ENDPOINTS OF RESUSCITATION

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OUTLINE

• Recognition and characterization of shock

• Principals of resuscitation

• Pearls and pitfalls of common resuscitation markers

• Practical algorithm
SHOCK

• “A state of tissue dysoxia in which energy (ATP) production is inadequate to meet metabolic needs”
  – Not hypotension
  – Relative hypotension
  – Balance oxygen demand and supply
INADEQUATE ENERGY PRODUCTION CAN BE DUE TO IMPAIRED OXYGEN DELIVERY, UTILIZATION, OR BOTH.
IMPAIRED OXYGEN DELIVERY IS MUCH MORE COMMON AND THE ONLY ONE THAT WE CAN INFLUENCE

\[
\text{DO}_2 = CO \times \text{CaO}_2
\]

\[
\text{CaO}_2 = \text{Hgb} \times \text{SaO}_2 \times 1.34 + \text{PaO}_2 \times 0.0031
\]

\[
\text{CO} = \text{HR} \times \text{SV}
\]

\[
\text{SV} = \text{Preload, contractility, afterload}
\]

\[
\text{DO}_2 = (\text{Hgb})(\text{S}_a \text{O}_2)(\text{HR})(\text{preload})(\text{contractility})(\text{afterload})
\]

Index to BSA
OXYGEN CONSUMPTION

\[ \text{VO}_2 = \text{CO} \times \text{CaO}_2 - \text{CO} \times \text{CvO}_2 \]

Index to BSA
RESUSCITATION

• “The timely, systematic, goal-directed, reversal of shock”
PRINCIPALS OF RESUSCITATION

- The patient must be in shock
- Earlier is better
- Frequent re-evaluation with objective, pre-specified targets
- Stop when these targets are achieved
EXCESSIVE VOLUME EXPANSION OF TRAUMA PATIENTS IS BOTH PREVALENT AND DANGEROUS

- Excess volume expansion results in organ dysfunction
- Geriatric population with intolerance to acute volume expansion
- Negative fluid balance correlates with improved survival in ARDS and sepsis
PRINCIPALS OF RESUSCITATION

- The patient must be in shock
- Early is better
- Frequent re-evaluation with objective, pre-specified targets
- Stop when these targets are achieved
EARLIER RESUSCITATION IS BETTER

“THE RESUSCITATION WINDOW”

1. Control Groups with Mortality Rates Greater than 20%

A. Goals to Supranormal Values After Organ Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Type</th>
<th>Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alia, 1999</td>
<td>63</td>
<td>Surg/Med</td>
<td>0.74 - 0.66</td>
<td>0.09</td>
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<tr>
<td>Yu, 1998</td>
<td>66</td>
<td>Surgical(&lt;75yr)</td>
<td>0.21 - 0.52</td>
<td>0.31</td>
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<tr>
<td>Yu, 1998</td>
<td>39</td>
<td>Surgical(&gt;75yr)</td>
<td>0.57 - 0.62</td>
<td>-0.04</td>
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<tr>
<td>Gattinoni, 1995</td>
<td>762</td>
<td>Tra/Surg/Med</td>
<td>0.49 - 0.48</td>
<td>0.01</td>
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<tr>
<td>Hayes, 1994</td>
<td>109</td>
<td>Surg/Med</td>
<td>0.50 - 0.30</td>
<td>0.2</td>
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<tr>
<td>Yu, 1993</td>
<td>70</td>
<td>Surgical</td>
<td>0.34 - 0.34</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Subtotal: 0.0 (+/- 0.07), p>0.05

B. Goals to Supranormal Values Before Organ Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Type</th>
<th>Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobo, 2000</td>
<td>42</td>
<td>Surgical</td>
<td>0.16 - 0.33</td>
<td>-0.17</td>
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<tr>
<td>Wilson, 1999</td>
<td>138</td>
<td>Surgical</td>
<td>0.04 - 0.37</td>
<td>-0.32</td>
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<tr>
<td>Bishop, 1995</td>
<td>115</td>
<td>Trauma</td>
<td>0.18 - 0.37</td>
<td>-0.19</td>
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<td>Boyd, 1993</td>
<td>107</td>
<td>Surgical</td>
<td>0.06 - 0.22</td>
<td>-0.17</td>
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<td>Tuchschmidt, 1992</td>
<td>70</td>
<td>Medical</td>
<td>0.50 - 0.72</td>
<td>-0.22</td>
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<td>Shoemaker, 1988</td>
<td>70</td>
<td>Tra/Surg</td>
<td>0.04 - 0.30</td>
<td>-0.26</td>
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<td>Schultz, 1985</td>
<td>70</td>
<td>Trauma</td>
<td>0.03 - 0.29</td>
<td>-0.26</td>
</tr>
</tbody>
</table>

Subtotal: -0.23 (+/- 0.07), p<0.05
• The patient must be in shock

• Early is better

• Frequent re-evaluation with objective, pre-specified targets

• Stop when these targets are achieved
MARKERS OF SHOCK AND RESUSCITATION ADEQUACY ARE THE SAME

**Upstream**
- Oxygen content
- Volume status
- Contractility

**Downstream**
- organ-specific
- global
  - $S_vO_2$
  - Products of anaerobic metabolism

**O_2**

**ATP**

**H+**

**lactate**

**BD**
UPSTREAM MARKERS ARE USEFUL FOR DETERMINING THE ETIOLOGY OF SHOCK

- Hypovolemic
- Hemorrhagic
- Cardiogenic
- Obstructive
- Vasodilitaory
TRADITIONAL UPSTREAM MEASUREMENTS ARE STATIC

- Heart Rate
- Blood Pressure
- Urine Output
- Central venous pressure
- Pulmonary artery occlusion pressure
- Ejection fraction
- Cardiac Output

Outside of grossly deranged values, we do not know if the measurement is too high, too low, or just right for any particular patient

CVP ≠ preload responsiveness
LIMITATIONS OF STATIC MEASURES

THE FRANK-STARLING CURVE

Which curve are we on?

family of curves
LIMITATIONS OF STATIC MEASURES
CENTRAL VENOUS PRESSURE

ROC AUC = 0.56

Chest 2008;134:172
CAN WE PREDICT THE RESPONSE BEFORE GIVING THE VOLUME?
DYNAMIC MEASUREMENTS OF VOLUME RESPONSIVENESS

• Predict the response of cardiac output to a physiologic change in pre-load (“auto” volume challenge)

• Determine the utility of volume expansion before it is given

• Quick, safe, and cheap

• **Examples:**
  – Pulse pressure variation
  – Passive leg raise
  – Respiratory variation in inferior vena cava diameter
SUMMARY: UPSTREAM MARKERS

- Useful for determining etiology of shock
- Dynamic better than static
- Main limitation: do not reveal adequacy of oxygen delivery
DOWNSTREAM MARKERS ARE USEFUL FOR DETERMINING IF SHOCK EXISTS, AND TRACKING RESUSCITATION EFFORTS

- Calculating/estimating oxygen delivery tells you nothing about the adequacy of that level of oxygen delivery.
DOWNSTREAM MARKERS: ORGAN SPECIFIC

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Sign/Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous</td>
<td>Lethargy, agitation, coma</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension, ST segment depression/ elevation, elevation of cardiac enzymes</td>
</tr>
<tr>
<td>Renal</td>
<td>Oliguria, decreased fractional excretion of sodium</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Feeding intolerance, adynamic ileus, stress ulceration/gastritis, enteritis, colitis</td>
</tr>
<tr>
<td>Hepatopancreaticobiliary</td>
<td>Hepatitis, centrilobar necrosis, cholestasis, acalculus cholecystitis, pancreatitis</td>
</tr>
</tbody>
</table>

Good rapid screening test for possibility of shock
DOWNSTREAM MARKERS: GLOBAL

Oxygen Delivery

- Normal
- $\downarrow S_v O_2$
- Increased $O_2$ extraction
- Anaerobic metabolism

Oxygen Consumption
Central venous ($S_{cv}O_2$) vs. mixed venous ($S_vO_2$)

- Normal $S_vO_2$ 70%
- $S_{cv}O_2 > S_vO_2$ by 5-15%
- Low values correlate with increased mortality
- Normalization correlates with improved survival
- Trend is more important than absolute value
**DOWNSTREAM MARKERS: GLOBAL- $S_vO_2$**

- **Advantages**
  - Early marker of tissue hypoperfusion
  - Continuous

- **Disadvantages**
  - Invasive
  - Labor intensive
  - False negatives
DOWNSTREAM MARKERS: GLOBAL-PRODUCTS OF ANAEROBIC METABOLISM

Glucose → pyruvate

Anaerobic:
- lactate
- $\text{H}^+$
- ATP

Aerobic:
- $O_2$
- Acetyl-Co-A
- ATP
- CO$_2$
- H$_2$O

$\text{Glucose} \rightarrow \text{pyruvate} \rightarrow \text{O}_2 \rightarrow \text{CO}_2, \text{H}_2\text{O}$
DOWNSTREAM MARKERS: GLOBAL-LACTIC ACIDOSIS

- **Type A:** tissue hypoxia $\Rightarrow$ excessive lactic acid production

- **Type B:** insufficient liver metabolism of lactate
  - Hepatic insufficiency
  - Pharmacologic
    - Propofol
    - Metformin
    - Highly Active Antiretroviral Treatment (HAART)

- Lactate:pyruvate ratio
The amount of base (mEq) that must be added to each liter of oxygenated blood to return the pH to 7.40 at a temperature of 37.0 and a pCO$_2$ of 40 mm Hg.

- Normal range -2 to +2
- Correlates with depth of shock
- Bicarbonate probably a reasonable substitute
- Caution: hyperchloremic non anion gap metabolic acidosis
Anion gap = $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$

$\uparrow\text{Cl}$ or $\downarrow\text{HCO}_3 = \text{nl AG}$

$\uparrow\text{Anion not measured} = \text{increased AG}$
Resuscitation with chloride-rich fluids can result in a worsening non anion gap, metabolic acidosis due to hyperchloremia.

This can be misinterpreted as worsening shock, which is then treated with chloride-rich fluids.

This misinterpretation is avoided by observing the serum chloride concentration and calculating the anion gap.
For each decrease in albumin of 1 g/dl, the expected AG decreases by 2.5
ALBUMIN AND THE ANION GAP

- Failure to correct the anion gap for hypoalbuminemia can lead to misinterpretation of an anion gap acidosis as a non anion gap acidosis.

- Example: base deficit 8, anion gap 10, albumin 2.0
  - What is the corrected anion gap?
  - What is the lactate?
ACIDOSIS ALGORITHM

Respiratory or metabolic?
- Check CO₂

Anion gap or non anion gap?
- Correct for albumin

Anion gap
- MUDPILES

Non anion gap
- HARDUP

Methanol
Uremia
Diabetic Ketoacidosis
Paraldehyde
Infection
Lactic Acidosis
Ethylene Glycol
Salicylates

Hyperalimentation
Acetazolamide use.
Renal tubular acidosis
Diarrhea
Uretosigmoid fistula
Pancreatic fistula
# Downstream Markers: Global

<table>
<thead>
<tr>
<th></th>
<th>Lactate</th>
<th>Base deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timeliness of information</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Arterial sample</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Specificity for tissue hypoperfusion</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Unaffected by impaired hepatic metabolism/medications</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Cost</td>
<td>$80</td>
<td>$120</td>
</tr>
</tbody>
</table>
ALGORITHM

Concern for shock

- History and exam
- Abnormal vital signs
- End organ malperfusion
- Age/comorbidities

Check global downstream marker of tissue perfusion

Characterize etiology of shock (upstream markers) → intervention

- Hypovolemic
- Hemorrhagic
- Cardiogenic
- Obstructive
- Vasodilatory

STOP

normal

abnormal
PATIENT IMPROVING, RESUSCITATION MARKER IS NOT

- **Lactate**
  - Check liver function
  - Check lactate:pyruvate ratio

- **Base deficit/bicarbonate**
  - Check chloride
  - Check anion gap
  - Check albumin

- **Assess for locoregional hypoperfusion**
SUMMARY

- Identify shock before embarking on resuscitation
- Downstream markers are used to diagnose shock and monitor resuscitation
- Upstream markers are used to characterize etiology of shock, and should be dynamic if possible
- Lactate and base deficit are comparable, provided a knowledge of potential pitfalls
SUMMARY

- Trends are more important than isolated values
- Stop resuscitation when pre-determined endpoints are reached
- Treat the whole patient, not isolated lab values
- If the patient is not responding to your efforts, you are either not being aggressive enough or you have the wrong diagnosis: START OVER
• 1,298 trauma patients

• Admission lactate and BD equally effective at predicting mortality (AUC 0.70, p<0.01)

• Over subsequent ICU course, lactate more sensitive than BD

• When BD normal, elevated lactate remained sensitive; not true for the opposite
Serum bicarbonate may replace the arterial base deficit in the trauma intensive care unit

Elizabeth FitzSullivan, B.S., Ali Salim, M.D., Demetrios Demetriades, M.D., Ph.D., Juan Asensio, M.D., Matthew J. Martin, M.D.*

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Presented at the 57th Annual Meeting of the Southwestern Surgical Congress, San Antonio, Texas, April 10–12, 2005
1. Left heart preload varies with respiration, increasing with inspiration and decreasing with expiration during mechanical ventilation.

2. This pre-load variation translates into PPV.

3. PPV is greater when the heart operates on the steep portion of the Frank-Starling curve.

4. Increased PPV predicts preload responsiveness.
PULSE PRESSURE VARIATION

PHYSIOLOGY

• Positive pressure ventilation: inspiration
  – ↑pleural pressure → compression of pulmonary veins → ↑LV preload → ↑CO → ↑BP
  – ↓venous return → ↓RV filling → ↓RV output → ↓LV output several beats later, during expiration
This variation is greater when the heart operates on the steep portion of the Frank-Starling curve.

Increased PPV predicts pre-load responsiveness.
PULSE PRESSURE VARIATION

PHYSIOLOGY

- $PPV = \frac{(P_{\text{max}} - P_{\text{min}})}{([P_{\text{max}} + P_{\text{min}}])/2}$

- $\geq 13\%$ predicts response to fluid

- Criteria for calculation
  - Sinus rhythm
  - Passive breathing (AC mode with good synchrony)
  - Tidal volume $> 8$ cc/kg
  - $P_{\text{max}}$ and $P_{\text{min}}$ must be calculated over the same respiratory cycle
40 septic shock patients given a volume challenge

Responders (\(\uparrow CI \geq 15\%\) by themodilution) vs. non-responders

RAP, PAOP, PPV, SPV before volume expansion

Using PPV threshold of \(\geq 13\%\), 94% sensitivity and 96% specificity.
PULSE PRESSURE VARIATION
LIMITATIONS

- Passive respiration
- Sinus rhythm
- Cumbersome
PASSIVE LEG RAISE

- Lifting the legs 45° induces a reversible “self volume challenge” of approximately 300 mL

- Maximal response at 60 seconds

- Response in cardiac output dependent upon preload responsiveness

- Not affected by arrhythmias or ventilator triggering
• 71 Ventilated med-surg ICU patients (predominantly septic shock)

• Attending-level decision to perform a fluid challenge secondary to
  – Hypotension (systolic < 90 mm Hg)
  – Oliguria (uo < 0.5 cc/kg for ≥ 2 hours)
  – Tachycardia
  – Mottled skin

• Measured PPV and aortic blood flow at baseline, after PLR, and after VE (500 mL NS over 10 minutes)

• Outcome = ≥15% increase in aortic blood flow (responders)
PASSIVE LEG RAISE
MONNET ET AL.

![Graph showing aortic blood flow (% change from Base1) with different markers for responders and non-responders.](image)
• ↑aortic blood flow of ≥ 10% with PLR; 97% sensitivity and 94% specificity for responsiveness

• ROC AUC=0.96
• N=30 patients without inspiratory effort or arrhythmia

• PPV ≥ 12% predicted response with 88% sensitivity and 93% specificity

• In this subgroup, ROC AUC for PLR and PPV were identical (0.91)
PASSIVE LEG RAISE
LIMITATIONS

• Patient positioning issues
  – Sympathetic discharge upon repositioning
  – Caution if elevated intracranial pressure

• Most accurate with continuous cardiac output monitoring
  – Confirm PLR resulted in an increase in pre-load
  – Measure cardiac output following PLR
  – Weaker correlation of PLR with PPV (ROC AUC 0.75) as compared to aortic blood flow (ROC AUC 0.96)
Mechanical ventilation induces cyclical changes in vena cava diameter that are reflected in changes in aortic flow within a few heart beats.

- **↑** IVC diameter during inspiration
- **↓** IVC diameter during expiration
- These changes are more pronounced in hypovolemic patients
Respiratory Variation in IVC Diameter

Technical Aspects

- **Sub-xiphoid**
- **2-5 cm from RA**
- **M mode**
- \[ \Delta D_{IVC} = \left( \frac{(D_{IVC_{max}} - D_{IVC_{min}})}{(D_{IVC_{max}} + D_{IVC_{min}})} \right) \times 100 \]
Respiratory Variation in IVC Diameter
Feissel et al.

• 39 ventilated patients with septic shock

• Clinical decision to perform a volume challenge secondary to
  – Tachycardia
  – Oliguria
  – Hypotension
  – Skin mottling
  – Worsening organ dysfunction

• Exclusion: ECHO evidence of RV failure

• 8mL/kg of 6% hydroxyethylstarch over 20 min)
Respiratory Variation in IVC Diameter
Feissel et al.

- **Sub-xiphoid, M mode view 3 cm from RA over 1 resp cycle**

- \[ \Delta D_{IVC} = \left( \frac{(D_{IVC_{max}} - D_{IVC_{min}})}{(D_{IVC_{max}} + D_{IVC_{min}})/2} \right) \times 100 \]

- **Outcome = ↑ aortic blood flow ≥ 15%**
Respiratory Variation in IVC Diameter
Feissel et al.

- $\Delta$ ABF weakly correlated with absolute (static) IVC measurements of $D_{IVC_{\text{max}}}$ & $D_{IVC_{\text{min}}}$

- Correlated highly with $\Delta D_{IVC}$

- $\Delta D_{IVC} \geq 12\%$ resulted in a PPV of 93% and a NPV of 92%
Respiratory Variation in IVC Diameter

Limitations

• Requires training

• User dependent

• Patient dependent
Conclusions

• Aggressive volume expansion is essential to early resuscitation in shock but may be detrimental subsequently.

• Determination of the optimal fluid management strategy for critically ill patients is limited by the inaccuracies of static measures of volume responsiveness.

• Dynamic measures of volume responsiveness are highly accurate in critically ill patients in septic shock.

• Such measurements may help to guide volume expansion, hasten correction of underlying pathology, and improve patient outcome.
SUBSEQUENT FLUID MANAGEMENT STRATEGY FOR CRITICALLY ILL PATIENTS REMAINS UNCLEAR

- What is the goal?
- When (if ever) does the goal change?
- How do we best measure goal attainment?
  - Accuracy
  - Practicality
  - Cost

![Graph showing survival probability over time](image)

Gattinoni et al. NEJM 1995

<table>
<thead>
<tr>
<th>Table 2. Outcomes of the Supranormal and Normal Resuscitation Cohorts*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Intra-abdominal hypertension</td>
</tr>
<tr>
<td>Abdominal compartment syndrome</td>
</tr>
<tr>
<td>Multiple organ failure</td>
</tr>
<tr>
<td>Death</td>
</tr>
</tbody>
</table>

*Data are given as percentage of patients. †P<.05.

• 89 MICU patients thought to benefit from volume expansion for any reason

• PLR test performance: sensitivity 81%, specificity 93%, PPV 91%, NPV 85%

• Less than 50% of ICU patients given a fluid bolus were volume responsive
SHOCK