Endpoints of Resuscitation for Circulatory Shock:
When Enough is Enough?

Emanuel P. Rivers, MD, MPH, IOM
Vice Chairman and Research Director
Departments of Emergency Medicine and Surgery
Henry Ford Hospital
Detroit, Michigan
erivers1@hfhs.org

Supplemental oxygen ± endotracheal intubation and mechanical ventilation
Central venous and arterial catheterization
Sedation and/or paralysis (if intubated)
CVP
8-12 mm Hg
MAP
<65 mm Hg ≥90 mm Hg
ScvO₂
<70% ≥70%
Goals achieved
Yes
Hospital admission
No

Crystalloid
Colloid
Vasopressor or Nitroglycerin
Transfusion of red cells to hematocrit ≥30%
Dobutamine & Digoxin
Communication Avoids Misunderstanding and Prevents Problems

Inflammatory Mediators Produce Cardiovascular Insufficiency

Increased Metabolic Demands: Fever, Tachypnea

Microvascular Alterations: Impaired Tissue Oxygen Utilization

Hypovolemia, Vasodilation & Myocardial Depression

Cytopathic Tissue Hypoxia

Fink, Crit Care Clin, 2002
The Purpose of Resuscitation
“Perhaps Forgotten”

The Problem
- Uniformity of terminology
- Uniformity of goals
- Under-resuscitation
- Over-resuscitation
- Multiple outcome measures in clinical trials
- How do we solve the problem?

Endpoints and Tools
- Global tissue hypoxia
- Optimum region

Delivery Dependent
- Endpoints and Tools
- VO2

Delivery Independent
- Critical DO2
- DO2

Endpoints of Resuscitation
- Happy Cell
- Mediators

Substrates
- O2
- ATP
- Glucose

Goal Directed Optimization of Cardiac Function
- VO2
- DO2
- PaO2
- Hemoglobin
- Cardiac Output

Hemodynamic
- Preload (CVP, PCWP)
- Afterload (MAP, SVR)
- Contractility (SV)
- Heart Rate (BPM)
- Shock Index (HR/SBP)
- Coronary Perfusion Pressure

Microcirculation
- Stress
- Pain
- Hyperthermia
- Shivering
- Work of breathing
Macro Endpoints

Delivery Dependent          Delivery Independent

VO2

Global tissue hypoxia

Optimum region

VO2

Critical DO2

DO2

Substrates

O2
ATP
Glucose

Goal Directed

Hemodynamic
- Preload (CVP, PCWP)
- Afterload (MAP, SVR)
- Contractility (SV)
- Heart Rate (BPM)
- Shock Index (HR/SBP)
- Coronary Perfusion Pressure
Effects of perfusion pressure on tissue perfusion in septic shock

• OBJECTIVE: To measure the effects of increasing MAP on systemic O2 metabolism and regional tissue perfusion in septic shock.

• DESIGN: Prospective study.

• SETTING: MICU and SICU patients in a tertiary care teaching hospital.

• PATIENTS: 10 patients with septic shock requiring pressor agents to maintain a MAP ≥ 60 mm Hg after fluid resuscitation to a PAOP ≥ 12 mm Hg.

LeDoux, Crit Care Med, 2000

Effects of perfusion pressure on tissue perfusion in septic shock

• INTERVENTIONS: Norepinephrine was titrated to MAPs of 65, 75, and 85 mm Hg in 10 patients with septic shock.

<table>
<thead>
<tr>
<th></th>
<th>65 mmHg</th>
<th>85 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Index</td>
<td>4.7 +/- 0.5 L/min/m2</td>
<td>5.5 +/- 0.6 L/min/m2 (p &lt; 0.03)</td>
</tr>
<tr>
<td>Lactate</td>
<td>3.1 +/- 0.9 mEq/L</td>
<td>3.0 +/- 0.9 mEq/L (NS)</td>
</tr>
<tr>
<td>A-Gastric pCO2</td>
<td>13 +/- 3 mm Hg</td>
<td>16 +/- 3 at 85 mm Hg</td>
</tr>
<tr>
<td></td>
<td>(1.7 +/- 0.4 kPa)</td>
<td>(2.1 +/- 0.4 kPa) (NS)</td>
</tr>
<tr>
<td>Urine Output</td>
<td>49 +/- 18 mL/hr</td>
<td>43 +/- 13 mL/h (NS)</td>
</tr>
</tbody>
</table>

LeDoux, Crit Care Med, 2000
CONCLUSIONS:

- Increasing the MAP from 65 mm Hg to 85 mm Hg with norepinephrine does not significantly affect
  - systemic oxygen metabolism
  - skin microcirculatory blood flow
  - urine output
  - splanchnic perfusion.

LeDoux, Crit Care Med, 2000

Radial artery pressure monitoring underestimates central arterial pressure during vasopressor therapy in critically ill surgical patients

Critical Care Medicine 1998;26:1646-1649

Todd Dorman, MD, FCCM; Michael J. Breslow, MD, FCCM; Pamela A. Lipsett, MD; Jeffrey M. Rosenberg, MD, PhD; Jeffrey R. Balser, MD, PhD; Yaniv Almog, MD; Brian A. Rosenfeld, MD, FCCM

- Radial artery pressure underestimates central pressure in hypotensive septic patients receiving high-dose vasopressor therapy.

- The higher mean femoral arterial pressures:
  - immediate reduction in norepinephrine infusions in 11 of the 14 patients.

- Clinical management, based on radial pressures, may lead to excessive vasopressor administration.
MESA, Ariz. — Two years ago, Jeff Lewis woke up in the hospital and learned he had no hands or feet. Considering the alternative, he's grateful to be alive. His limbs were amputated to save him from a deadly circulatory infection.

“I thought it was some kind of evil joke,” he says. “All right,” I wanted to say. The joke’s over. Where are my hands and feet?”

Three weeks earlier, Lewis, 53, had awakened with a raging fever he thought was the flu. The high school math teacher rarely missed a day of school, but that morning he went to the hospital. Lewis had a common strep B infection that usually is fought off by the spleen. But his spleen had been removed after a shooting accident 20 years before, which left him vulnerable to the infection.

Lewis's body went into sepsis, or toxic shock. As the blood supply decreased to his extremities, the infection spread to his fingers and toes and eventually reached his forearms and shins.

So doctors amputated Lewis' hands and forearms below the elbow and his feet and shins below the knee.
Early changes in organ function predict eventual survival in severe sepsis.

Mortality (%)

- 20% No Vasopressor
- 37% No Vasopressor to Low Dose Vasopressor
- 58% No Vasopressor to High Dose Vasopressor
- 54% Low Dose Vasopressor

% Receiving Vasopressors

- 0-6 hours: 15%
- 6-72 hours: 15%
- 0-72 hours: 15%
An ICU Therapy Forever Changed

- A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy
Stop An International Crisis

- Transfusions do make a difference in shock or global tissue hypoxia states.
- Conservative management during the convalescent phase.

Abuse to the clinician after giving blood

Hemodilution After Volume

- No difference in blood transfused over 72 hours between groups
- 3.6 Liters More Fluid
- 60 ml
- 108 ml
Transfusion decisions depend on the clinical state.

Delivery independent VO\textsubscript{2} delivery dependent VO\textsubscript{2}

VO\textsubscript{2} SVO\textsubscript{2} OER Lactate

Hemodynamic Phases of Sepsis

- Even S\textsubscript{v}O\textsubscript{2} is a combination of various tissue beds.
- The coronary circulation is at the highest risks.
Transfusion Decisions Depend on the Clinical State

- **Delivery Independent**
  - VO₂
  - SVO₂
  - OER
  - Lactate

- **Delivery Dependent**
  - VO₂
  - SVO₂
  - OER
  - Lactate

**Dietrich, Critical Care, Med, 2000**

**Marik, JAMA, 2000**

**Herbert, NEJM, 2001**

**Vincent, JAMA, 2002**
### Transfusion Studies

<table>
<thead>
<tr>
<th>Setting</th>
<th>ED</th>
<th>ICU</th>
<th>ICU</th>
<th>ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (hours)</td>
<td>&lt;1</td>
<td>24 hours</td>
<td>Over 2 weeks</td>
<td>Up to 48 hours</td>
</tr>
<tr>
<td>Age</td>
<td>62-67</td>
<td>57-58</td>
<td>53-59</td>
<td>49.6</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.3 – 11.4</td>
<td>8.2-8.2</td>
<td>10.1-12.2*</td>
<td>9.9</td>
</tr>
<tr>
<td>Lactate (mM/L)</td>
<td>6.9 - 7.7</td>
<td>1.8±1.8 -1.8±2.1</td>
<td>----</td>
<td>2.6</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>48.6 - 49.2</td>
<td>----</td>
<td>----</td>
<td>69.5</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>5.3 - 6.1</td>
<td>----</td>
<td>----</td>
<td>Resuscitated</td>
</tr>
<tr>
<td>Cardiac Index</td>
<td>1.7 – 1.9</td>
<td>----</td>
<td>----</td>
<td>3.4</td>
</tr>
</tbody>
</table>

| APACHE      | 20.4±7.4 - 21.4±6.9    | 20.9±7.3 - 21.3±8.1  | 16.5-13.5            | ----                 |
| Mortality And Endpoints | 56-30.5 %             | 22.2 vs. 28.1% (0.05) | 18.5-10% ICU 22 -17% 28 day | Decreased pH |

In shock or global tissue hypoxia? | 100% | 16-13% | 20-23% | Excluding dialysis patients, patients likely to die in 24 hours and patients in established septic shock (systolic blood pressure <90 mmHg).
Substrates
- O₂
- ATP
- Glucose

Goal Directed
- DO₂
  - Hemoglobin
  - Cardiac Output

VO₂
- Stress
- Pain
- Hyperthermia
- Shivering
- Work of breathing

Hemodynamic
- Preload (CVP, PCWP)
- Afterload (MAP, SVR)
- Contractility (SV)
- Heart Rate (BPM)
- Shock Index (HR/SBP)
- Coronary Perfusion Pressure

VO₂
- Stress
- Pain
- Hyperthermia
- Shivering
- Work of breathing

Oxygen loading
Oxygen extraction
Tissue demand
Oxygen delivery

Central venous oxygen content (SvO₂)
Head and upper extremities

Arterial oxygen content (SaO₂)

Venous oxygen content (SvO₂)
Using Metabolic Endpoints

- VO₂
  - Stress
  - Pain
  - Hyperthermia
  - Shivering
  - Work of breathing

- DO₂
  - PaO₂
  - Hgb
  - Cardiac Output

- ScvO₂

- SvO₂

- 70-75%
Lactate and Outcome

(Mizock, Dis Mon, 1989) (Weil, Circulation, 1970)

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 hrs</td>
<td>27</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>24-48 hrs</td>
<td>21</td>
<td>6</td>
<td>77.8</td>
</tr>
<tr>
<td>&gt;48 hrs</td>
<td>3</td>
<td>19</td>
<td>13.6</td>
</tr>
</tbody>
</table>

(Abramson and Scalea, J Trauma, 1993)
Δ Lactate (ED Admission - ED Discharge)
ED Length of Stay (hrs)

- No clearance
  - <0 mM/L/hr
- Intermediate clearance
  - 0-1 mM/L/hr
- High clearance
  - >1 mM/L/hr

Δ Lactate (ED Admission - ED Discharge)
ED Length of Stay (hrs)

N = 114

Δ Lactate (ED Admission - ED Discharge)
ED Length of Stay (hrs)

N = 243

Quartiles of Lactate Clearance
Early Lactate Clearance

Time (hr)

Mortality (%)

No Clearance Intermediate Clearance High Clearance

% Lactate Clearance Quartiles and mean Biomarker Levels over 72 Hours

Caspase-3 (ng/mL)

Lactate Clearance Quartiles
% Lactate Clearance Quartiles and mean Biomarker Levels over 72 Hours

Substrates
- O₂
- ATP
- Glucose

Goal Directed
- VO₂
  - Stress
  - Pain
  - Hyperthermia
  - Shivering
  - Work of breathing
- DO₂
  - PaO₂
  - Hemoglobin
  - Cardiac Output

Hemodynamic
- Preload (CVP, PCWP)
- Afterload (MAP, SVR)
- Contractility (SV)
- Heart Rate (BPM)
- Shock Index (HR/SBP)
- Coronary Perfusion Pressure

Microcirculation

Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock.

Yves S. Sirot, NB, BSN, MDCM; Monique Trudel, MD; Daniel de Blicq, MD, PhD; Jacques Coteur, MD, RN; Jean Louis Vite, MD, PhD, FCCM

Crit Care Med 2004 Vol. 32, No. 9
The oxygen consumption-delivery relationship

A: Under-resuscitated delivery (cytopathic tissue hypoxia)

B: Resuscitated delivery

C: Lactate

D: Microcirculatory Dysfunction

Diffusion limitation

Utilization limitation

Mitochondria

ATP production
Nitroglycerin in septic shock after intravascular volume resuscitation
Peter E Sprock, Can Ince, Martin J Gadlen, Keschen R Mathura, Heleen M Oudemans-van Straaten, Dirk F Zuidstra
Lancet 2002

- Orthogonal polarization spectral (OPS) imaging allows visualisation of the microcirculation.
- Assessing microcirculatory flow in septic-shock patients who had a MAP > 60 mm Hg and CVP > 12 mm Hg.
- The infusion of 0.5 mg of nitroglycerin resulted in a marked increase in microvascular flow on OPS imaging.
- Improved recruitment of the microcirculation could be a new resuscitation endpoint in septic shock.

Micro-Circulatory Defects

- Extravascular inflammatory stimulus
  - Aggregation
  - Adherence
- Intravascular inflammatory stimulus
  - "anti-adhesion" therapy
  - Edema
  - Hemorrhage
  - Thrombosis
- Vascular occlusion and vasopressor use
  - Ischemia
  - and
  - Cellular
  - Hypoxia
30-minute infusion of a vasodilator, prostacyclin (5 ng/kg/min in 27 critically ill patients with acute respiratory failure and measured:
O2 delivery and uptake to tissues
Extraction ratio (uptake/delivery)

• **In the survivors:**
  – O2 extraction ratio fell
  – VO\textsubscript{2} increased.

• **In the patients who died:**
  – O2 extraction ratio rose
  – VO\textsubscript{2} did not change.

Conclusion: (an underappreciated endpoint)

– Substantial O2 debt or cryptic shock in patients who subsequently die.

– Inadequate tissue oxygenation may be difficult to recognize

– Important mechanism in the development of irreversible multiple organ failure.
Oxygen Debt: To Pay or Not to Pay

Direct Association of Decreased VO₂ Increased Mortality

- Cardiac arrest (Rivers, Chest, 1994)
- Trauma (Moore, J of Trauma, 1992)
- Sepsis (Tuchschmidt, Chest, 1991)
- Acute myocardial infarction (Rady, Chest, 1993)
- Heart transplantation (Mancini, J Clin Monit, 1991)
- Liver transplantation (Chest, 1992)
- ARDS (Appel, Chest, 1992)
Substrates
- O₂
- ATP
- Glucose

Endpoints of Resuscitation
- VO₂
  - Stress
  - Pain
  - Hyperthermia
  - Shivering
  - Work of breathing
- Lactate
- Base Deficit
- (a-v)CO₂
- SvO₂
- pHi
- DO₂

Goal Directed
- DO₂
  - PaO₂
  - Hemoglobin
  - Cardiac Output
- Hemodynamic
  - Preload (CVP, PCWP)
  - Afterload (MAP, SVR)
  - Contractility (SV)
  - Heart Rate (BPM)
  - Shock Index (HR/SBP)
  - Coronary Perfusion Pressure

Microcirculation

Metabolic Endpoints of Resuscitation

Delivery Dependent
- ScvO₂
- (a-v)pCO₂
- Gastric Tonometry
- Sublingual Cap.
- Base Deficit
- Lactate

Critical DO₂

Delivery Independent
- VO₂
  - O₂ extraction
  - Optimum region
- DO₂

Optimum region
Pulmonary Artery Catheter in the ICU

Global tissue hypoxia

Optimum region
(a-v) pCO₂ Gradient < 5 mmHg

- PaCO₂↓ but PvCO₂↑ in circulatory failure and low flow states
  (Mecher, Crit Care Med, 1990)

- Inverse relationship between CI and (a-v) pCO₂
  (Ducey, Crit Care Med, 1992), (Durkin, J Crit Care, 1993)

- ↑(a-v) pCO₂ increases mortality
  (Bakker, Chest, 1992)

(a-v) pCO₂ and Cardiac Index

\[
\ln(\text{CI}) = 1.942 - 0.18(a-mv)p\text{CO}_2 \\
\text{r}^2 = 0.87
\]

\[
\ln(\text{CI}) = 1.884 - 0.173(a-cv)p\text{CO}_2 \\
\text{r}^2 = 0.90
\]

N = 83

Cuschieri, Rivers and Donnino, Int Care Med, 2005)
Sublingual Capnometry

<table>
<thead>
<tr>
<th></th>
<th>healthy volunteers</th>
<th>without clinical signs of shock</th>
<th>physical signs of circulatory shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSL CO₂ mm Hg</td>
<td>45.2 +/- 0.7</td>
<td>53 +/- 8</td>
<td>81 +/- 24</td>
</tr>
<tr>
<td>Lactate (mM/L)</td>
<td>&lt; 2.5</td>
<td>&gt;2.5</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>5</td>
<td>20</td>
<td>26</td>
</tr>
</tbody>
</table>

When $P_{SL} \text{CO}_2 > 70$ mm Hg, its positive predictive value for the presence of physical signs of circulatory shock was 1.00.

When it was <70 mm Hg, it predicted survival with a predictive value of 0.93.
Base Deficit

- Amount of base required to titrate 1L blood to normal pH.
- Indicator of volume deficit.
- Guide to resuscitation in trauma patient. (Davis, J Trauma, 1988)
- Affected by administration of bicarbonate, temp, ETOH, heparin.

Can I use Base Deficit or Anion Gap?

<table>
<thead>
<tr>
<th>Lactate Range mmol/L</th>
<th>Serum HCO3&gt;22 and A.G. &lt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0 to 6.9</td>
<td>11.1%</td>
</tr>
<tr>
<td>7.0 to 9.9</td>
<td>8.3%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0%</td>
</tr>
</tbody>
</table>

Wira and Rivers, Crit Care Med, 2005
The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock*

Emanuel P. Rivers, MD, MPH; James A. Kruse, MD; Gordon Jacobsen, MS; Kant Shah, MD; Manisha Loomba, MD; Ronny Otero, MD; Ed W. Childs, MD

Crit Care Med, 2007
Shock on Admission: Predictor of PICU Ventilation in the Pediatric Sepsis Syndrome

Sira Estanes, MD, Francesco 1604x Condeo, MD, Gabriel 1604x Della, MD
Research

Hemodynamic goals in randomized clinical trials in patients with sepsis: a systematic review of the literature

Jonathan E Serransky¹, Seema Nour², Gregory M Susla³, Dals M Needham¹, Steven Hollenberg⁴ and Peter Pronovost⁵

Research

Hemodynamic goals in randomized clinical trials in patients with sepsis: a systematic review of the literature
Jonathan E. Serransky, Seema Nour, Gregory M. Susla, Dals M. Needham, Steven Hollenberg, and Peter Pronovost

- Most sepsis clinical trials reviewed did not include hemodynamic goals of therapy. Of note, the four largest clinical trials evaluating novel therapies in patients with sepsis did not specify hemodynamic goals of treatment.

- For those 13 studies identified in our systematic review, there was wide variation in hemodynamic measures selected and the hemodynamic goals chosen.

- Further research is necessary to determine whether this lack of consistency in hemodynamic goals may contribute to heterogeneity in treatment effects for clinical trials of novel sepsis therapies.


Before-after study of a standardized management of septic shock
Scott T. Micek, PharmD; Kameg Roubinian, M

A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: A randomized controlled trial
Chuyou Lin, Chien-Ying Liu, Nan-Pin Kuo

The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective implementation of an evidence-based “standard operating procedure” and outcome in septic shock
Andres Kurtz, MD; Petra Niederlin, MD; Michael Bauer, MD

Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol
Nathan I. Shapiro, MD, MPH; Michael D. Howell, MD; Daniel Talmor, MD, MPH; Dermot Lanney, Long Ngo, PhD; Jon Buras, MD, PhD; Richard E. Wolfe, MD; J. Woodrow Weiss, MD; Alan Lisbon, MD


Research

Community Hospital of Nontrauma

CHEST
A publication of the American College of Chest Physicians

31
Early goal-directed therapy of septic shock in the emergency room: Who could honestly remain skeptical?*

Jean Carlet, MD
Infectious Diseases
Department
Fondation Hôpital Saint-Joseph
Paris, France

Crit Care Med 2006 Vol. 34, No. 11

Optimization Trials
“A Closer Look”

Endpoints of Resuscitation

Substrates
- $\text{O}_2$
- ATP
- Glucose

Goal Directed
- $\text{DO}_2$
- $\text{SpO}_2$

Hemodynamic
- Preload (CVP, PCWP)
- Afterload (MAP, SVR)
- Contractility (SV)
- Heart Rate (BPM)
- Shock Index (HR/SBP)
- Coronary Perfusion Pressure

Microcirculation
- Stress
- Pain
- Hyperthermia
- Shivering
- Work of breathing

Happy Cell
- Base Deficit
- pH
- Lactate
- $\text{SvO}_2$

Mediators

$\text{DO}_2$
- Hemoglobin
- Cardiac Output