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\textsubscript{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\textsubscript{2} delivery issue has been examined by studies of supranormal O\textsubscript{2} delivery and studies of the utility of mixed venous O\textsubscript{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 pH$i$ is predictive of survival.
2. Persistently high base deficit or low pH$i$ (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 pH 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\textsubscript{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\textsubscript{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\textsubscript{2} delivery may actually have increased mortality. In contrast, Boyd, et al (18), found that, after fluid resuscitation, increasing O\textsubscript{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\textsubscript{2} delivery goal of 600 ml/min/m\textsuperscript{2} or 500 ml/min/m\textsuperscript{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\textsubscript{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\textsubscript{2} saturation (SvO\textsubscript{2}) levels should reflect the adequacy of O\textsubscript{2} delivery to tissues in relation to global tissue O\textsubscript{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\textsuperscript{2}), supranormal CI (>4.5 L/min/m\textsuperscript{2}), or normal SvO\textsubscript{2} (>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\textsubscript{2} delivery until lactate concentration normalized.
and O₂ 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, O₂ delivery index, and O₂ 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 O₂ 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 O₂ 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 ≥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°C), severe metabolic acidosis (base deficit >12 mmol/L), and a combination (temperature <35.5°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 ≥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 O₂ 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 ≥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 ≥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 O₂ 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 CO₂, as measured by end-tidal CO₂. Tyburski, et al (60), prospectively studied 106 trauma patients who required operations. Survivors had higher end-tidal CO₂, lower arterial-end tidal CO₂ differences, and decreased alveolar dead space ratio (estimated as the arterial-end tidal CO₂ difference/arterial PCO₂) 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 PCO₂ and subsequent decrease in tissue pH. Because CO₂ diffuses so readily across tissues and fluids, the PCO₂ 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 CO₂ is allowed to diffuse into the balloon for a specific period of time. The PCO₂ in the saline is then measured. Intramucosal pH (pHi) can be calculated based on the Henderson-Hasselbach equation. Continuous CO₂ 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, O₂ delivery, and O₂ 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 O₂ transport parameters in survivors and nonsurvivors. Survivors and nonsurvivors had similar O₂ delivery, but nonsurvivors had greater O₂ consumption, O₂ extraction ratio, and lactate levels; and lower pHi, mixed venous pH, and mixed venous PO₂. 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 O₂ transport or decreasing O₂ demand if the pHi decreased below 7.35 or 0.1 units below the previous value. Survival was similar between groups.
if the initial pH was low, but the protocol improved survival in those patients with initially normal pH. 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\textsubscript{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 pH ≥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 pH (<7.32) initially or subsequently. Three of these 8 developed complications and 2 died. All 7 with normal pH had uncomplicated recoveries. They found no correlation between initial pH and ISS, shock, lactate, or acute physiologic and chronic health evaluation (APACHE) II scores. Chang, et al (26), similarly found that pH <7.32 was a good predictor of MODS and mortality. Based deficit and mixed venous O\textsubscript{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 pH. All patients who developed MODS had pH <7.1.

Threshold values for pH and for the gastric mucosal-arterial CO\textsubscript{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 pH <7.25 and gap of >18 mm Hg. The CO\textsubscript{2} gap is a better indicator of gut “dysoxia” than pH, which is a calculated variable that may be altered by arterial bicarbonate levels (71).

Using pH as an endpoint (≥7.3) for resuscitation was compared to supranormal O\textsubscript{2} transport variables (O\textsubscript{2} delivery index of 600 mL/min/m\textsuperscript{2} and a O\textsubscript{2} consumption index of >150 mL/min/m\textsuperscript{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 pH or O\textsubscript{2} transport variables was similar. The only parameter that remained different between groups was pH. Looking at both groups, delay in achieving pH goals was more predictive of organ system failure, complications, and death than achieving the O\textsubscript{2} transport goals. The gap between gastric mucosal and arterial CO\textsubscript{2} was similarly predictive. In the postresuscitation period, persistently low or decreasing pH was an early signal of complications.

Technologic limitations of measuring gastrointestinal PCO\textsubscript{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\textsubscript{2} or removing CO\textsubscript{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\textsubscript{2} electrode that could continuously measure PCO\textsubscript{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 O₂ saturation of hemoglobin in tissue (StO₂ = HbO₂/[HbO₂+Hb]) during resuscitation in trauma patients. They found that StO₂ correlated with systemic O₂ delivery, base deficit, and lactate. This correlation was better than that found with gastric mucosal PCO₂ and PCO₂ gap (difference between gastric PCO₂ and arterial PCO₂).

NIRS technology allows the simultaneous measurement of tissue PO₂, PCO₂, 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, PCO₂, and PCO₂ gap were not as sensitive. Simultaneous measurements of tissue PO₂, PCO₂, 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 PO₂ and PCO₂ 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 O₂ supply, are tightly coupled to cytochrome a,a₃ redox, reflecting mitochondrial O₂ 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 SvO₂; 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 O₂ and CO₂ 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


4. American College of Surgeons Committee on Trauma: Advanced Trauma Life Support Course for Doctors, 1997. American College of Surgeons, Chicago, IL, USA.


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<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Boyd, O</td>
<td>Oxygenc Consumption and Distribution in Relation to Outcome. JAMA 269:1774-1779.</td>
</tr>
</tbody>
</table>

**Conclusions:**
- Resuscitation to goal values of oxygen transport variables may reduce morbidity and mortality in high-risk surgical patients.
- Oxygen consumption and delivery goals are important endpoints for resuscitation in critically ill patients.
- Failure to achieve goal values may be associated with increased mortality.
- Oxygen transport parameters, such as cardiac index, oxygen delivery, and oxygen consumption, are important indicators of outcome.

**Evidence:**
- Multiple prospective studies have evaluated the impact of goal-directed resuscitation on outcomes.
- Controlled trials have shown improved outcomes in patients resuscitated to goal values for cardiac index, oxygen delivery, and oxygen consumption.
- Observational studies have also suggested a relationship between goal achievement and improved outcomes.

**Class of Evidence:**
- Level I: Prospective randomized trials
- Level II: Prospective studies
- Level III: Retrospective or case-control studies

**Recommendations:**
- Resuscitation should be guided by goal values for oxygen transport parameters.
- Failure to achieve goal values should prompt reevaluation of resuscitation strategies.
- Continuous monitoring of oxygen transport parameters is recommended for high-risk patients.
## Additional Invasive Hemodynamic Monitoring Parameters

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Mixed Venous Oxygen Saturation</td>
<td>SVo2 &gt; 70% during resuscitation improves outcome.</td>
</tr>
<tr>
<td></td>
<td>SVo2 &lt; 70% during resuscitation is associated with increased mortality.</td>
</tr>
</tbody>
</table>
Endpoints of Resuscitation

Abou-Khalil, B 1994

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 resuscitation effort and to adjust the fluid and inotrope load. Invasive monitoring should include: central venous pressure, pulmonary artery pressure, cardiac output, and mixed venous oxygen saturation.

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 other indicators of tissue oxygenation to guide fluid and inotrope management.

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 significant lower incidence of multiple organ failure and death. Also the patients in the normal group maintained a higher RVEDI throughout the resuscitation period. These findings suggest that maintaining a high RVEDI during fluid resuscitation may improve outcome.

Chang, MC 1998

II Prospective study of critically-ill trauma patients. Resuscitation with fluids, blood, and inotropes led to rapid normalization of lactate levels. Survivors had lower heart rates, stroke work, left ventricular power, and better oxygen delivery.

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

II Maintaining LVP > 320 during resuscitation was associated with improved BD clearance and lower rates of organ dysfunction.

Chang 2002

II Prospective study of critically-ill trauma patients. Resuscitation with fluids, blood, and inotropes based on left ventricular power output and ventricular-arterial coupling led to rapid base deficit clearance and improved myocardial efficiency.

Kincaid, EH 2001

II Prospective study of critically-ill trauma patients who needed a pulmonary artery catheter. Ventricular compliance curves were constructed during volume loading using RVEDVI measurements.
<table>
<thead>
<tr>
<th>Arterial Base Deficit</th>
<th>Endpoints of Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>© 2003 Eastern Association for the Surgery of Trauma</td>
<td></td>
</tr>
</tbody>
</table>

### Rutherford, EJ 1992


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


II Age, ISS + >6u RBC 1st 12 hrs post injury were early predictors of MOF. BD and lactate were also helpful.

### Bannon, MP 1995


II BD and LA are better than central venous oxygen saturation (ScvO2) as indicators of blood loss as measured by peritoneal shed blood and by transfusion requirement.

### Davis, JW 1996


II Admission BD can be used to identify patients at risk for increasing transfusion requirements and ICU + hosp LOS.

### Botha, AJ 1997


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 reflects differences in metabolic acidosis between survivors and non-survivors as determined by pH determination.

### Eberhard, LW 2000


II The ED base deficit (BD) and the total crystalloid volume in 24h predict the development of ALI while the 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 hyperchloremic acidosis from other causes.

### 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 poor outcome and mortality.
Base deficit as a guide to volume replacement in the resuscitation of trauma patients.

- Siegel, JH 1990
  Both extracellular base deficit and the volume of blood transfused in the first 24 hours were significant predictors of mortality.

- Falcone, RE 1993
  Multivariate analysis revealed that only Trauma Score and age are predictive of survival. Base deficit is an important predictor of mortality.

- Davis, JW 1997
  The presence of ETOH results in significantly worse base deficit despite lower ISS and higher Ps in ETOH positive patients. BD <-6 remained a significant predictor of major injury regardless of ETOH level.

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  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.

- Dunham, CM 2000
  Base deficit level indicating major injury is increased with ethanol. J Emer Med 18:165-71.
  The presence of ETOH results in worsening of the base deficit independent of other variables. Risk of major injury increases when BD <-4.1 in ETOH positive patients vs. <-1.1 in ETOH negative patients.

- Rixen, D 2000
  Maximum oxygen debt (BD) and lactate correlate with early ARDS and death. Maximum BD and lactate were independent predictors of outcome.

- Kincaid, EH 2001
  Admission base deficit in pediatric trauma: a study using the National Trauma Data Bank. J Trauma 51:332-5.
  Base deficit is a useful guide to volume resuscitation.
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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.

Dunne, J 2002
Lactate and base deficit in trauma: does alcohol impair their predictive accuracy?
J Trauma 53:188 (abstract).

Eachempati, SR 2002
Factors associated with mortality in patients with penetrating abdominal vascular trauma.

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Serum bicarbonate as an endpoint of resuscitation in critically ill patients.
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Serial lactate determinations during circulatory shock.

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Lactate clearances and survival following injury.
J Trauma 35:584-589.

Manikis, P 1995
Correlation of serial blood lactate levels to organ failure and mortality after trauma.

Mikulaschek, A 1996
Serum Lactate Is Not Predicted by Anion Gap or Base Excess after Trauma Resuscitation.
J Trauma 40:218-224.

McNelis J 2001
Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit.

End-tidal Carbon Dioxide

Tyburski, JG 2002
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Surg Inf 4: (in press)

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Surg Inf 4: (in press)
Gastric Tonometry

Gutierrez, G 1992

Comparison of gastric intramucosal pH with measures of oxygen transport and consumption in critically ill patients.


IpHi, 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.


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.

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 endpoints of resuscitation after major trauma: global oxygen transport indices versus organ.

JACS 183:145-54.

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.


Comparison of 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.


Low pHi predicts increased risk of death. pHi <7.35 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.

Although a variety of resuscitation endpoints correlated with surviving critical illness, only pHi at 24h proved an independent predictor of survival.

Weil, MH 1999

Sublingual capnography: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock.


Prospective 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 PCO2 for detecting hemorrhage in patients with penetrating trauma.

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In a prospective, observational study, sublingual CO2 levels correlate with blood loss.

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### Endpoints of Resuscitation

**Near Infrared Spectroscopy**

<table>
<thead>
<tr>
<th>Author</th>
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<tbody>
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<td>Continuous PO2 and PCO2 monitoring and tissue perfusion.</td>
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<tr>
<td>Tatevossian, RG</td>
<td>2000</td>
<td>Transcutaneous oxygen and carbon dioxide electrodes as early warning of tissue hypoxia and hemodynamic shock.</td>
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**Subcutaneous Oxygen and Carbon Dioxide Electrodes**

<table>
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<tr>
<th>Author</th>
<th>Year</th>
<th>Study Details</th>
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<tbody>
<tr>
<td>Drucker, W</td>
<td>1996</td>
<td>Subcutaneous tissue oxygen pressure: a reliable index of peripheral perfusion in humans after severe trauma.</td>
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<tr>
<td>Roumen, RMH</td>
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<td>Comparison of clinical information gained from tissue PO2 and PCO2 and hemodynamic monitoring in multiple trauma patients.</td>
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<tr>
<td>Waxman, K</td>
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<td>A method to determine the adequacy of resuscitation using tissue PO2 monitoring.</td>
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<td>1987</td>
<td>Assessment of perfusion in postoperative patients using tissue PO2 measurements.</td>
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<td>Gote, H</td>
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<td>Gomber, RNH</td>
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<td>Comparison of clinical information gained from tissue PO2 and PCO2 and hemodynamic monitoring in multiple trauma patients.</td>
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**Subcutaneous Carbon Dioxide Electrodes**

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<tr>
<td>Millard, PK</td>
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<td>Tissue resuscitation: accurate tissue carbon dioxide measurement during and after shock.</td>
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<tr>
<td>Toff, 120</td>
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Patients with severe trauma who developed MOF were found to have reduced mitochondrial oxidative function. At 12 hours of resuscitation mitochondrial dysfunction was more prevalent in skeletal muscle and subcutaneous tissue.

MOF patients displayed abnormal mitochondrial oxidative function. At 12 hours of resuscitation mitochondrial dysfunction was more prevalent in skeletal muscle and subcutaneous tissue.

Regional tissue oxygenation during hemorrhage: Can near infrared spectroscopy be used to monitor blood loss? Shock 18:440-444.

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 indices monitored on standard hemoglobin saturation monitors. Blood loss correlated with regional hemoglobin saturation.


Hb O2 saturation was monitored non-invasively and simultaneously in skeletal muscle and subcutaneous tissue. Skeletal muscle O2 targeted system was delivered. Authors suggest that these monitoring modalities could be used in combination with BD and lactate to guide resuscitation.

Evidence for early supply independent mitochondrial dysfunction in patients developing MOF was found. At 12 hours of resuscitation mitochondrial dysfunction was more prevalent in skeletal muscle and subcutaneous tissue.

MOF patients displayed abnormal mitochondrial oxidative function. At 12 hours of resuscitation mitochondrial dysfunction was more prevalent in skeletal muscle and subcutaneous tissue.

Regional tissue oxygenation during hemorrhage: Torella, F 2002.

Near infrared spectroscopy was used to monitor blood loss. Blood loss correlated with regional hemoglobin saturation in the cerebral cortex and left calf muscle, as well as oxygenation indices monitored on standard hemoglobin saturation monitors. Blood loss correlated with regional hemoglobin saturation.