Targeted resuscitation strategies after injury

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Purpose of review

The management of the traumatically injured patient has evolved during the past half century despite continually high morbidity and mortality rates. The management of the trauma victim requires timely intervention and damage control in an attempt to maintain normal hemodynamic parameters and adequate systemic perfusion. There is a fine balance between oxygen delivery and consumption, and when this is perturbed, oxygen debt may ensue. The presence of ongoing oxygen debt is rather deleterious, resulting in an inflammatory cascade that can lead to multisystem organ dysfunction. The rapid identification and restoration of oxygen debt are central to the resuscitation of the critically ill patient, be it the result of sepsis or trauma.

Recent findings

Resuscitation end points have evolved that allow the physician to more rapidly identify a perturbation between oxygen delivery and consumption. Moreover, end points allow uniformity in gauging the adequacy of resuscitation: preventing under- and overresuscitation and serving as a basis to compare outcome measures in resuscitation trials. Recent technologic advances have allowed a greater wealth of clinical data that can be obtained via less invasive means. Examples of this include esophageal Doppler monitoring, sublingual capnography, orthogonal polarization spectral imaging, and lithium dilution cardiac output determinations. These devices can be used in concert with more traditional resuscitation end points (*ie*, lactate and base deficit) to maximize oxygen delivery and correct tissue dysoxia. In addition, the management of hemorrhagic shock is continuing to evolve and challenge the dogmatic practices of normotensive resuscitation.

Summary

This review addresses (1) resuscitation end points to optimize cardiac function, (2) resuscitation end points to assess the microcirculation, (3) recent developments in the management of hypotensive hemorrhagic shock, and (4) the translation of early goal-directed therapy from septic shock to use in trauma. Past findings are reflected on and direction for future investigation and clinical practice based on recent clinical advances is provided.

Keywords

resuscitation end points, oxygen delivery, trauma, shock, monitoring, outcome

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Abbreviation

HSD   hypertonic saline dextran

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Introduction

Since 1963, when R. Adams Cowley first described the "golden hour" as it applies to the management of traumatically injured individuals, a great deal of a research and clinical advancement has occurred with regard to trauma resuscitation. To date, trauma remains a leading cause of mortality in the United States and the western hemisphere. In the United States, trauma is the fifth leading cause of mortality among all age groups and is the leading cause of mortality in the 15–44 age group [1]. In the absence of mortality, these figures do not include the lifelong disabilities to the patient and the burden to the family. Despite the advances of trauma center development and the implementation of Advanced Trauma Life Support Guidelines, physicians remain challenged to combat the sequelae of trauma.

The economic burden of trauma as a disease entity should not be taken lightly. In 2000, the total cost accrued in the United States as a result of motor vehicle collisions was $230.6 billion, which represents 2.3% of the gross domestic product [2]. According to the most recent 7th World Conference on Injury Prevention and Safety Promotion sponsored by the World Health Organization, violence-related injuries account for a tremendous financial burden to society with expenditures nearing 4% of the gross domestic product [3]. The continual development of trauma resuscitation strategies in terms of improved resuscitation end points and technologic advances in regard to monitoring devices and therapies are imperative to reduce mortality rates and the economic constraints of trauma care. This article provides an overview of resuscitation end points and monitoring modalities that are in use currently and the developing strategies that are geared toward improving trauma victim outcomes. Last, the resuscitation principles applied in septic shock share many commonalities with those of trauma victims; the application of early goal-directed therapy principles is discussed.

Shock and resuscitation: what we know today

Historically, the resuscitation of trauma patients was based on clinical findings, timely hemorrhage and damage control, and hemodynamic monitoring. Hemodynamic monitoring begins with the use of vitals signs where normalization of heart rate, blood pressure, and urine output are considered the initial or macro end points of resuscitation. Even hemodynamic monitoring presents one of the first challenges because, despite normalization of vital signs, a state of compensated shock may persist in a large cohort of patients [4]. Resuscitation end points have been identified in an attempt to better identify and treat patients in a state of compensated shock.

Shock, although a simplistic term, has a complex definition and has a long history in medicine. The definition of shock was not set forth until the 1800s when John Collins Warren called it a "momentary pause in the act of death" and Samuel D. Gross in 1872 called it a "rude unhinging on the machinery of life" [5]. The diagnosis of shock in an individual with overt hypotension and tachycardia is rather obvious. Complexities arise when conventional vital signs are normal but ongoing cellular damage continues; under these circumstances, a form of compensated shock is present. Shock is better defined as the presence of inadequate end-organ perfusion, which results in an imbalance of tissue oxygen delivery to meet the metabolic demands of the tissue. The inability to correct this hemodynamic perturbation results in an accumulation of tissue oxygen debt. The presence of ongoing oxygen debt has been associated with increased morbidity and mortality [6,7].

The pathogenic link from oxygen debt to organ dysfunction and death is complex and continues to evolve. Irrespective of the insult, tissue hypoxia is a potent stimulus to inflammation [8]. This hypoxic stimulus results in a humoral and cellular interaction with the endothelium. This endothelial disruption and its ensuing secondary injury is one of the first steps to organ dysfunction and mortality. Although the traumatic injury itself may stimulate inflammation through tissue injury and additional paralleling stimulus to inflammation, global tissue hypoxia accompanies this traumatic insult.

End points of resuscitation: diagnostic and therapeutic roadmaps to reversing tissue hypoxia

One of the intended goals of trauma resuscitation is to provide the metabolic substrates, *ie*, oxygen, to meet the consumptive demands of the tissues. The point at which these consumptive demands are met is called the critical oxygen delivery. Under ideal circumstances, the measurement of this critical delivery can be obtained using a pulmonary artery catheter but frequently the resuscitation is performed in the absence of this definitive procedure. Therefore, resuscitation end points are metabolic surrogates of meeting the critical oxygen delivery (Fig. 1).

The additional merits of using end points or resuscitation are to have uniformity of resuscitation terminology and uniformity of goals or end points that would avoid under- and overresuscitation and serve as a basis to compare outcome measures in resuscitation clinical trials. This will allow us to compare the methodologies and physiologic rationale for hypothesis generation and interpreting results.

Ultimately, resuscitation involves sending metabolic substrates to the heart using the heart as the organ of distribution. The heart is best used by manipulating preload, afterload, and contractility while minimizing heart rate, thereby maintaining adequate coronary perfusion pressure (Table 1). Systemic oxygen delivery or DO_2 (hemoglobin, oxygen saturation, and cardiac output) is increased until system oxygen consumption or VO_2 (all variables) is optimized. Adequate microcirculatory function is required to achieve VO_2 goals, thus tools such as the orthogonal polarization spectral and direct measurement of VO_2 are helpful in assessing these end points [9]. After meeting microcirculatory demands, the tissue response to these therapeutic manipulations can be ascertained by using metabolic end points such as lactate, base deficit, central venous or mixed venous oxygen saturation, gastric tonometry, and inflammatory mediators (Fig. 2). An overview of the various resuscitation end points and the devices currently available to monitor the adequacy of microcirculatory flow are depicted in Table 2.

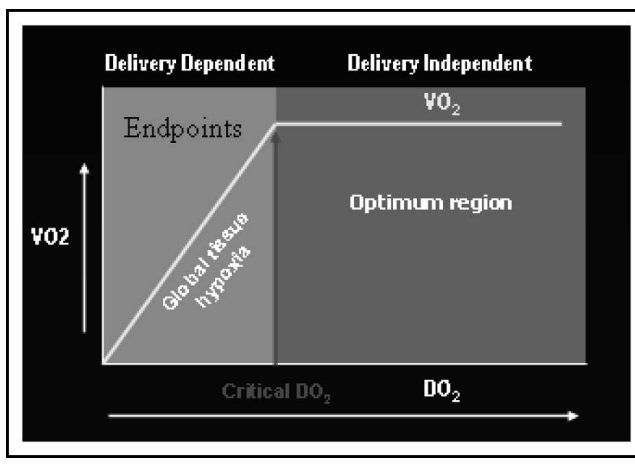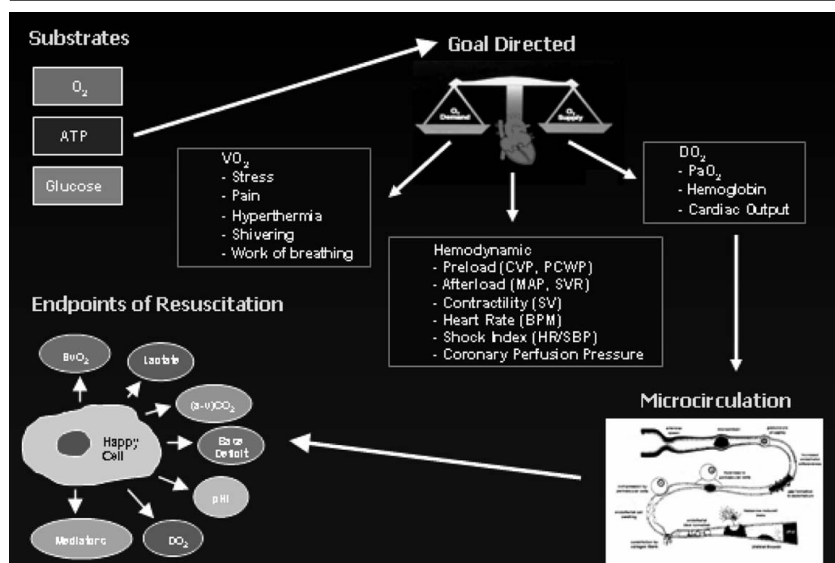**Figure 1. Relationship between oxygen delivery and consumption**

Table 1. Resuscitation end points aimed to optimize cardiac function

Modality	Review of current literature
Preload assessment	
Right ventricular ejection fraction (RVEDVI)	A new generation of thermodilution pulmonary artery catheters allows bedside determination of right ventricular function and calculation of the RVEDVI. Proven to be more reliable indicator of cardiac preload than cardiac filling pressures [10,11]. More reliable than wedge pressure during mechanical ventilation at all levels of positive end-expiratory pressure [12]. Improved outcomes and splanchnic perfusion when RVEDVI maintained $\geq$120 mL/m^2 [13,14].
Esophageal Doppler monitoring (EDM) (CardioQ, Deltex Medical Inc., Chichester, UK)	EDM measures blood flow in descending aorta via a probe inserted similarly to a nasogastric tube with a Doppler probe at the tip. Technique was first described in 1971 [15] and later refined by Singer *et al.* in 1989 [16]. Excellent correlation to thermodilution and Fick. EDM provides measurement of corrected flow time (FTc) as a measure of cardiac preload. Stronger correlation between FTc and cardiac output than wedge pressure [17,18].
Pulse contour analysis (Pulsion Medical, Munich, Germany	Continuous cardiac output derived from interpretation of arterial pressure waveform, which is proportional to stroke volume. Validated to cardiac output determined by thermodilution [19,20]. Pulse contour devices allow measurement of intrathoracic blood volume (ITBV), suggested to be a better indicator of cardiac preload than pulmonary arterial wedge pressure and central venous pressure [21–23].
Afterload	
Optimal blood pressure in penetrating trauma	The mainstay of present-day resuscitation from hemorrhagic shock is the rapid restoration of circulating blood volume. Controversy exists regarding this principle. Specifically, bleeding may be exacerbated as a result of a delusional coagulopathy and secondary clot disruption [24]. Stern *et al.* [74] in a hemorrhagic shock swine model demonstrated greater hemorrhage volumes and increased mortality in a group resuscitated to mean arterial pressure $\geq$80 mm Hg compared with hypotensive groups. Bickell *et al.* [25] evaluated the benefit of delayed fluid resuscitation compared with immediate resuscitation in hypotensive patients who sustained penetrating torso injuries. The survival rate was greater in the delayed resuscitation group (70% *vs* 62%, $P = 0.04$) and a trend to lower intraoperative blood loss compared with the immediate resuscitation group.
Contractility	
Pulse contour analysis (PCCO)	Besides preload assessment, PCCO can also measure cardiac output continuously. Buhre *et al.* [20] compared PCCO with thermodilution and showed high correlation ($r^2 = 0.88$) with mean bias of 0.003 L/min. In 26 patients undergoing cardiac surgery with either normal or diminished (<45%) ejection fractions, cardiac output determinations between PCCO and thermodilution were comparable [19]. However, bias increased after marked changes in systemic vascular resistance. Therefore, recalibration of the device is necessary, especially when changes in arterial pressure develop.
Lithium dilution cardiac output LiDCO) (LiDCO Ltd., London, UK)	A limitation of PCCO devices is need for calibration with cardiac output derived from another source (*ie*, pulmonary artery catheter). Lithium chloride is injected into the right atrium via a central venous catheter and is measured distally via a sensor attached to an arterial catheter. Cardiac output is derived from an equation using the area under the lithium-time dilution curve [26]. LiDCO correlates well with pulmonary artery thermodilution cardiac output measurements obtained through central venous [27] and peripheral venous injection [28]. In addition, no need for calibration with other sources.
Esophageal Doppler monitoring (EDM)	In addition to preload assessment (corrected flow time), continuous cardiac output can be obtained by measuring peak velocity. Cardiac output validated to thermodilution (see above). Proven benefit in reducing postoperative recovery times after major surgery [29,30] and in patients with sepsis [31]. In a canine model of hemorrhagic shock, EDM cardiac output accurately reflected the direction and magnitude of changes in cardiac output, most notably during massive hemorrhage [32].
Thoracic electrical bioimpedance (TEB) (BioZ, Cardiodynamics, San Diego, CA)	TEB is the electrical resistance of the thorax to high-frequency, very low voltage currents. Bioimpedance is inversely related to the thoracic fluid content, and cardiac output is derived from changes in impedance during the cardiac cycle. Numerous validation studies with various cardiac output determinations exist. Conclusions from a metaanalysis of 154 studies comparing TEB with thermodilution demonstrated utility and trend analysis but not accuracy for diagnostic interpretation; repeated measures correlation (r^2: 0.71, healthy; 0.59, cardiac; and 0.67, critically ill [33]. Notwithstanding, several studies have shown clinical utility of TEB monitoring in surgical and blunt trauma patients. Velmahos *et al.* [34] prospectively studied 134 blunt trauma victims shortly after admission to the emergency department and showed excellent correlation ($r = 0.83$, $P < 0.001$) to that of thermodilution CO measurements. Shoemaker *et al.* [35] prospectively studied 680 critically ill patients (trauma and nontrauma) with 2192 simultaneous bioimpedance and thermodilution cardiac output measurements. An excellent correlation ($r = 0.85$, $P < 0.001$) was evident, which led the authors to conclude that noninvasive systems may be acceptable alternatives when invasive monitoring is unavailable.
Heart rate	
Optimal heart rate	Oxygen delivery depends on arterial oxygen content, hemoglobin concentration, and heart rate. Maximizing heart rate will result in improved oxygen delivery. Optimal heart rate is between 60 and 100 bpm; however, excessive heart rates may be deleterious. A plateau effect of heart rate on cardiac output occurs at >110 bpm [36]. In cases of shock with heart rate >120 bpm, vasoactive agents should be reassessed to minimize the use of a β agonist.
Heart rate variability (HRV)	HRV is a technique that measures the heart rate beat-to-beat variability. The presence of substantial beat-to-beat variability appears to reflect a healthy interaction between the body's oscillators [37]. Used to predict morbidity and mortality in various conditions [39]. Pontet *et al.* [39] demonstrated that patients with reduced HRV on ICU admission were more likely to progress to multiorgan dysfunction. In addition, an association with illness severity and HRV in emergency department patients with sepsis has been demonstrated by Barnaby *et al.* [40].
Coronary perfusion pressure (CPP)	
Effects of heart rate on CPP	Optimal CPP > 60 mm Hg. Heart rate is coupled with perfusion pressure on a beat-to-beat basis [41].
Rate pressure product (RPP)	RPP = HR × SBP. Can be used to predict myocardial oxygen demand [42].

Figure 2. Resuscitation end points

BPM, beats per minute; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; PCWP, SBP, systolic blood pressure; SV, SVR.

Hemorrhagic shock: in search of the optimal resuscitation strategy

During the past half century, resuscitation of the patient with hemorrhagic shock involved rapid restoration of circulating blood volume in an attempt to maintain vital organ perfusion. A wealth of animal studies has led us to question this approach; restoration of normal blood pressure before definitive damage control has been associated with increased blood loss in swine [74,75], dogs [76], sheep [77], and rats [78]. Aggressive crystalloid infusion results in a dilution of red blood cells and clotting factors. The resulting coagulopathy in the presence of a normal blood pressure can dislodge the hemostatic clot and in turn further aggravate hemorrhage. Moreover, several animal trials have identified reduced oxygen delivery in the setting of normotensive resuscitation of hemorrhage shock [74,78].

Bickell *et al.* [25] compared the effects of immediate versus delayed fluid resuscitation in hypotensive patients following penetrating torso trauma. They demonstrated improved survival in the delayed resuscitation group (70%) compared with the immediate resuscitation group (70% *vs* 62%, *P* = 0.04) and a trend to less serious complications during hospitalization (23% *vs* 30%, *P* = no significance). Aggressive intravenous fluid administration has also resulted in the increased incidence of abdominal compartment syndrome with resultant multiorgan failure [47]. In addition, current resuscitation strategies may further aggravate inflammation that causes organ dysfunction. Lactated Ringer solution has been demonstrated to activate neutrophils during hemorrhagic shock [79,80]. Even more concerning is the observation that blood transfusions contain proinflammatory mediators that both prime and activate neutrophils [81–83]. In light of the various deleterious aspects associated with rapid

crystalloid and blood replacement, it appears wise to pursue an alternative resuscitation strategy. This revised strategy should focus on controlled hypotensive resuscitation along with the use of intravenous fluid adjuncts such as hypertonic saline and Ringer ethyl pyruvate until hemostasis is attained.

The ideal target blood pressure during resuscitation of hemorrhagic shock continues to be elusive. Although a wealth of studies have proven detrimental effects of resuscitation on normal blood pressure parameters, a controlled hypotensive resuscitation protocol needs further investigation. In 2002, Dutton *et al.* [84] expanded on the findings of the Houston investigators Bickell *et al.* [25] and compared two different fluid resuscitation protocols in patients with hemorrhagic shock (blunt or penetrating). Fluid administration was directed at maintaining a systolic blood pressure of 70 mm Hg versus >100 mm Hg. One hundred ten patients were enrolled and were well matched for anatomic injury, injury severity scores, and probability of survival based on the TRISS methodology. The authors concluded that there was no difference in mortality rates between the low and normal blood pressure resuscitation protocols. These results along with future investigation will better delineate appropriate blood pressure end points in both blunt and penetrating hemorrhagic shock.

Given the growing concerns regarding the safety of massive infusions of lactated Ringer solution, the search for other volume expanders has evolved. In 1980, a report by Velasco *et al.* [85] showed that a small volume of hypertonic saline was as effective as large-volume crystalloids in providing intravascular volume expansion during hemorrhagic shock. A metaanalysis of both hypertonic saline and hypertonic saline dextran (HSD) in the treatment of

Table 2. Assessment of the microcirculation

Modality	Review of current literature
Global perfusion end points	
Oxygen delivery (DO_2I)	The presence of ongoing oxygen debt is the result of an imbalance between oxygen delivery and oxygen consumption at the cellular level. Oxygen delivery (Do_2I) is a function of hemoglobin (Hgb), arterial oxygen saturation (Sao_2), and cardiac index (CI) and is represented mathematically as $Do_2 = CI \times 13.4 \times Hgb \times Sao_2$. Oxygen consumption ($Vo_2I$) is the difference in oxygen saturation between arterial and venous blood and is derived from, $Vo_2 = CI \times 13.4 \times Hgb \times (Sao_2 - Smvo_2)$. Shoemaker *et al.* [43–45] have championed supranormal Do_2I as a resuscitation end point. The premise is that oxygen debt would be repaid upon attaining predefined goals: $CI > 4.5$ L/min/m^2, $Do_2I > 600$ mL/min/m^2 and $Vo_2I > 170$ mL/min/m^2. Their efforts have conferred reduced morbidity and mortality rates in critically ill patients. Other investigators have been unable to replicate the results of Shoemaker *et al.* A metaanalysis by Heyland *et al.* [46] concluded that there is no significant reduction in mortality by use of supranormal end points. Resuscitation to supranormal may even be harmful, whereas an increased incidence of abdominal compartment syndrome was demonstrated by Balogh *et al.* [47].
Base deficit (BD)	Base deficit is the amount of base (mmol) required to titrate 1 L of whole blood to a normal pH, assuming normal physiologic values of Pao_2, $paco_2$ and temperature. Davis *et al.* [48] was the first to stratify BD into mild (2 to −5), moderate (−6 to 14), and severe (>−15) categories, which correlated with volumes of crystalloid infusion and blood replacement administered over the first 24 hours after injury. Rutherford *et al.* [49] concluded that BD was associated with increased mortality rates and is an "expedient and sensitive measure of both the degree and the duration of inadequate perfusion."
Lactate	Lactate accumulation is most notable under anaerobic conditions. Broder and Weil [50] demonstrated that critically ill patients with lactate >4 mmol/L had a survival rate of 11% [50]. The time to clear lactic acidosis and the absolute lactate level are both suitable resuscitation end points and reflect poor outcomes [51,52]. A portable lactate analyzer has been used among athletes and has shown excellent correlation to whole blood measurements ($r = 0.96$) [53].
Regional perfusion end points	
Gastric tonometry	Gastric tonometry takes advantage of the fact that the splanchnic vascular bed, as reflected by the gastric intramucosal pH(pHi), is the first to be affected during the onset of shock and is the last to be corrected after resuscitation [54]. The pHi decreases as splanchnic perfusion is reduced. However, pHi shows poor correlation with lactate and base deficit [55–57]. In addition, several limitations are noted: calibration time of 30–60 minutes and exogenous bicarbonate administration falsely elevates pHi.
Sublingual capnography	Use is based on the premise that inadequate global tissue perfusion is reflected by systemic hypercarbia. As an extension of gastric tonometry, the esophageal mucosa serves as an excellent site to measure Pco_2 [58]. Sublingual capnography is highly predictive of circulatory shock and correlates with increasing lactate levels [59]. Marik and Bankov [60•] demonstrated in 54 critically ill patients that the initial $Pslco_2$ and the $Pslco_2$–$Paco_2$ gradient were highly predictive of discriminating survivors from nonsurvivors.
Near-infrared spectroscopy (NIRS)	NIRS allows for the optimization of oxygen delivery and consumption specifically at the tissue level. Near-infrared light (700–1000 nm) readily penetrates skin, bone, muscle, and soft tissue where it is absorbed by oxygenated chromophores (hemoglobin, myoglobin, and cytochrome aa3 oxidase). Tissue oxygen saturation (Sto_2) is derived from a complex algorithm of the ratio of absorption between the individual chromophores. In large animal hemorrhagic shock models, skeletal muscle Sto_2) as determined by NIRS showed close correlation with measurements of systemic oxygen delivery [61] and was superior to that of lactate, base excess, or Svo_2 [62]. McKinley *et al.* [63] demonstrated changes in skeletal muscle Sto_2 to parallel Do_2I during the resuscitation of severely injured trauma patients.
Orthogonal polarization spectral (OPS) imaging (Cytoscan, Cytometrics, Exton, PA)	OPS imaging provides direct visualization of the microcirculation using the reflection of polarized light on hemoglobin molecules. De Backer *et al.* [64] was the first to report direct visualization of microvascular blood flow in critically ill patients. The density of sublingual vessels decreased significantly in patients with sepsis compared with controls (Figure 3). In addition, the proportion of perfused vessels also decreased with sepsis, most notably in the small vessels. The proportion of perfused vessels in total was higher in survivors than in nonsurvivors; an inverse relationship with lactate levels was also evident.
Mitochondrial function	
NIRS	NIRS also has the potential to simultaneously monitor the redox state of cytochrome aa3, which reflects mitochondrial oxygen consumption [65]. In 24 severely injured trauma patients, those who displayed early evidence of mitochondrial dysfunction during resuscitation were seven times more likely to develop multisystem organ failure. Simonson *et al.* [66] showed reduced oxidative capacity as identified by NIRS during sepsis.
Cytopathic hypoxia	Despite optimization of cardiac output and normalization of oxygen delivery, there is evidence to suggest that ongoing cellular hypoxia persists as a result of mitochondrial dysfunction resulting from cytopathic hypoxia [67]. The precise mechanism of cytopathic hypoxia is yet unknown; several different biochemical mechanisms have been postulated: diminished delivery of pyruvate into the mitochondrial tricarboxylic acid cycle [68], reversible inhibition of cytochrome aa3 by nitric oxide [69,70], irreversible inhibition of mitochondrial enzyme function by peroxynitrite [71], and depletion of cellular stores of nicotinamide adenine dinucleotide (NAD*/NADH) as a result of activation of poly(ADP-ribose) polymerase-1 [72,73].

hypotension associated with traumatic injury suggests that hypertonic saline is no better than isotonic crystalloids, but HSD may confer an improvement in mortality [86]. Subgroup analysis identified the greatest benefit with HSD in the setting of shock with concomitant severe closed head injury. A follow-up analysis by the same authors in the setting of penetrating trauma provided greater insight into the utility of HSD [87•]. Although no detrimental effects were associated with HSD compared with isotonic crystalloids among all patients, there was a significant treatment benefit in those requiring surgery. Survival was greater in the HSD group requiring operative repair compared to the conventional treatment group (84.5% *vs* 67.1%, *P* = 0.01).

A further benefit in the use of hypertonic solutions is the diminished inflammatory response that is evident with the use of hypertonic saline [88–90] and HSD [91,92]. Another intravenous fluid with immunomodulatory effects is Ringer ethyl pyruvate solution. Reactive oxygen species have been implicated as important mediators in a variety of conditions, including hemorrhagic shock [93,94] and ischemia/reperfusion injury [95,96]. Ringer ethyl pyruvate solution has been found to reduce structural and functional damage after mesenteric ischemia/reperfusion in rats [97,98]. In addition, Ringer ethyl pyruvate solution has been associated with improved survival compared with conventional isotonic fluids during hemorrhagic shock [99] and endotoxemia [100,101]. Further investigation is warranted in the management of hemorrhagic shock, sepsis and ischemia/reperfusion injury.

There is clearly an ongoing evolution in the management of hypotensive hemorrhagic shock. In spite of continued reviews and metaanalyses that suggest crystalloid are superior to colloids in trauma, in a recent large randomized trial, no outcome difference in trauma patients were noted except that albumin increases mortality when trauma is accompanied by head injury Future therapies will likely involve a multifaceted approach, one that focuses on controlled hemorrhage in combination with volume expanders such HSD. In addition, the impact of proinflammatory mediators during hemorrhagic shock must not be overlooked and strategies that impede the generation of inflammatory mediators such as REPS are promising.

Building the bridge between research and improved trauma outcomes: a case for goal-directed therapy

End points of resuscitation will continue to evolve as the science and technology advances. However, at some point, the translation from bench to beside has to occur and this involves clinical utility or reducing these concepts to practice. Therefore, the best resuscitation end points will be those that have an ease of use and readily obtained and interpretable although used across a variety of clinical settings such as the emergency department, operating room, and the ICU. These end points must be used in an appropriately defined patient population so as to allow a uniformity of resuscitation terminology and goals that would avoid under- and overresuscitation and serve as a basis to compare outcome measures in resuscitation clinical trials. This will allow us to compare the methodologies and physiologic rationale for hypothesis generation and interpreting results. In doing this, we will avoid the pitfalls and controversies that have surrounded the instruments of resuscitation science such as the pulmonary artery catheter.

End points of resuscitation are thus part of a road map to restore tissue normoxia, and this requires coordinated

Figure 3. Orthogonal polarization spectral videomicroscope image of sublingual mucosa in a healthy individual (A) and a patient with sepsis (B)

Courtesy De Backer, 2002 [64].

Figure 4. Early goal-directed therapy for sepsis, study design (A) and early goal-directed therapy resuscitation protocol (B)
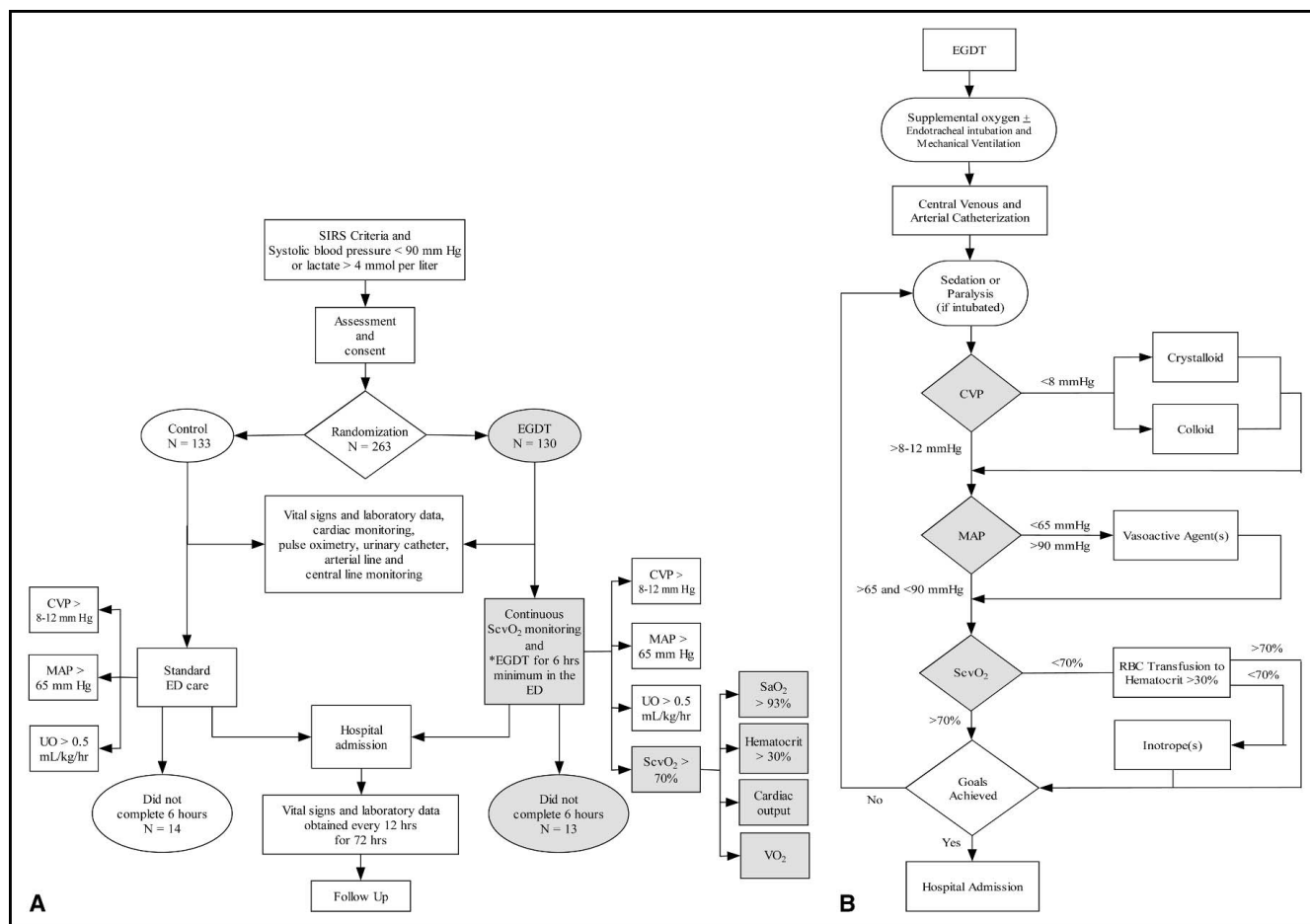
CVP, central venous pressure; ED, emergency department; EGDT, early goal-directed therapy; MAP, mean arterial pressure; RBC, red blood cell; SIRS, UO, urine output.

adjustment of a sequence of variables to meet this goal. However, goal-directed resuscitation in critical illness has been a controversial topic to say the least. Is one end point superior over another or is it the timing of the resuscitation? Examining these resuscitation studies by metaanalysis reveals that a common theme seen in those studies with improved mortality is early resuscitation in high-risk patients and patients with evidence of global tissue hypoxia.

The concept of goal-directed therapy has been extended to medical and surgical patients presenting with severe sepsis and septic shock with significant reductions in morbidity, mortality, and health care resource consumption [102]. In this prospective, randomized, placebo-controlled, blinded (ICU clinicians were blinded to randomization) study by Rivers *et al.*, patients presenting with clinical evidence of infection with a mean arterial pressure <90 mm Hg after 20–40 mL/kg volume challenge or a lactate level >4 mmol/L were given an early goal-directed protocol for 6 hours at the most proximal aspect

of the hospital presentation, the emergency department, before operative or ICU intervention. The protocol is outlined in Figures 3b and 4a.

This study showed significantly reduced inpatient mortality (30.5% *vs* 46.5%, *P* = 0.009). Over 6 to 72 hours, patients who received early goal-directed therapy had a significantly higher mean central venous oxygen saturation (70.4% ± 10.7% *vs* 65.3% ± 11.4%), lower lactate (3.0 ± 4.4 mmol/L *vs* 3.9 ± 4.4 mmol/L), lower base deficit (2.0 ± 6.6 mEq/L *vs* 5.1 ± 6.7 mEq/L), and higher pH (7.40 ± 0.12 *vs* 7.36 ± 0.12) (all *P* ≤0.02). Similarly, over the same period, mean APACHE II (13.0 ± 6.3 *vs* 15.9 ± 6.4), SAPS II (36.9 ± 11.3 *vs* 42.6 ± 11.5), and MODS (5.1 ± 3.9 *vs* 6.4 ± 4.0) were significantly lower in the early goal-directed therapy versus control group (all *P* < 0.001). However, among patients surviving to hospital discharge, the control group had a significantly longer hospital length of stay (18.4 ± 15.0 days *vs* 14.6 ± 14.5 days, *P* = 0.04). There is evidence that this protocol-based study may extend to patients after injury because similar results

have been seen when applied to trauma patients and patients after cardiothoracic surgery.

Conclusion

Targeted resuscitation strategies after injury comprise early identification of high-risk patients and the use of resuscitation end points as a road map to apply therapies in a goal-directed fashion to establish tissue normoxia. The tools used to obtain these end points and guide therapy are subject to user variability (knowledge), which gives rise to inconsistent outcome studies. Recent goal-directed trials that address these issues are showing more positive outcomes, which adds an exciting page to this new chapter of resuscitation research.

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