CLINICAL PRACTICE GUIDELINE: ENDPOINTS OF RESUSCITATION

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I. STATEMENT OF THE PROBLEM

Severely injured trauma victims are at high risk of development of the multiple organ dysfunction syndrome (MODS) or death. To maximize chances for survival, treatment priorities must focus on resuscitation from shock (defined as inadequate tissue oxygenation to meet tissue O_2 requirements), including appropriate fluid resuscitation and rapid hemostasis. Inadequate tissue oxygenation leads to anaerobic metabolism and resultant tissue acidosis. The depth and duration of shock leads to a cumulative oxygen debt (1). Resuscitation is complete when the oxygen debt has been repaid, tissue acidosis eliminated, and normal aerobic metabolism restored in all tissue beds. Many patients may appear to be adequately resuscitated based on normalization of vital signs, but have occult hypoperfusion and ongoing tissue acidosis (compensated shock), which may lead to organ dysfunction and death. Use of the endpoints discussed in this guideline may allow early detection and reversal of this state.

Without doubt, resuscitation from hemorrhagic shock is impossible without hemostasis. Fluid resuscitation strategies prior to obtaining hemostasis in patients with uncontrolled hemorrhage, usually victims of penetrating trauma, remain controversial. No fluid resuscitation may lead to death from exsanguination, whereas aggressive fluid resuscitation may "pop the clot" and lead to more bleeding. "Limited", "hypotensive", and/or "delayed" fluid resuscitation may be beneficial, but clinical trials have yielded conflicting results (2,3). This clinical practice guideline will focus on resuscitation after achieving hemostasis and will not address the issue of uncontrolled hemorrhage further.

The traditional markers of "successful" resuscitation, including restoration of normal blood pressure, heart rate, and urine output, remain the standard of care per the Advanced Trauma Life Support Course (4). When these parameters remain abnormal, i.e., uncompensated shock, the need for additional resuscitation is clear. After normalizing these parameters, up to 85% of severely injured trauma victims still have evidence of inadequate tissue oxygenation based on findings of an ongoing metabolic acidosis or evidence of gastric mucosal ischemia (5,6). This condition has been described as compensated shock. Recognition of this state and its rapid reversal are critical to minimize risk of MODS or death. Consequently, better markers of adequate resuscitation for severely injured trauma victims are needed.

Goals of the Guideline

1) To demonstrate that the proposed endpoint(s) is (are) useful for stratifying the patients' severity of physiologic derangement.
2) To demonstrate that the proposed endpoint(s) is (are) useful for predicting risk of development of MODS or death.
3) To determine the endpoint(s) for resuscitation that would predict survival without organ system dysfunction if a defined level is achieved within a certain time frame.
4) To improve patient survival and morbidity (organ system dysfunction) by use of appropriate resuscitation endpoint(s).

Proposed Endpoints

The proposed endpoints of resuscitation fall into 2 categories: global and regional. The global O_2 delivery issue has been examined by studies of supranormal O_2 delivery and studies of the utility of mixed venous O_2 saturation. Other global hemodynamic parameters that have been explored include right ventricular end-diastolic volume, left-ventricular stroke work index, and

left-ventricular power output. Similarly, global acid-base status has been explored using base deficit and lactate levels.

On the regional level, compensated shock disproportionately decreases blood flow to the splanchnic bed to maintain cerebral and coronary blood flow. Examination of gut-related parameters may be useful as a marker of the severity of shock and also to demonstrate the pathophysiologic connection between gut ischemia and later MODS. Gastric ischemia can be monitored using gastric tonometry. Intramucosal pH (pHi) or the gap between intramucosal and arterial PCO_2 can be utilized. Skeletal muscle blood flow is similarly decreased during shock. Intramuscular pH and PCO_2 can be monitored. Regional cellular oxygenation can be monitored using near infrared spectroscopy or tissue electrodes.

From a clinical perspective, in addition to direct clinical utility, other issues to consider for potential resuscitation endpoints include: general availability, cost, speed, invasiveness, and risk.

II. PROCESS

The committee agreed upon the potential endpoints to be considered. Literature for review included: human, trauma patients, and some attempted connection between the proposed endpoint and patient outcome (morbidity, survival, etc), not just process variables. Some non-trauma studies of critically ill patients were also included particularly if the parameter seemed promising in other surgical patients. Similarly, some non-human studies of promising techniques are discussed; though not part of the main review or recommendations. Medline and EMBASE were searched from 1980 to 2001.

III. RECOMMENDATIONS

A. Recommendations Regarding Stratifying Physiologic Derangement

Level 1

1. Standard hemodynamic parameters do not adequately quantify the degree of physiologic derangement in trauma patients. The initial base deficit, lactate level, or gastric pHi can be used to stratify patients with regard to the need for ongoing fluid resuscitation, including packed red blood cells and other blood products, and the risks of MODS and death.
2. The ability of a patient to attain supranormal O_2 delivery parameters correlates with an improved chance for survival.

Level 2

1. The time to normalization of base deficit, lactate, and pHi is predictive of survival.
2. Persistently high base deficit or low pHi (or worsening of these parameters) may be an early indicator of complications, e.g., ongoing hemorrhage or abdominal compartment syndrome.
3. The predictive value of the base deficit may be limited by ethanol intoxication or a hyperchloremic metabolic acidosis, as well as administration of sodium bicarbonate.

Level 3

1. Right ventricular end diastolic volume index (RVEDVI) measurement may be a better indicator of adequate volume resuscitation (preload) than central venous pressure or pulmonary capillary wedge pressure (PCWP).

2. Measurements of tissue (subcutaneous or muscle) O_2 and/or CO_2 levels may identify patients who require additional resuscitation and are at risk for MODS and death.
3. Serum bicarbonate levels may be substituted for base deficit levels.

B. Recommendations Regarding Improved Patient Outcomes

Level 1

There is insufficient data to formulate a level 1 recommendation.

Level 2

1. During resuscitation, attempts should be made to increase O_2 delivery to normalize base deficit, lactate, or pHi during the first 24 hours. The optimal algorithms for fluid resuscitation, blood product replacement, and the use of inotropes and/or vasopressors have not been determined.

IV. SCIENTIFIC FOUNDATION

A. Oxygen delivery

Shoemaker, et al (7,8), reviewed the hemodynamic profiles of high risk surgical patients who survived vs those who did not. They found that survivors had significantly higher O_2 delivery and cardiac index (CI) values than nonsurvivors. The parameters included: CI ($\geq$4.5 L/min/m^2), O_2 delivery ($\geq$600 mL/min/m^2), and O_2 consumption ($\geq$170 mL/min/m^2). In a prospective study of high-risk surgical patients, using these parameters as goals for resuscitation resulted in decreased complications, length of stay, and hospital costs (9). This group then recommended adding to the "ABCs" of resuscitation: "D" for increased delivery of O_2 and "E" for ensuring extraction and utilization of O_2 by tissues (10).

In severely injured patients, this group similarly found that attaining supranormal hemodynamic parameters improved survival and decreased the frequency of organ failures (11). They then prospectively tested the hypothesis that using the values of survivors as goals for resuscitation rather than the "normal" values for these parameters would improve survival. Fleming, et al (12), randomized patients to be resuscitated to the supranormal values above vs standard hemodynamic variables. The supranormal group had fewer organ failures and shorter hospital stays, particularly when the values were attained within 24 hours of injury. Mortality was slightly better at p=0.08. In a randomized trial in victims of severe trauma, Bishop, et al (13), found that resuscitating to supranormal values of cardiac index, O_2 delivery, and O_2 consumption compared to normal vital signs, urine output, and central venous pressure decreased the risk of MODS and death. Oxygen delivery was augmented by volume loading, followed by dobutamine infusion if necessary, and, finally, blood transfusions up to hemoglobin of 14 gm/dL.

Others have tried to duplicate these findings with limited success. Moore, et al (14), utilized a resuscitation protocol aimed at maximizing O_2 delivery. Patients who did not reach the established goals by 12 hours were at increased risk for developing MODS. Durham, et al (15), found that resuscitation to the O_2 delivery and/or consumption parameters defined by Shoemaker did not improve the rate of MODS or death compared to conventional parameters. Patients in both groups had similar goals for preload based on PCWP or RVEDV and hemoglobin. Patients who did not attain the supranormal O_2 delivery values were at high risk of developing MODS, regardless of group assignment. Thus, given adequate volume resuscitation, O_2 delivery parameters may be more useful as predictors of outcome than as endpoints for resuscitation. In

trauma patients, Velmahos, et al (16), found that early optimization of O_2 delivery parameters did not improve outcome. In this study, 40% of the control patients achieved these parameters spontaneously compared to 70% of the protocol patients. Again, attaining these parameters seemed to be more predictive of survival than useful as goals of resuscitation. None of the patients who attained these parameters died, compared to 30% of those who did not, regardless of group assignment.

The means used to attain the O_2 delivery goals may be an important issue that has not been adequately explored. In the original studies by the Shoemaker group, the protocol consisted of volume loading with crystalloids and blood, followed by enhancement of cardiac output with dobutamine (7,8). In a heterogeneous group of medical and surgical critically-ill patients, Hayes, et al (17), found that use of dobutamine to help augment O_2 delivery may actually have increased mortality. In contrast, Boyd, et al (18), found that, after fluid resuscitation, increasing O_2 delivery with dopexamine in high-risk surgical patients improved mortality and rate of complications.

A recent study by McKinley, et al (19), using a bedside computerized decision support tool suggested that there was no difference in outcome between an O_2 delivery goal of 600 ml/min/m^2 or 500 ml/min/m^2. The latter group required less fluid for resuscitation. Outcome was not compared to other endpoints.

Several methodological issues regarding these studies should be noted. First, these studies can not be totally blinded. Second, patients in the control arms often attain the same physiologic endpoints as those in the treatment arm. Third, control of other aspects of management is variable. Fourth, entrance criteria vary from one study to another.

Heyland, et al (20), reviewed the evidence for supraphysiologic goals for O_2 delivery in surgical patients and found no overall benefit, but a suggestion of benefit if the goals are achieved preoperatively. More recently, Kern and Shoemaker (21) reviewed all randomized clinical trials of hemodynamic optimization in high-risk patients, both medical and surgical. They grouped the studies by the timing of intervention (before or after the onset of organ dysfunction) and mortality in the control group. They found improved overall mortality only in the studies with interventions initiated before the onset of organ failure and mortality of >20% in the control group. Thus, it seems that optimization of hemodynamic variables should be initiated as early as possible during resuscitation. The greatest benefit seems to be in the sickest groups of patients.

B. Mixed venous oxygen saturation

Use of mixed venous O_2 saturation (SvO_2) levels should reflect the adequacy of O_2 delivery to tissues in relation to global tissue O_2 demands. In a general population of critically ill patients, Gattinoni, et al (22), resuscitated patients to a normal CI (2.5-3.5 L/min/m^2), supranormal CI (>4.5 L/min/m^2), or normal SvO_2 ($\geq$70%). There were no differences in mortality or MODS.

C. Additional Invasive Hemodynamic Monitoring Parameters

Occult cardiac dysfunction may be an issue in many trauma patients. Scalea, et al (23), instituted a protocol of early invasive hemodynamic monitoring of high-risk geriatric blunt trauma victims. They found that monitoring identified occult shock early and may have helped to prevent MODS and death. These investigators (5) even found that young victims of penetrating trauma often had evidence of hypoperfusion. They utilized a protocol of volume resuscitation, inotropes, and blood transfusions to increase O_2 delivery until lactate concentration normalized

and O_2 consumption was no longer flow dependent. Patients who did not normalize lactate or reach their hemodynamic goals by 24 hours were at high risk of dying.

Recognizing that fluid resuscitation is the primary treatment for trauma patients in hemorrhagic shock, indicators of adequate volume status, i.e., optimized preload, are needed. Central venous and pulmonary capillary wedge pressures are useful, but have limitations in critically ill patients due to changes in ventricular compliance (edema, ischemia, or contusion) and intrathoracic pressure (mechanical ventilation). The group at Bowman Gray School of Medicine has explored the use of a variety of parameters that can be measured or calculated using a pulmonary artery catheter.

In the face of potentially variable ventricular compliance and intrathoracic pressure, measurement of RVEDVI may more accurately reflect left ventricular preload than CVP or PCWP. This value can be determined using a right ventricular ejection fraction/oximetry volumetric catheter. Cheatham, et al (24), demonstrated that CI correlates better with RVEDVI than PCWP up to very high levels of positive end-expiratory pressure. This same group (25) examined 79 consecutive critically ill trauma patients. Patients with splanchnic hypoperfusion as defined by low gastric mucosal pHi had a high risk of developing MODS and death. These patients also had lower RVEDVI than those with normal pHi. PCWP, CI, O_2 delivery index, and O_2 consumption index did not correlate with pHi. Chang, et al (26), examined hemodynamic parameters in patients with normal vs low gastric pH after severe trauma. Normalized pHi and high RVEDVI were strongly associated with better outcomes. Recently, Kincaid, et al (27), suggested that the optimal RVEDVI for each patient could be calculated based on measurements of ventricular compliance.

Chang, et al (28), compared the hemodynamic variables left ventricular stroke work index (LVSWI=stroke index x mean arterial pressure x 0.0144) and left ventricular power output (LVP=cardiac index x [mean arterial pressure-central venous pressure]), which encompass blood pressure and flow, with the purely flow-derived hemodynamic and O_2 transport variables as predictors of outcome in critically-ill trauma patients. The only variables that significantly correlated with lactate clearance and survival were heart rate, LVSWI and LVP. Using the ventricular pressure-volume relationships, they found that survivors also had better ventricular-arterial coupling, as determined by a lower ratio of afterload (aortic input impedance) to contractility (ventricular end-systolic elastance). They then prospectively resuscitated patients attempting to achieve the survivors' level of LVP (>320 mm Hg x L/min/m2) (29). This group of patients (n=20) was compared to a group of patients from a previous prospective study (n=39). The patients resuscitated to the LVP goal normalized their base deficit sooner and had a lower risk of developing organ system failure. The difference in survival did not reach statistical significance. In a separate study, these investigators (30) found that improved ventricular-arterial coupling during resuscitation was associated with improved myocardial efficiency (ratio of stroke work to total myocardial energy output as measured via the pressure-volume loop) and decreased base deficit.

D. Arterial base deficit

Inadequate tissue O_2 delivery leads to anaerobic metabolism. The degree of anaerobiosis is proportional to the depth and severity of hemorrhagic shock. This should be reflected in the base deficit and lactate level. Arterial pH is not as useful as it will be "defended" by the body's compensatory mechanisms (31). A recent study by Eachempati, et al (32), suggests that serum

bicarbonate concentrations, which may be more readily available than arterial blood gases, correlate very well with base deficit values.

Because of its availability and rapidity, the base deficit has been extensively studied. Davis, et al (33), retrospectively found that higher base deficit was associated with lower blood pressure on admission and greater fluid requirements. They stratified patients' level of illness as mild (base deficit 2-5 mmol/L), moderate (base deficit 6-14 mmol/L), or severe (base deficit >14 mmol/L). Two-thirds of patients with an increasing base deficit had ongoing blood loss. Rutherford, et al (34), added that base deficit correlated with mortality and enhanced the predictive value of the TRISS methodology (35). Falcone, et al (36), further suggested a good correlation between base deficit and blood product requirements, although they did not find base deficit to independently correlate with mortality. Sauaia, et al (37), found that base deficit, lactate, and transfusion requirements were predictive of the development of multiple organ failure. Age and injury severity score (ISS) were also important variables.

The importance of a normal base deficit may vary with different patient populations. Davis, et al (38), found that a base deficit of $\geq$6 mmol/L is a marker of severe injury in all patients, but a normal base deficit was associated with an ISS of >16 in patients older than 55 years more often than in younger patients.

Base deficit changes over time may add to the utility of these levels. Davis, et al (31), found that changes in base deficit over time were more predictive of survival than pH levels. Kincaid, et al (39), further found that, among trauma patients who normalized their lactate levels, those that had persistently high base deficit had greater risk of MODS and death. These patients also demonstrated impaired O_2 utilization, as evidenced by lower O_2 consumption and O_2 utilization coefficient. Rixen, et al (40), similarly found that an increase in base deficit between arrival at the hospital and admission to the intensive care unit identified trauma patients with hemodynamic instability, high transfusion requirements, metabolic and coagulation abnormalities, and an increased risk of death.

Using a multivariate analysis, Siegel, et al (41), found that base deficit and initial 24 hour blood transfusion requirements were independently predictive of mortality. Lactate levels and ISSs were not. The combination of Glasgow Coma Scale and base deficit produced the best predictive model.

In victims of penetrating trauma, Eachempati, et al (42), found that worst base deficit in the first 24 hours, blood pressure on admission, and estimated blood loss were predictive of mortality by univariate analysis. Only base deficit remained predictive by multivariate analysis.

To determine preoperative factors that could predict outcome in the most severely injured patients, Krishna, et al (43), retrospectively examined 40 patients with multivisceral trauma (ISS >35) who required urgent operations for hemorrhage. Using base deficit, core temperature, and ISS, they could predict outcome with 92.5% accuracy. Severe hypothermia (<33^{o}C), severe metabolic acidosis (base deficit >12 mmol/L), and a combination (temperature <35.5^{o}C and base deficit >5 mmol/L) were strong predictors of death.

Elevated base deficit is not only predictive of mortality, but of complications, such as the need for blood transfusions and organ failure, particularly the acute respiratory distress syndrome (ARDS). Davis, et al (44), found that admission base deficit correlated with need for blood transfusion (72% if base deficit $\geq$6 mmol/L vs 18% if base deficit <6 mmol/L), length of stay, ARDS, renal failure, coagulopathy, and MODS. Eberhard, et al (45), found that the initial base deficit was significantly higher in patients who developed acute lung injury compared to those who did not. Rixen and Siegel (46) found that both high lactate and base deficit during the first

24 hours of admission were associated with high interleukin-6 levels and ARDS, especially within the first 4 days of admission. Botha, et al (47), found that base deficit values correlated with neutrophil CD11b expression, suggesting that inflammatory processes are involved in the relationship between severity of post-traumatic shock and later development of MODS and death.

Bannon, et al (48), prospectively studied 40 patients who required operations for truncal injuries to see what factors would best determine which patients were at the greatest risk of developing hemodynamic instability. They found that both base deficit and lactate levels correlated with transfusion requirements, whereas mixed venous O_2 saturation did not.

Almost all studies of base deficit have focused on adults. Kincaid, et al (49), found that base deficit can also reflect injury severity and risk of mortality in pediatric patients. Admission base deficit correlated with systolic blood pressure, ISS, and revised trauma score. Base deficit >8 mmol/L corresponded with a 25% mortality risk. This was corroborated by Randolph, et al (50)

Base deficit levels may be confounded by a number of factors. Alcohol intoxication can worsen base deficit for similar levels of injury severity and hemodynamics after trauma. Dunham, et al (51), suggest that a base deficit of $\geq$4.1 mmol/L should be concerning in intoxicated patients, whereas a base deficit of 1.1 is concerning in non-intoxicated patients. Davis, et al (52), found no difference in length of stay regardless of alcohol level. A base deficit of $\geq$6 mmol/L was still predictive of a significant injury and need for blood transfusion. Using an even larger database (15,179 patients), Dunne, et al (53), found that, although 21% of patients had ingested alcohol and 7% had used other drugs, admission lactate and base deficit remained as significant independent predictors of outcome.

In addition, development of a hyperchloremic metabolic acidosis from resuscitation with normal saline or lactated Ringer's solution can increase base deficit for the same degree of injury severity (54). Acidosis secondary to hyperchloremia is associated with a lower mortality than that from other causes, particularly lactic acidosis.

Eachempati, et al (32), have shown that serum bicarbonate levels, which may be more readily available from some labs, correlate well with base deficits. Administration of sodium bicarbonate will at least transiently improve base deficit and bicarbonate levels and confound their use as endpoints for resuscitation. There is little role for sodium bicarbonate in the treatment of hemorrhagic shock.

E. Arterial lactate

Vincent, et al (55), showed that not only were initial lactate levels important, but the response of the lactate level to an intervention, such as fluid resuscitation, would add predictive value in patients with noncardiogenic circulatory shock. Abramson, et al (56), studied patients who had severe trauma and were resuscitated to supranormal values of O_2 transport (8). They found that the time needed to normalize serum lactate levels was an important prognostic factor for survival. All patients who had normalized lactate levels at 24 hours survived; those patients who normalized their levels between 24 and 48 hours had a 25% mortality rate; those that did not normalize by 48 hours had an 86% mortality rate. McNelis, et al (57), found a similar trend in post-operative surgical patients admitted to the ICU. Manikas, et al (58), further found that initial and peak lactate levels, as well as the duration of hyperlactatemia, correlated with the development of MODS after trauma.

In theory, the severity of metabolic acidosis secondary to tissue hypoperfusion should be similarly reflected in lactate levels and anion gap or base deficit. In 52 critically ill trauma patients, Mikulaschek, et al (59), found that lactate levels were higher in nonsurvivors than in survivors. Similar correlations were not true for anion gap or base deficit. Correlations between these variables were poor. The total number of patients was small and the lactate levels were used to guide resuscitative efforts.

F. End-tidal Carbon Dioxide Levels

Reduced cardiac output and/or abnormal distribution of pulmonary blood flow can lead to increased pulmonary dead space. This can then lead to an increase in the difference between arterial and alveolar CO_2, as measured by end-tidal CO_2. Tyburski, et al (60), prospectively studied 106 trauma patients who required operations. Survivors had higher end-tidal CO_2, lower arterial-end tidal CO_2 differences, and decreased alveolar dead space ratio (estimated as the arterial-end tidal CO_2 difference/arterial PCO_2) compared to nonsurvivors.

G. Gastric tonometry

The stomach has been called the canary of the body (61). As systemic perfusion decreases, blood flow to the most vulnerable organs (brain and heart) is maintained at the expense of other organs (skin, muscle, kidneys, and gut). In theory, detection of subclinical ischemia to these organs would allow identification of patients who require additional resuscitation despite seemingly normalized vital signs. Gastric tonometry is based on the finding that tissue ischemia leads to an increase in tissue PCO_2 and subsequent decrease in tissue pH. Because CO_2 diffuses so readily across tissues and fluids, the PCO_2 in gastric secretions rapidly equalizes that in the gastric mucosa. For gastric tonometry to be accurate, it is necessary to withhold gastric feedings and suppress gastric acid secretion. A semi-permeable balloon is placed into the stomach attached to a special nasogastric tube. The balloon is filled with saline and CO_2 is allowed to diffuse into the balloon for a specific period of time. The PCO_2 in the saline is then measured. Intramucosal pH (pHi) can be calculated based on the Henderson-Hasselbach equation. Continuous CO_2 electrodes are also available.

In a group of 59 surgical ICU patients, Gys, et al (62), found that pHi correlated with sepsis score. Patients with pHi <7.32 had a mortality of 37% whereas those with higher pHi all survived. Doglio, et al (63), showed that lower pHi correlated with development of MODS and increased mortality in critically ill patients, particularly if the low pHi persisted for >12 hours. Maynard, et al (64), suggested that pHi was a better predictor of mortality in a general ICU population than arterial pH, base deficit, and lactate levels. Interestingly, CI, O_2 delivery, and O_2 uptake were not different between survivors and nonsurvivors. In contrast, Boyd, et al (65), found that markers of metabolic acidosis (base deficit and bicarbonate levels) correlated well with pHi. Finding base deficit of >4.65 had a 77% sensitivity and a 96% specificity of predicting pHi of <7.32. In 22 medical and surgical ICU patients, Gutierrez, et al (66), compared pHi to O_2 transport parameters in survivors and nonsurvivors. Survivors and nonsurvivors had similar O_2 delivery, but nonsurvivors had greater O_2 consumption, O_2 extraction ratio, and lactate levels; and lower pHi, mixed venous pH, and mixed venous PO_2. All patients who died had pHi values <7.32.

In a separate study, Gutierrez, et al (67), randomized critically ill patients to standard treatment vs a protocol that called for increasing O_2 transport or decreasing O_2 demand if the pHi decreased below 7.35 or 0.1 units below the previous value. Survival was similar between groups

if the initial pHi was low, but the protocol improved survival in those patients with initially normal pHi. In contrast, Gomersall, et al (68), resuscitated patients in a general ICU using a standardized protocol to maintain mean arterial pressure >70 mmHg, systolic blood pressure >90 mmHg, urine output >0.5 ml/kg/hr, hemoglobin >8 g/dl, blood glucose <12 mmol/L, arterial O_2 saturation >94%, and correction of uncompensated respiratory acidosis. Patients were then randomized to continued standard therapy or additional fluid resuscitation and/or dobutamine to achieve pHi $\geq$7.35. There were no differences between groups in mortality, MODS, or length of stay.

In trauma patients, Roumen, et al (69), prospectively studied 15 blunt trauma patients who required operations. Eight had low pHi ($\leq$7.32) initially or subsequently. Three of these 8 developed complications and 2 died. All 7 with normal pHi had uncomplicated recoveries. They found no correlation between initial pHi and ISS, shock, lactate, or acute physiologic and chronic health evaluation (APACHE) II scores. Chang, et al (26), similarly found that pHi <7.32 was a good predictor of MODS and mortality. Based deficit and mixed venous O_2 saturation were also independently associated with mortality, but at 24 hours, the only factor that was different between patients who developed MODS and those who did not was pHi. All patients who developed MODS had pHi <7.1.

Threshold values for pHi and for the gastric mucosal-arterial CO_2 gap were explored by Miller, et al (70), using a cohort of 114 trauma patients. The ability to predict MODS and death was maximized with pHi <7.25 and gap of >18 mm Hg. The CO_2 gap is a better indicator of gut "dysoxia" than pHi, which is a calculated variable that may be altered by arterial bicarbonate levels (71).

Using pHi as an endpoint ($\geq$7.3) for resuscitation was compared to supranormal O_2 transport variables (O_2 delivery index of 600 mL/min/m^2 and a O_2 consumption index of >150 mL/min/m^2) in a prospective, randomized study of 57 trauma patients by Ivatury, et al (72,73). The resuscitation protocol included volume loading with crystalloid and blood followed, if necessary, with inotropic support using dobutamine. Treatment goals were achieved in almost all patients. Time taken to optimize pHi or O_2 transport variables was similar. The only parameter that remained different between groups was pHi. Looking at both groups, delay in achieving pHi goals was more predictive of organ system failure, complications, and death than achieving the O_2 transport goals. The gap between gastric mucosal and arterial CO_2 was similarly predictive. In the postresuscitation period, persistently low or decreasing pHi was an early signal of complications.

Technologic limitations of measuring gastrointestinal PCO_2 should be kept in mind. The original, manual technique using a semi-permeable balloon is cumbersome. An airflow tonometer in which the balloon is automatically filled with air and the air is removed after a set period of time is also now approved by the Food and Drug Administration. Both methods could theoretically change the environment within the stomach by either adding O_2 or removing CO_2. Fiberoptic systems using a spectrophotometric method for continuous monitoring are being developed. Wall, et al (74), found that the airflow and fiberoptic devices correlated well with each other *in vitro*, but simultaneous samples *in vivo* during hemorrhagic shock and resuscitation in dogs differed significantly. The fiberoptic values were greater than the airflow values. The authors recommend using the fiberoptic approach since it does not interfere with the local gas environment. Imai, et al (75), recently reported on the utility of a different type of CO_2 electrode that could continuously measure PCO_2 in the stomach.

An intriguing new approach to determine regional hypercarbia during shock is the use of sublingual PCO_2 monitoring. Weil, et al (76), demonstrated that sublingual PCO_2 correlates with lactate levels, presence of shock, and survival in a small group of acutely ill patients. Povoas, et al (77), compared duodenal and sublingual PCO_2 to mesenteric blood flow during hemorrhagic shock in pigs. Strong correlations were found between both PCO_2 values and mesenteric blood flow. Studies in humans are in progress. In victims of penetrating trauma, Baron, et al (78), showed that sublingual PCO_2 was elevated in patients with ongoing bleeding.

H. Tissue oxygen and carbon dioxide electrodes

Measurements of transcutaneous O_2 and CO_2 levels may also be predictive of death in critically ill patients based on the same principles of gastric tonometry. Drucker, et al (79), utilized an optical sensor (optode) placed into subcutaneous tissues to examine peripheral perfusion. They first demonstrated that this probe worked as well as a standard Clark electrode and then demonstrated in animals that the subcutaneous PO_2 decreased rapidly during hemorrhagic shock and increased with resuscitation, although not always to baseline, suggesting ongoing peripheral vasoconstriction. Finally, in 18 trauma patients, they found that many still had low subcutaneous PO_2 levels despite adequate resuscitation by standard clinical criteria.

Göte, et al (80), measured subcutaneous PO_2 in 10 patients undergoing emergency intestinal surgical procedures using a tonometer implanted in the abdominal wall. They found that subcutaneous PO_2 values were higher in the survivors.

Tatevossian, et al (81), measured transcutaneous PO_2 and PCO_2 in critically ill trauma patients. Patients who died had lower transcutaneous PO_2 values, higher transcutaneous PCO_2 values, and longer periods of time with transcutaneous PCO_2 values >60 torr. All patients died who had transcutaneous PCO_2 values >60 torr for >30 min.

Waxman, et al (82), took this concept one step further by measuring deltoid muscle PO_2 via a needle-mounted probe before and after an O_2 challenge. Their hypothesis was that patients who were adequately resuscitated would respond with an increase in tissue PO_2 since flow-dependent O_2 consumption would not be present. Tissue PO_2 would not increase if flow dependent O_2 consumption is present and cells consume all additional O_2. Responders (n=6) during acute trauma resuscitations had lower ISS, higher revised trauma scores, and shorter hospital stays than nonresponders (n=9). In 14 trauma patients already in the intensive care unit, response to the O_2 challenge test correlated very well with evidence of flow dependency via pulmonary artery catheterization.

Jonsson, et al (83), had previously used a similar technique to show that many patients who underwent abdominal surgical procedures were suboptimally perfused.

I. Near infrared spectroscopy (NIRS)

Measurement of skeletal muscle oxyhemoglobin levels by NIRS offers a non-invasive method for monitoring adequacy of resuscitation in terms of normalizing tissue oxygenation. In pigs undergoing hemorrhagic shock, Cohn, et al (84), showed that gastric tissue O_2 saturation, measured continuously with a prototype side-illuminating NIRS nasogastric probe, decreased rapidly, correlating with superior mesenteric artery (SMA) blood flow. The correlation of SMA flow with tonometric CO_2 in the jejunum was not as good.

In human volunteers donating 470 ml of whole blood, Torella, et al (85), found that cerebral cortex and calf muscle O_2 saturation measured by NIRS decreased in proportion to

blood loss. The oxygenation index ([oxygenated hemoglobin]-[deoxygenated hemoglobin]) also decreased proportionally.

McKinley, et al (86), studied O_2 saturation of hemoglobin in tissue (StO_2 = $HbO_2/[HbO_2+Hb]$) during resuscitation in trauma patients. They found that StO_2 correlated with systemic O_2 delivery, base deficit, and lactate. This correlation was better than that found with gastric mucosal PCO_2 and PCO_2 gap (difference between gastric PCO_2 and arterial PCO_2).

NIRS technology allows the simultaneous measurement of tissue PO_2, PCO_2, and pH. During hemorrhagic shock, Puyana, et al (87,88), found in pigs that intra-abdominal organs respond differently. Small bowel pH changed most rapidly during shock and resuscitation. Gastric mucosal pH, PCO_2, and PCO_2 gap were not as sensitive. Simultaneous measurements of tissue PO_2, PCO_2, and pH of solid organs, particularly the liver, may provide even better prediction of outcomes and better endpoints for resuscitation (89,90).

Sims, et al (91), found that placement of a fiberoptic multiparameter sensor into skeletal muscle could also be useful for monitoring the severity of hemorrhagic shock in pigs, as well as the adequacy of resuscitation. They found that both PO_2 and PCO_2 changed rapidly during shock and resuscitation, whereas pH decreased, but did not return to baseline. The pH correlated best with blood loss. Persistently low pH and hypercarbia resulted from ongoing bleeding and incomplete resuscitation despite normalized blood pressure.

In addition to monitoring tissue oxygenation, NIRS can provide information regarding mitochondrial function. Normally, tissue oxyhemoglobin levels, reflecting local O_2 supply, are tightly coupled to cytochrome a,a_3 redox, reflecting mitochondrial O_2 consumption. Cairns, et al (92), found that 8 of 9 trauma patients who developed multiple organ failure had decoupling of these values, whereas only 2 of 16 patients who did not develop multiple organ failure had decoupling.

J. Physical Examination

Despite all the interest in laboratory values, as well as data from invasive and non-invasive monitoring devices, used to determine the adequacy of resuscitation, one should not discount the value of a good physical examination. Kaplan, et al (93), examined the ability of 2 intensivists to diagnose hypoperfusion by physical examination of patients' extremities. The intensivists described the patients' extremities as either warm or cool. Compared with patients with warm extremities, those with cool extremities had lower CI, pH, bicarbonate levels, and SvO_2; and higher lactate levels.

V. SUMMARY

During resuscitation from traumatic hemorrhagic shock, normalization of standard clinical parameters such as blood pressure, heart rate, and urine output are not adequate to guarantee survival without organ system dysfunction. Numerous parameters including hemodynamic profiles, acid-base status, gastric tonometry, and regional measures of tissue O_2 and CO_2 levels have been studied. Many can be useful for predicting risk of organ failure and death. Studies comparing use of these parameters as endpoints for resuscitation protocols, however, have failed to show clear benefit in terms of patient outcomes. At present, it seems prudent to use one of these endpoints rather than relying on standard clinical parameters.

VI. FUTURE INVESTIGATION

The ideal parameter to use as an endpoint for resuscitation would be reliable, easy to use, non-invasive, safe, and cheap. Well-controlled clinical trials comparing parameters as endpoints for resuscitation are needed, but these are difficult to control because of lack of blinding, bias (by investigators and device manufacturers), and need for strict control of resuscitation protocols. In addition, comparing to a standard of care may become more difficult, perhaps even unethical, given that use of at least one parameter has become practically standard.

The next critical, unanswered question, once "optimal" endpoint(s) are determined, is how to achieve them. How do we know that the patient is adequately volume loaded? Once volume loaded, which inotropes and/or vasopressors are best for achieving the chosen endpoint? What should the optimal hematocrit be early in resuscitation?

Another set of important unanswered questions relate to subsets of trauma patients. The search for the "holy grail", i.e., a single endpoint that works for all trauma patients, may be unrealistic. For example, acid-base parameters may not work in patients with acid-base disturbances that are acute (alcohol intoxication) or chronic (renal failure). For older patients, beta-blockade and heart rate control may be valuable and use of inotropes that increase myocardial work along with massive volume loading may be detrimental.

Answering these questions will require systematic approaches to the problem in the context of coordinated research efforts. Multi-center studies should be instituted to achieve the large numbers of patients that will be needed to complete the studies in a timely fashion and to assure utility of the technique across a variety of patient populations and physician practices.

VII. REFERENCES

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First author	Year	Title	Class of evidence	Conclusions
Oxygen Delivery				
Shoemaker, WC	1988	Prospective trial of supranormal values of survivors and therapeutic goals in high risk surgical patients. Chest 94:1176-86.	I	Resuscitating to preordained oxygen transport variables may reduce morbidity and mortality in high-risk surgical patients.
Boyd, O	1993	A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgery. JAMA 270:2699-2707.	I	Results: A 75% reduction in mortality (5.7% vs 22.2% P=0.015) and halving of the mean number of complications per patient in the protocol group (P=0.008)
Hayes, MA	1994	Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330:1717-22.	I	9 patients achieved goals with volume alone, 50 control, 50 tx. In-house mortality for the nine was zero. In house mortality was LOWER in the control group than the treatment group (34% vs 54% P=0.04
Bishop, MH	1995	Prospective, Randomized Trial of Survivor Values of Cardiac Index, Oxygen Delivery, and Oxygen Consumption as Resuscitation Endpoints in Severe Trauma. J Trauma 38:780-787.	I	CI, DO2I, VO2I therapeutic goals achieved within the first 24 hrs were associated with decreased mortality, organ dysfunction, and ICUand vent days.
Durham, RM	1996	The Use of Oxygen Consumption and Delivery as Endpoints for Resuscitation in Critically III Patients. J Trauma 41:32-40.	I	The incidence of organ failure and death is similar for patients resuscitated based in O2 transport parameters vs conventional parameters. Given adequate vlume resuscitation O2 based parameters are more useful as predictors of outcome than as endpoints of resuscitation.
Velmahos, GC	2000	Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. Ann Surg 232:409-18.	I	2 Conclusions and one comment: 1. No difference in mortality, organ failure, sepsis, LOS between the two groups, 2. Death rate was zero among patients who achieved optimal values compare to 30% among those who didn't. Comment: age younger then 40 years old was the only independent factor of the ability to reach optimal values
Shoemaker, WC	1973	Physiologic patterns in surviving and nonsurviving shock patients: Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. Arch Surg 106:630-636.	II	Cardiorespiratory patterns of non survivors surgical/trauma patients were characterized by reduced cardiac output, high pulmonary vascular resistance, and reduced oxygen transport. They proposed that these should be used as defined criteria for therapeutic goals.

Shoemaker, WC	1988	Tissue oxygen debt as a determinant of lethal and non-lethal postoperative organ failure. Crit Care Med 16:1117-1120.	II	The maximum cumulative oxygen debt is significantly less in patients without organ failure than that of nonsurvivors and survivors with organ failure. Oxygen consumption is not different between the 3 groups intraoperatively.
Fleming, A	1992	Prospective trial of supranormal values as a goal of resuscitation in severe trauma. Arch Surg 127:1175-1181.	II	Supranormal DO2 vs normal. No change in mortality. Fewer organ failures, shorter ICU LOS, less vent days. ?randomized
Moore, FA	1992	Incommensurate oxygen consumption in response to maximal oxygen availability predicts postinjury multisystem organ failure. J Trauma 33:58-67.	II	Fifteen of these patients (38%) did not meet this VO2 goal at 12 hours. The patients had elevated lactate levels and also predicted MOF
Bishop, MH	1993	Relationship between supranormal circulatory values, time delays, and outcome in severely traumatized patients. Crit Care Med 21:56-63.	II	Severely traumatized patients may improve survival if 'supranormal values of DO2 and VO2 are achieved by 24 hours.
Heyland, DK	1996	Maximizing oxygen delivery in critically ill patients: A methodologic appraisal of the evidence. Crit Care Med 24:517-524.	II	Mortality is unchanged when DO2 and VO2 are driven to "supraphysiologic" levels in critically ill patients.
McKinley, BA	2002	Normal versus supranormal oxygen delivery goals in shock resuscitation: the response is the same. J Trauma 53:825-832	II	Non-randomized study of 2 oxygen delivery goals (600 vs 500 ml/min/m^2) implemented with a computer-based protocol. The outcomes were the same, although less fluid was needed in the lower oxygen delivery cohort.
Shoemaker, WC	1983	Use of physiologic monitoring to predict outcome and to assist clinical decisions in the critically ill postoperative patients. Am J Surg 146:43-50.	III	Goals of resusc. to achieve median values of cardio-pulmonary parameters retrospectively derived from a survivor group were associated with improved outcome.
Mixed Venous Oxygen Saturation				
Gattinoni, L	1995	A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med 333:1025-32.	I	Maximization of CI > 4.5 or SvO2 > 70% did not reduce morbidity or mortality in critically ill patients.
Additional Invasive Hemodynamic Monitoring Parameters				
Scalea, TM	1990	Geriatric blunt multiple trauma: improved survival with early invasive monitoring. J Trauma 30:129-136.	II	Emergent invasive monitoring identifies occult shock early, limits hypoperfusion, and will help prevent MOF and improve survival.

Abou-Khalil, B	1994	Hemodynamic responses to shock in young trauma patients: Need for invasive monitoring. Crit Care Med 22:633-639.	II	Young trauma patients have substantial but clinically occult myocardial depression after shock and most of these patients require inotropes to optimize and clear circulating lactate. Early invasive monitoring is necessary to define the adequacy of the cardiac response and individually taylor therapy. Patients who do not optimize and clear their lactate within 24 hours may not survive.
Chang, MC	1994	Gastric tonometry supplements information provided by systemic indicators of oxygen transport. J Trauma 37:488-94.	II	Low pHi correlates with morbidity and mortality in surgical patients. These values may be used in conjunction with oxygen transport variables to manage these patients.
Chang, MC	1997	Cardiac preload, splanchnic perfusion, and their relationship during resuscitation in trauma patients. J Trauma 42:577-82.	II	Patients in the normal group had a statistically sig. lower incidence multpile organ failure and death. Also the patients in the normal group maintained a higher RVEDI throught the res. Conclusions: Supranormal levels of preload during shock resuscitation are ass. with better outcome. Keeping the RVEDVI > 100 may improve outcome
Chang, MC	1998	Redefining cardiovascular performance during resuscitation: Ventricular stroke work, power, and the pressure-volume diagram. J Trauma 45:470-478	II	Prospective study of critically-ill trauma patients. Resuscitation with fluids, blood, and inotropes with a goal of rapid normalization of lactate level. Survivors had lower heart rates, stroke work, levt ventricular power, and vetricular-arterial coupling.
Cheatham, ML	1998	Right ventricular end-diastolic volume index as a predictor of preload status in patients on positive end-expiratory pressure. Crit Care Med 26:1801-1806.	II	RVEDVI better predicts volume state and response to volume infusion than PAOP pressure
Chang, MC	2000	Maintaining survivors' values of left ventricular power output during shock resuscitation: a prospective pilot study. J Trauma 49:26-33.	II	Maintaining LVP > 320 during resusc. was associated with improved BD clearance and lower rates of organ disfunction
Chang	2002	Improving ventricular-arterial coupling during resuscitation from shock: Effects on cardiovascular function and systemic perfusion. J Trauma 53:679-685	II	Prospective study of critically-ill trauma patients. Resuscitation with fluids, blood, and inotropes based on left ventricular power output ventricular-arterial coupling led to rapid base deficit clearance and improved myocardial efficiency.
Kincaid, EH	2001	Determining optimal cardiac preload during resuscitation using measurements of ventricular compliance. J Trauma 50:665-669	III	Prospective study of critically-ill trauma patients who needed a pulmonary artery catheter. Ventricular compliance curves were constructed during volume loading using RVEDVI measurements.

Arterial Base Deficit				
Rutherford, EJ	1992	Base deficit stratifies mortality and determines therapy. J Trauma 33:417-23.	II	Based deficit is an expedient and sensitive measure of both the degree and duration of hypoperfusion. It is a useful clinical tool and enhances predictive ability of revised trauma score and TRISS.
Sauaia, A	1994	Early predictors of postinjury multiple organ failure. Arch Surg 129:39-45.	II	Age, ISS + >6u RBC 1st 12 hrs post injury were early predictors of MOF. BD and lactate were also helpful.
Bannon, MP	1995	Central venous oxygen saturation, arterial base deficit, and lactate concentration in trauma patients. Am Surg 61:738-45.	II	BD and LA are better than central venous oxygen saturation (ScvO2)as indicators of blood loss as measured by peritoneal shed blood volume, preop hypotension and transfusion requirement
Davis, JW	1996	Admission base deficit predicts transfusion requirements and risk of complications. J Trauma 41:769-74.	II	Admission BD can be used to identify pts. at risk for increasing transfusion requirements and ICU + hosp LOS.
Botha, AJ	1997	Base deficit after major trauma directly relates to neutrophil CD11b expression: a proposed mechanism of shock-induced organ. Intens Care Med 23:504-9.	II	The degree of metabolic acidosis after trauma correlates with CD11b receptor expression on circulating neutrophils
Davis, JW	1998	Base deficit is superior to pH in evaluating clearance of acidosis after traumatic shock. J Trauma 44:114-8.	II	Base deficit reveals differences in metabolic acidosis between survivors and non-survivors not identified by pH determination. Base deficit is a better mark of acidosis clearance after shock.
Eberhard, LW	2000	Initial severity of metabolic acidosis predicts the development of acute lung injury in severely traumatized patients. Crit Care Med 28:125-31.	II	The ED base deficit(BD) and the total crystalloid volume in 24h predict the development of ALI while total number of transfusions does not
Brill, SA	2001	Base Deficit Does not Predict Mortality When it is Secondary to Hyperchloremic Acidosis. Shock	II	Hyperchloremic metabolic acidosis is a common cause of metabolic acidosis in the SICU and is associated with lower mortality than metabolic acidosis from other causes. Hyperchloremic metabolc acidosis can be induced by LR resuscitation and may lead to inappropriate clinical interventions due to the incorrec presumption of ongoing tissue hypoxia.
Randolph	2002	Resuscitation in the pediatric trauma population: admission base deficit remains an important prognostic indicator. J Trauma 53:838-842	II	Retrospective study of pediatric trauma patients admitted to an intensive care unit. Admission BD is associated with shock, poor outcome, and mortality. Failure to clear BD was associated with 100% mortality.

Davis, JW	1988	Base deficit as a guide to volume resuscitation. J Trauma 28:1464-7.	III	Base deficit is a useful guide to volume replacement in the resuscitation of trauma patients
Siegel, JH	1990	Early physiologic predictors of injury severity and death in blunt multiple trauma. Arch Surg 125:498-508.	III	Both extracellular base deficit and the volume of blood transfused in the first 24 hours were significant predictors of mortality.
Falcone, RE	1993	Correlation of metabolic acidosis with outcome following injury and its value as a scoring tool. World J Surg 17:575-9.	III	Multivariate analysis revealed that only Trauma Score and age are predictive of survival. Base deficit is an important predictor of volume of blood needed.
Davis, JW	1997	Effect of alcohol on the utility of base deficit in trauma. J Trauma 43:507-10.	III	The presence of ETOH results in significantly worse base deficit despite lower ISS and higher Ps in ETOH positive patients.. Despite this finding BD <-6 remained a significant predictor of major injury regardless of ETOH level.
Davis, JW	1998	Base deficit in the elderly: a marker of severe injury and death. J Trauma 45:873-7.	III	Base deficit < -6 is a marker of severe injury and significant mortality in all trauma patients, but it is particularly ominous in patients 55 years of age and older. Patients older than 55 years may have significant injuries and mortality risk without manifesting a base deficit out of the normal range
Kincaid, EH	1998	Elevated arterial base deficit in trauma patients: a marker of impaired oxygen utilization. JACS 187:384-92.	III	A persistently high arterial base deficit is associated with altered O2 utilization and increased MOF and mortality
Krishna, G	1998	Physiological predictors of death in exsanguinating trauma patients undergoing conventional trauma surgery. ANZ J Surg 68:826-9.	III	Strong predictors of death(after multiple logistic regression outcome could be predicted with 92.5% accuracy) were: Base deficit >12 mEq/L or T < 33degrees C or a combination of Temp 35.5 to 33.5 AND a Base Deficit of of 5-12 mEq/L
Dunham, CM	2000	Base deficit level indicating major injury is increased with ethanol. J Emer Med 18:165-71.	III	The presence of ETOH results in worsening of the base deficit independent of other variables. Risk of major injury increases when BD is <-4.1 in ETOH positive patients vs. <-1.1 in ETOH negative patients.
Rixen, D	2000	Metabolic correlates of oxygen debt predict posttrauma early acute respiratory distress syndrome and the related cytokine response. J Trauma 49:392-403.	III	Maximum oxygen debt (I.e. increased BD and lactate) correlates with early ARDS and death.
Kincaid, EH	2001	Admission base deficit in pediatric trauma: a study using the National Trauma Data Bank. J Trauma 51:332-5.	III	In injured children admission base deficit predicts injury severity and predicts mortality. BD less than -8 could represent potentially lethal injury and ucompensated shock.

Rixen, D	2001	Base deficit development and its prognostic significance in posttrauma critical illness: An analysis by the trauma registry of the Deutsche Gesellschaft Fur Unfallchirurgie. Shock 15:83-89.	III	Base deficit is an early indicator to identify patients that will show hemodynamic instability, high transfusion requirements,metabolic and coagulatory decompensation as well as probability of death. This was true for both initial admission and icu admission. With a worsening of BD form hospital to ICU admission there was an increased mortality.
Dunne, J	2002	Lactate and base deficit in trauma: does alcohol impair their predictive accuracy? J Trauma 53:188 (abstract).	III	Using a large database of trauma patients, the authors found that many patients had ingested alcohol or other drugs. Lactate and base deficit levels still were predictive of outcome.
Eachempati, SR	2002	Factors associated with mortality in patients with penetrating abdominal vascular trauma. J Surg Res 108:222-226.	III	In patients with penetrating abdominal trauma, the only factor that independently predicted mortality was base deficit. Blood pressure on admission and blood loss were predictive in univariate analysis.
Eachempati	2003	Serum bicarbonate as an endpoint of resuscitation in critically ill patients. Surg Inf 4: (in press)	III	Using a large dataset from trauma patients, the authors found a strong correlation between base deficit and serum bicarbonate levels.
Arterial Lactate Levels				
Vincent, JL	1983	Serial lactate determinations during circulatory shock. Crit Care Med 11:449-451.	II	Serial lactate determinations are more prognostic of survival than a lone initial value
Abramson, D	1993	Lactate clearances and survival following injury. J Trauma 35:584-589.	II	Time to normalize LA is prognostic of survival
Manikis, P	1995	Correlation of serial blood lactate levels to organ failure and mortality after trauma. Am J Emerg Med 13:619-622.	II	1) initial LA and peak LA were higher in non-survivors 2) initial LA, peak LA and duration of LA correlated with organ failures
Mikulaschek, A	1996	Serum Lactate Is Not Predicted by Anion Gap or Base Excess after Trauma Resuscitation. J Trauma 40:218-224.	II	Lactate, base excess, and anion gap do not correlate after resuscitation.
McNelis J	2001	Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit. Am J Surg 182:481-485	III	Retrospective study of postoperative ICU patients. Time to clear lactate correlated with mortality.
End-tidal Carbon Dioxide				
Tyburski, JG	2002	End-tidal CO_2-derived values during emergency trauma surgery correlated with outcome: a prospective study.	II	Prospective study of trauma patients who required an urgent operation. Survivors had higher end-tidal CO_2 levels, lower arterial-end tidal CO_2 differences, and decrease alveolar dead space ratio.

Gastric Tonometry				
Gutierrez, G	1992	Comparison of gastric intramucosal pH with measures of oxygen transport and consumption in critically ill patients. Crit Care Med 20:451-7.	I	pHi, mixed venous pH and PO2, OER, lactate all different between survivors and nonsurvivors. Final values - pHi and SvO2 worse in nonsurvivors.
Gutierrez, G	1992	Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet 339:195-9.	I	Keep pHi>7.35 or standard care. No benefit if initial pHi <7.35. Improved survival in patients with normal initial pHi.
Ivatury, RR	1995	Gastric mucosal pH and oxygen delivery and oxygen consumption indices in the assessment of adequacy of resuscitation after trauma. J Trauma 39:128-34.	I	pHi may be an important marker for resuscitation adequacy and an early indicator of post-resuscitation complications.
Ivatury, RR	1996	A prospective randomized study of end points of resuscitation after major trauma: global oxygen transport indices versus organ. JACS 183:145-54.	I	pHi marker of adequate resuscitation. Normalized later than DO2, lactate, and BD
Gomersall, CD	2000	Resuscitation of critically ill patients based on the results of gastric tonometry: A prospective, randomized controlled trial. Crit Care Med 28:607-614.	I	Compared standard tx with standard tx plus colloids and dobutamine for low pHi. No difference in outcome.
Doglio, GR	1991	Gastric mucosal pH as a prognostic index of mortality in critically ill patients. Crit Care Med 19:1037-40.	II	Low pHi predicts increased risk of death, sepsis, MOF. Worst if persists at 12 h.
Maynard, N	1993	Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory, failure. JAMA 270:1203-10.	II	Although a variety of resuscitation endpoints correlated with surviving critical illness, only pHi at 24h proved an independent predictor of death by logistic regression
Weil, MH	1999	Sublingual capnography: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock. Crit Care Med 27:1225-1229.	II	Prospective, criterion study of acutely-ill patients and normal volunteers. Sublingual PCO2 correlates with lactate level, presence of shock, and survival.
Baron, BJ	2002	Diagnostic utility of sublingual PCO_2 for detecting hemorrhage in patients with penetrating trauma. Acad Emerg Med (abstract)	II	In a prospective, observational study, sublingual CO_2 levels correlated with blood loss.
Gys, T	1988	The prognostic value of gastric intramural pH in surgical intensive care patients. Crit Care Med 16:1222-4.	III	pHi< 7.32 may correlate wth short-term mortality.

Boyd, O	1993	Comparison of clinical information gained from routine blood-gas analysis and from gastric tonometry for intramural pH. Lancet 341:142-146.	III	Prospective study of patients who required a pulmonary artery catheter. Base deficit and bicarbonate levels correlated well with pHi.
Roumen, RMH	1994	Gastric tonometry in multiple trauma patients. J Trauma 36:313-316.	III	Gastric pHi may predict morbidity in severely injured patients.
Miller, PR	1998	Threshold values of intramucosal pH and mucosal-arterial CO2 gap during shock resuscitation. J Trauma 45:868-72.	III	In trauma patients, the ability to predict death and multiple organ failure is maximized when pHi < 7.25 and gastric mucosal to arterial carbon dioxide gap is greater than 18 mm Hg.
Subcutaneous Oxygen and Carbon Dioxide Electrodes				
Jonsson, K	1987	Assessment of perfusion in postoperative patients using tissue pO2 measurements. Br J Surg 74:263-7.	II	Subcutaneous tissue oxygen tension was measured as an index of perfusion in 44 postoperative patients.12 of 30 patients were found to be underperfused by the authors definition and was not recognized by clinical criteria.
Waxman, K	1994	A method to determine the adequacy of resuscitation using tissue oxygen monitoring. J Trauma 36:852-856.	II	Monitoring tissue PO2 during an inspired O2 challenge may be a useful test to detrmine the adequacy of resuscitation. A negative O2 challenge was considered indicative of flow dependant O2 consumption and it was seen in 60 % of patients during acute resuscitation.
Tatevossian, RG	2000	Transcutaneous oxygen and CO2 as early warning of tissue hypoxia and hemodynamic shock in critically ill emergency patients. Crit Care Med 28:2248-53.	II	Continous PtO2 and PtCO2 monitoring evaluate tissue perfusion and serve as early warning in critically ill patients
Gote, H	1990	Tissue oximetry as a possible predictor of lethal complications after emergency intestinal surgery. Surg Res Comm 7:243-249.	III	Subcutaneous PO2 was measured in 10 patients undergoing emergency intestinal surgical procedures using a tonometer implanted in the abdominal wall. Subcutaneous PO2 values were higher in the survivors.
Drucker, W	1996	Subcutaneous tissue oxygen pressure: a reliable index of peripheral perfusion in humans after injury. J Trauma 40(3 Suppl):S116-22.	III	An optode probe which uses fluorescent techniques accurately measures the partial pressure of oxygen in subcutaneous tissues. This measurement correlates with the adequacy of resuscitation and tissue perfusion.
Near Infrared Spectroscopy				

Cairns, CB	1997	Evidence for early supply independent mitochondrial dysfunction in patients developing multiple organ failure after trauma. J Trauma 42:532-6.	II	Patients with severe trauma who developed MOF were found to display abnormal mithocondrial oxidative function. At 12 hours of resuscitation MOF and non-MOF patient did not have statiscally different DO2 or VO2, lactate was higher in MOF group. 89% of MOF have abnormal NIR values comapred to 13 % of nonMOF patients
Torella, F	2002	Regional tissue oxygenation during hemorrhage: Can near infrared spectroscopy be used to monitor blood loss? Shock 18:440-444.	II	Human volunteers undergoing donation of 470 ml blood were studied. Blood loss correlated with regional hemoglobin saturation in the cerebral cortex and left calf muscle, as well as oxygenation index (oxygenated -deoxygenated hemoglobin concentration).
McKinley, BA	2000	Tissue hemoglobin O2 saturation during resuscitation of traumatic shock monitored using near infrared spectrometry. J Trauma 48:637-42.	III	Hb O2 saturation was monitored non invasively and simultaneously in skeletal muscle and subcutaneous tissue. Skeletal muscle O2 tracked systemic O2 delivery. Authors sugest that it could be used in combination with BD and lactate to guide resuscitation