoiding the need for a PAC; however, it is often higher than S_vO_2, since it is only measuring regional oxygen extraction. Although absolute values differ, trends between the two measurements generally correlate [28]. Based on the work of Rivers *et al.*, a goal $S_{cv}O_2$ of greater than 70% has become a part of the early goal-directed therapy recommendations in the Surviving Sepsis Campaign guidelines [29,30]. In a prospective observational trial, Hernandez *et al.* [31▪] demonstrated that rapid normalization of $S_{cv}O_2$ was associated with survival, further validating the utility of this measure as an endpoint in resuscitation.

Echocardiography

Transthoracic echocardiography (TTE) has gained popularity as a bedside tool to assess volume status and CO. Gunst *et al.* [32] have demonstrated that trauma surgeons with a moderate amount of training can reliably obtain estimates of cardiac index that correlate well with PAC measurements. Ferrada *et al.* [33] used TTE to define the inferior vena cava (IVC) as flat (<2 cm) in hypotensive surgical patients, which increased to fat (>2 cm) after a fluid bolus. Hypotension resolved in 97% of patients after this bolus. In a retrospective review of 148 bedside TTEs, this group demonstrated that a flat IVC on initial bedside TTE is associated with higher rates of ICU admission, transfusion requirements, and mortality among trauma and acute care surgery patients [34]. Finally, in a prospective randomized trial, they demonstrated that TTE could be used to successfully guide therapy in hypotensive trauma patients [35▪▪]. These data suggest that bedside TTE is a useful endpoint in resuscitation.

METABOLIC ENDPOINTS

Shock causes regional hypoxia because of impairment in DO_2. Anaerobic metabolism results in producing only two ATP molecules and pyruvate, rather than the 36 ATP molecules that are produced under aerobic conditions. Pyruvate is converted to lactic acid, causing worsening lactic acidosis as the shock state and prolonged severe tissue hypoperfusion persist (Fig. 1) [36]. Based on this physiology, metabolic endpoints can be measured to assess global tissue hypoxia and the systemic extent of shock.

Lactate

Lactate is the direct by product of systemic hypoperfusion. It is well established that initial lactate correlates with clinical outcome [37], further reinforced by a recent study in trauma patients that demonstrated a lactate level of 3.4 mmol/l or greater was predictive of inhospital mortality [38▪]. In multiple studies in trauma and surgical patients, prolonged time to lactate clearance (defined as lactate level < 2 mmol/l) has been associated with increased mortality, ranging from 42.5 to 86%, if not cleared within 48 h [39–41]. Lactate levels have been used to guide resuscitation. In a recent randomized trial, patients randomized to a lactate-guided resuscitation (10% or greater lactate

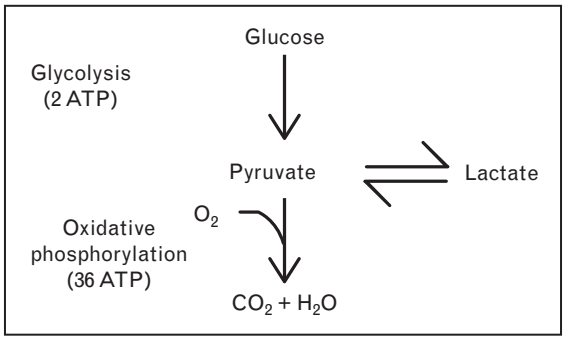

FIGURE 1. Glycolysis. Glucose is converted into pyruvate with the generation of two ATP. In the presence of oxygen, 36 ATP are produced during oxidative phosphorylation along with carbon dioxide and water. Under anaerobic conditions, oxidative phosphorylation cannot be performed, and pyruvate is converted into lactate [36].

clearance) versus $S_{cv}O_2$ guided strategy ($S_{cv}O_2 > 10\%$) in the emergency department demonstrated a 6% lower inhospital mortality [42]. In a randomized trial of patients with hyperlactemia in the medical ICU, a lactate-guided resuscitation (decrease lactate by 20% or more per 2 h for the initial 8 h of ICU stay) resulted in lower inhospital mortality, shorter ICU admission, and faster wean from mechanical ventilation versus the nonlactate-guided resuscitation group [43]. In sum, isolated serum lactate levels provide some prognostic information; however, lactate levels trended over time are more valuable. Data suggest that lactate may provide a useful resuscitation endpoint; however, specific lactate goals have not been defined.

Base deficit, pH

Base deficit (BD) provides a useful adjunct measure of tissue hypoperfusion and acidosis. It is defined as the amount of base required to raise 1 l of whole blood to a normal pH.

$$BD = -[(HCO_3) - 24.8 + (16.2 \times (pH - 7.4))]$$

Base deficit has been well defined by Davis *et al.* [44] according to severity: mild (2–5 mmol/l), moderate (6–14 mmol/l), or severe (>15 mmol/l). Worsening deficits directly correlated with the volume of crystalloid and blood replaced within the first 24 h. In a more recent retrospective review of more than 16 000 trauma patients, base deficit was classified into four categories, from <2 mmol/l to >10 mmol/l, with increasing classification linearly correlated to mortality, transfusion, and coagulopathy [45▪]. Base deficit is a superior measure of metabolic acidosis than pH, because of compensatory measures in place to maintain a normal pH and bicarbonate values, which may be affected by ventilatory status, is predictive of transfusion requirements and stratifies mortality among trauma patients [44,46,47]. Increased base deficit has been associated with numerous shock related complications, including renal failure, acute respiratory distress syndrome, multiorgan failure, and acute lung injury [46,48]. Base deficit values are influenced by hyperchloremic acidosis after isotonic saline administration, renal failure, diabetic ketoacidosis, and chronic carbon dioxide (CO_2) retention. In summary, base deficit is rapidly obtainable, has been well studied, and is superior to pH as a resuscitation end point; however, a single value alone cannot be used as an endpoint.

New metabolic markers

In addition to conventional metabolic measures of resuscitation, stress-related protein candidate measures have been proposed. In a recent double-blind prospective trial, arrival serum concentrations of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), heat shock protein 27 (HSP27), and soluble P-selectin (sP-selectin) were compared to SBP, base deficit, heart rate, shock index, and oxygen saturation (StO_2) in their ability to predict multiorgan dysfunction and death after injury from trauma. Each marker was comparable or better than currently used tests [49▪]. Although this study suggests that additional markers are on the horizon to assess the response to shock, these assays are not widely available and take time to perform.

Regional endpoints

Many techniques to evaluate global tissue microcirculation have been developed. Gastric tonometry and sublingual capnography have been evaluated as a means to estimate systemic acidosis and hypoperfusion by measuring pCO_2 concentrations in the gastrointestinal tract. Unfortunately, gastric tonometry does not correlate well with lactate or base deficit [50,51], and there are limited data to support the use of sublingual capnography relative to other resuscitation endpoints that have been discussed [52]. Near-infrared spectrometry (NIRS) is another technique, which can be used to measure peripheral StO_2 using a spectrometer placed on the thenar eminence of the hand. NIRS values have been shown to be significantly decreased among trauma patients with severe shock and have correlated well with base deficit (Fig. 2) [53,54]. However, other studies have failed to show a relationship between StO_2 and heart rate, MAP, and $S_{cv}O_2$ [55]. In light of these findings,

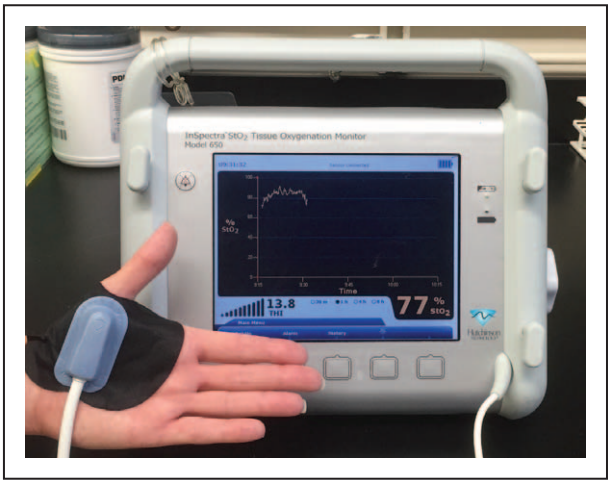

FIGURE 2. Near-infrared spectroscopy. Picture of near-infrared spectroscopy instrument with spectrometer placed on the thenar eminence of the hand used to measure StO_2. [InSpectra StO_2 Tissue Oxygenation Monitor (model 650), Hutchinson Technology, Inc, Hutchinson, Minnesota, USA].

these regional endpoints should not be used alone as measures of resuscitation.

HEMOSTATIC RESUSCITATION AND HEMORRHAGE CONTROL: A FOURTH ENDPOINT?

Recent efforts have focused on the concept of damage control resuscitation, defined as rapid hemorrhage control through early administration of blood products in a balanced ratio, prevention and correction of coagulopathy, and minimization of crystalloid fluids [56]. In hemorrhagic shock, ongoing bleeding perpetuates the shock state, so the rapid correction of coagulopathy and prompt resuscitation with blood products to replenish intravascular volume is essential. Studies to examine the optimal ratio of red blood cells, plasma, and platelets have been conducted. In 2013, the Prospective, Observational, Multicenter, Major Trauma Transfusion study group prospectively studied the timing and quantity of blood product transfusion in critically injured trauma patients [57▪▪]. They demonstrated that higher ratios plasma and platelets were associated with lower mortality in patients who received at least three units of blood products in the first 24 h after admission. In the Pragmatic, Randomized Optimal Platelet and Plasma Ratios study, severely injured trauma patients were prospectively randomized to receive plasma, platelets, and red blood cells in a 1 : 1 : 1 ratio compared with a 1 : 1 : 2 ratio [58▪▪]. The study demonstrated that patients randomized to the 1 : 1 : 1 group were less likely to die from exsanguination by 24 h; however, there was no significant difference in mortality between groups. The results of these studies suggest damage control resuscitation with early administration of a balanced ratio of blood products and hemorrhage control should be considered an endpoint of resuscitation.

Further focus on interventions to achieve hemostasis have been investigated, primarily using thrombelastogram (TEG) measurement. TEG was developed as a real time evaluation of clotting by measuring the viscoelastic properties of whole blood (Fig. 3) [59▪,60]. It has been used to guide resuscitation efforts

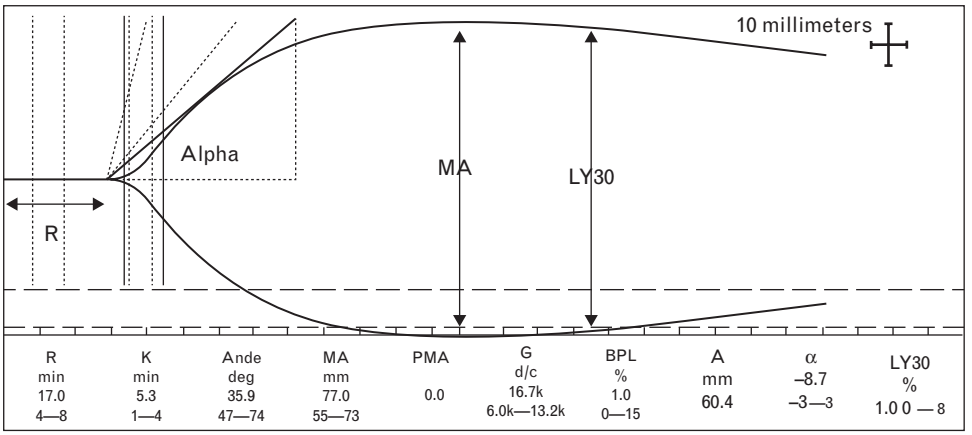

FIGURE 3. Thrombelastogram tracing. Representative thrombelastogram tracing (image used from original article by Van *et al.* [60]). *R* is the time (minutes) to initial fibrin formation and represents clotting factor activity. *K* is the elapsed time until the amplitude of the tracing reaches 20 mm (minutes) and represents a combination of soluble factor activity and fibrin cross-linking. Alpha angle (degrees), is the rate of clot strengthening, and primarily assesses fibrin cross-linking. Maximum amplitude, or MA (millimeters), of the tracing is the overall clot strength and primarily reflects platelet function. LY30 represents the degree of clot lysis at 30 min and assesses fibrinolysis. Coagulation index (CI) is a composite score representing a global assessment of coagulation, and can be calculated from the variables *R*, *K*, alpha angle, and MA.

in surgical patients in hemorrhagic shock, primarily in trauma, transplant, and cardiothoracic surgery. Recent efforts to define effective hemostatic strategies using TEG have been conducted, primarily focused on trauma-induced coagulopathy [61▪,62]. One driver of trauma-induced coagulopathy is hyperfibrinolysis [63–65]. Much enthusiasm has been generated to achieve hemostasis by countering hyperfibrinolysis with transexamic acid (TXA), an antifibrinolytic agent; however, there is a subgroup of patients who develop hypercoagulability after TXA administration [66]. Using TEG, Moore *et al.* [67▪▪] recently demonstrated that hyperfibrinolysis does not universally occur in trauma patients, and that some patients develop fibrinolysis shutdown, which is associated with increased mortality. They therefore caution that TXA should only be used in those with hyperfibrinolysis and may benefit from its use, and not in those with fibrinolysis shutdown. In a follow-up study, Moore *et al.* [68▪▪] demonstrated that plasma-based resuscitation strategies prevent tissue plasminogen activator-mediated hyperfibrinolysis. Given the evidence that damage control resuscitation, with early administration of blood products in a balanced ratio and prevention and correction of coagulopathy improve outcomes, and that TEG can be effectively used to guide these interventions, hemostasis should be considered an endpoint in resuscitation.

CONCLUSION

The final common endpoint in shock is diminished tissue oxygenation leading to anaerobic metabolism and metabolic acidosis. Although there are numerous ways to measure resuscitation in these patients, no one method is superior. Rather, a combination of approaches must be used based on patient factors and individual and institutional expertise. In trauma, hemorrhagic shock predominates. We therefore suggest a fourth end point in resuscitation – damage control resuscitation. Perhaps the most important approach to these patients includes efforts to achieve hemostasis using appropriate ratios of blood products early in the resuscitation period, as well as controlled resuscitation strategies with permissive hypotension that limit crystalloid infusion.

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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