Why not measure intravascular volume to determine endpoint of fluid resuscitation?

Mihae Yu MD, FACS
Professor of Surgery University of Hawaii
Medical Director of Surgical Intensive Care Unit

Queen’s Medical Center
Program Director of Surgical Critical Care Fellowship
Funding from Queen Emma Research Fund, American Foundation for Safe Blood, Daxor Co.
What is our goal? What tools do we need?

- Deliver oxygen to the cells to generate ATP.
- Essential ingredients:
  - Hemoglobin – binds O2
  - Pulmonary system - oxygenation
- Cardio-Vascular system: heart to carry O2 to the tissues, and a vascular system which contains the essential ingredients of fluid, nutrition, hemoglobin-oxygen
What tools do we need?

- Red cell volume ≠ Hemoglobin, Hct (in relationship to plasma)
- Intravascular volume ≠ surrogate markers (anything BUT volume)
- Cardiac output
- Tissue perfusion parameters:
  - Global parameters: lactic, ScvO2, SVO2,
  - Tissue parameters: PtcO2, Perfusion index, StO2, tonometers

GOAL: cellular bioenergetics
One guideline suits all
Protocol driven

Regressing: improving the individual components which help to achieve our goal

Getting oxygen to the cells

Cardiac function
Pulmonary system
Vascular system: red cell volume,
And plasma volume
Synonyms for Blood volume

- Intravascular volume
- Circulating Blood volume
- Effective circulating blood volume
We are 60% water: 40% of TBW is inside the cells (ICF) 20% TBW is outside the cells (ECF): 15% TBW is in the Interstitium (space between the vessel and cells), 5% is in intravascular space (plasma volume).

Inside the vessels live: RBC (carry O2), plasma, albumin (oncotic pressure), nutrition.

Blood Volume = Plasma + RBC (7% of TBW)
Pathologic states (shock), capillary membrane leaks albumin and fluid to interstitium. Interstitial fluid increases **EDEMA: TOTAL BODY FLUID EXCESS, INTRAVASCULAR VOLUME?**

Difficult to assess blood volume clinically
POST-resuscitation: malnutrition - low albumin, cirrhotic
All roads lead to “euvolemia”: every guideline

- ACC/AHA guidelines in chronic CHF patients.
- Septic shock, trauma, critically ill: adequate preload.
- First basic principle in treatment of all patients: EUVOLEMIA
- BUT HOW?
Debate of the century in resuscitation...

- What is the patient's intravascular volume?
- Heated discussions at bedside, diuresis vs fluids
- Endpoint of fluid resuscitation?
- Endpoint of red cell transfusion?
Technology is catching up

\[ C_1 \times V_1 = C_2 \times V_2 \]

V.F. Fairbanks, et al.

Principles of measurement

- Albumin not treated as foreign material but does transudate at a rate which is a semilogarithmic function of its concentration in plasma.
- Inject tagged I-131 over 1 minute push, wait 12 minutes (full mixing)
  5 Samples every six minutes
- Multipoint analysis and extrapolate to time zero to compensate for transudation of albumin from plasma. Slope gives information on how quickly albumin is leaking, “capillary leak”.
Hct: red cell volume to BV (PV + RBCV)

Measure PV (I-131), Measure Hct, Calculate RBCV
Normal RBCV + Normal PV
Euvolemic Anemia: Low RBCV + High PV = Hct 30%
Hypovolemic Anemia: Low RBCV + High PV = Hct 30%
Size matters: absolute mL vs relative to baseline BV
Compare to what? What is normal for that person?

- 70 mL/kg (not at extremes of wt)
- (Feldschuh, Circulation 1977;56:605): % deviation from norm is better than wt or BSA (validated with actual BV measurements)
- Patients height
- Optimum weight associated with longevity (metropolitan life table)
- Patients current weight
- Patients wt deviation from optimum weight, plot against measured BV
% deviation from ideal wt.
Better than:
ml/kg, ht, wt, BSA.
<table>
<thead>
<tr>
<th></th>
<th>Whole Blood Volume</th>
<th>Red Cell Volume</th>
<th>Plasma Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>±8%</td>
<td>±10%</td>
<td>±8%</td>
</tr>
<tr>
<td><strong>Mild Deviation</strong></td>
<td>±9-16%</td>
<td>±11-20%</td>
<td>±9-16%</td>
</tr>
<tr>
<td><strong>Moderate Deviation</strong></td>
<td>±17-24%</td>
<td>±21-30%</td>
<td>±17-24%</td>
</tr>
<tr>
<td><strong>Severe Deviation</strong></td>
<td>±25-32%</td>
<td>±31-40%</td>
<td>±25-32%</td>
</tr>
<tr>
<td><strong>Extreme Deviation</strong></td>
<td>&gt;32%</td>
<td>&gt;41%</td>
<td>&gt;32%</td>
</tr>
</tbody>
</table>
Blood Volume Analysis

**Patient Demographics**
- **Patient Name:** [Redacted]
- **DOB:** [Redacted]
- **Gender:** Female
- **Weight:** 36.30 kg
- **Height:** 147.30 cm
- **Deviation from Ideal Weight:** -23.8%
- **Age:** 78
- **Analyzed On:** [Redacted]
- **Injectate Lot:** V141710-712
- **Location:** [Redacted]

**Patient Sample Counts**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Time</th>
<th>Hct-A (%)</th>
<th>Hct-B (%)</th>
<th>Avg Hct</th>
<th>Count-A</th>
<th>Count-B</th>
<th>Avg Count</th>
<th>Unadjusted Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample 1</td>
<td>12:00</td>
<td>37.3</td>
<td>37.3</td>
<td>37.3</td>
<td>16097</td>
<td>16553</td>
<td>16325</td>
<td>2998</td>
</tr>
<tr>
<td>Sample 2</td>
<td>18:00</td>
<td>37.3</td>
<td>37.3</td>
<td>37.3</td>
<td>641</td>
<td>645</td>
<td>643</td>
<td>3024</td>
</tr>
<tr>
<td>Sample 3</td>
<td>24:00</td>
<td>37.3</td>
<td>37.3</td>
<td>37.3</td>
<td>8811</td>
<td>8838</td>
<td>8825</td>
<td>3081</td>
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<tr>
<td>Sample 4</td>
<td>30:00</td>
<td>37.3</td>
<td>37.3</td>
<td>37.3</td>
<td>8758</td>
<td>8759</td>
<td>8754</td>
<td>3114</td>
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<tr>
<td>Sample 5</td>
<td>36:00</td>
<td>37.3</td>
<td>37.3</td>
<td>37.3</td>
<td>8624</td>
<td>8583</td>
<td>8604</td>
<td>3169</td>
</tr>
</tbody>
</table>

**Blood Volume Analysis Results**
- **Room Background Count:** 38
- **Tube:** Sprayed EDTA (1.00)
- **Sample Acquisition Time:** 1 min. 30 sec.
- **Isotope:** Indium-111
- **Dose:** 20 microCurie

<table>
<thead>
<tr>
<th>Component</th>
<th>BV Result</th>
<th>Patient Ideal</th>
<th>Deviation From Ideal</th>
<th>Excess/Deficit %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Blood Volume</td>
<td>2910 mL</td>
<td>3127 mL</td>
<td>-217 mL</td>
<td>-6.9% Normal Deficit</td>
</tr>
<tr>
<td>Red Blood Cell Volume</td>
<td>978 mL</td>
<td>1127 mL</td>
<td>-149 mL</td>
<td>-13.2% Mild Deficit</td>
</tr>
<tr>
<td>Plasma Volume</td>
<td>1932 mL</td>
<td>2000 mL</td>
<td>-68 mL</td>
<td>-3.4% Normal Deficit</td>
</tr>
</tbody>
</table>

**Blood Volume Interpretation Guideline**

- **BV, PV Deviation (%):**
  - Normal: 0 to 8
  - Mild: 8 to 16
  - Moderate: 16 to 24
  - Severe: 24 to 32
  - Extreme: >32
  - **BVA (mL):**
    - Normal: 978 mL
    - Mild: 1127 mL

**Sample Data Analysis**

- **Standard Deviation:**
  - Patient Result: 2910
  - Acceptance Range: 0.172% or 10.8 mL
  - **Graph:**
    - 2910 mL
    - Slope: 0.23 %/min

**Albumin Transudation Analysis/Slope (%/min):**

- **Patient:**
  - Reference Range:
    - Normal: 0 to 0.4
    - High: 0.4 to 0.8
    - **Unusually High:** 0.5
**interpretation**

- Whole BV value is noted first, then RBCV followed by PV.
- Red cell volume is interpreted in relation to the whole blood volume. It is a normal physiologic response for plasma volume to expand when red cell volume diminishes. PV changes in a direction to maintain homeostasis for whole blood volume (this may not occur in the critically ill).
Last century: Surrogate markers to guide fluid management, creatures of habit (ABV)

- **BP**: late sign due to hormonal response and compensation: 60% low, 30% normal, 10% high (Little RA). “Adequate BP” may be higher than 90 mmHg (Eastridge BJ).

- **HR**: Heart rate (HR) is not a reliable guide to detect hypotension (victorino 2003).

- “Adequate UO” adequate depends on the concentrating ability of the kidneys and nitrogenous waste. Oliguria is a late sign of RF. (Brown 1980).

- I+O, weights (third spacing fluid), BUN/creatinine
Current guide to fluid management (ABV)

- BE, LA - poor perfusion, guide to amount of fluid? timing
- CXR discrimination for cardiac filling pressures is poor (ely 01)
- Central cardiac measurement: CVP, PAOP, CI, SVI
- SVV, PPV: volume responsiveness of the heart
- BNP
CVP ≥8? Pressure ≠ Volume


- BV is better correlated with improved CO and SV than CVP (Kuntscher)

- Hemorrhagic shock rats and transfusion, better relationship between BV and hepatocellular function, than CVP or CO (Wang 94)
Fantasy of equating Pressure to Volume (sccm 2015)

97 simultaneous data points on 50 patients; day 1,2 after resuscitation. 15% with normal/hi CVP were hypovolemic

<table>
<thead>
<tr>
<th>Number of Data Points in Each Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV&lt;0%</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>CVP&lt;8mmHg</td>
</tr>
<tr>
<td>CVP 8-12 mmHg</td>
</tr>
<tr>
<td>CVP&gt;12 mmHg</td>
</tr>
</tbody>
</table>
Outcome studies of Cvp ≥8

- CVP ≥8 (Rivers 01, Murphy 09, fisherman 04, westphal 06) and up to 15 mm Hg (Moore 06)
- Treatment are part of a bundled care, and makes the impact of individual component difficult to assess (Barochia 2010).
- Individual components have room for improvement
CVP, PAOP ≠ Blood volume

- The PAOP seems to have better correlation to cardiac response than CVP (Wagner 1998, michard 2002, Androne 2004).
- Poor relationship between BV and PAOP (Shippy-84, Oohashi 05, Alrawi 02, Jones 2000).
- BV correlate best with CO (Alrawi 02)
SICU patients, n=20 with 29 data points

Correlation PAOP r=.44 and p=.02.

For PAOP ≤12 (n=6): 2 were hyper and 4 were euvolemic.

For PAOP 13-18 (n=14): 9 hypervolemic, 4 euvolemic and 1 hypovolemic.

For PAOP >18 (n=9): 6/9 hypervolemic, 3 euvolemic.
Blood volume vs PAOP
N=97 (SICU patients): 0-8% BV, vs >8% BV

- PAOP <12 mm Hg (n=16): 4/16 (25%) Hypervolemic
- PAOP 12-17 mm Hg (n=40): 28/40 (70%) Hypervolemic
- PAOP ≥18 mm Hg (n=40): 7/40 (18%) (Hypovolemic)
Time frame

- 2004: pilot study
- 2004-2006: close observation of the product
- 2007-9: PRT
First observational phase: sample analyzed in New York

Identify patients who need the information (all have edema): BP, UO, HR, unexplained acidosis, ↑BUN or Creatinine, I+O, PaO₂, BNP, PAC, CXR

Treat patients with traditional information.


6 less fluid, 3 less blood, 2 more blood, 2 more fluid. SEE THE DELAY IN CLINICAL MANIFESTATIONS by 1-2 days.
40 subsequent SICU patients (n=86 episodes of BV): change in treatment occurred in 36% of instances, desirable response in 39%, and no negative response

- BP, HR, urine output, low PaO2, increasing renal dysfunction, vasopressor requirements, inability to wean.
Other studies...

- (BP, HR, UO, Urine sodium, Hemoglobin (Hb)) may lead to different fluid management in 30-50% of the time in ICU patients if BV results were used (Stephan 2001).

- Unexpected BV results depends on the type of patients studied. Shoemaker 73 and Stephan 01 found unsuspected hypovolemia in 50% of ICU patients.
PRT (Pilot 2004; PRT 2007)

- Septic shock/severe sepsis
- SBP <90 mm Hg, or >40 mm Hg decrease from known baseline) after 30 ml/kg fluid bolus and requiring vasopressors, and with a history of cardiac disease or concurrent myocardial dysfunction.
- PaO2/FiO2 <150, or intrapulmonary shunt ≥20% while on PEEP ≥12 cm H20, with CXR findings of infiltrates.
PAC is alive and well … in a few places

- Backing of Outcome studies (Shoemaker 88, Yu 98,)
- Friese 06- mortality benefit in older patients (61-90), and in pts with shock (BE -11), ISS >25 (retrospective 1933 vs 51,379).

PAC still of value, familiarity of use, how you use it (condemn those who condemn – based on no data, just opinion)

- Reliable source of CI, Svo2, PAP, RV function
Goals of treatment within 24 hrs: (traditional + tissue perfusion goals)

- BP >100 mm Hg or within 40 mm Hg from known baseline.
- Heart rate <100 beats/minute
- Urine output >0.5 ml/kg/hour
- Lactate to normal values within 24 hours of resuscitation
- DO2 adequate to achieve SvO2 ≥70% and PtcO2 (Oxygen Challenge test ≥25 mm Hg).
What is the optimum BV in the ICU patients?

- Blood volume and plasma volume should be about 500 ml in excess of predicted norms and if tolerated, a normal red cell mass should be the goal. (shoemaker 1973)
- Intravascular volume expansion (marx 06)
- 500 ml excess in PV of 3000 = 16% (0-16% of ideal)
- 40% deficit RBCV (not well tolerated)
- Goal 0 to -20% deficit RBCV
Treatment: PAC vs PAC + BV

- Crystalloid/colloid infusion of 250-500 mL or blood infusion if Hct was <35 (keep Hct between 25-35, RBCV 0 to -20%)
- Milrinone at 0.375 μg/kg/min or dobutamine at 2 - 5 μg/kg/min, with titration to desired cardiac index to achieve the perfusion goal.
- Norepinephrine or epinephrine starting at 1 μg/min minute titrated to desired blood pressure if hypotensive despite adequate preload.
- PAOP: pulmonary artery occlusion pressure. Measured with PEEP turned to zero if PEEP is ≥15 cm H2O to account for thoracic pressure influence on PEEP. (carter 85)
Guessing at bedside: Control blinded to BV results
(parameters requiring treatment, guess, treatment, response)

- **BV #1**: 12-36 hours after starting resuscitation. Steady state
- **BV#2**: 24-36 hours after BV #1. Equilibration
- **BV#3**: 24-36 hours after BV #2. Possible fluid mobilization.
- **BV#4**: between day 5-7 after study enrollment. Capture secondary events.
### PARAMETERS NEEDING TXMENT

| SBP (<100 mm Hg or > 40 mm drop fr baseline) | SBP |
| HR (>100) | HR |
| UOP (<0.5 mL/kg/hr) | UOP |
| Lactic acid level high | Lactic acid level |
| PaO2/FiO2 <150 | PaO2/FiO2 |
| Cardiac Index (if SVO2 <70 or failed OCT test) | Cardiac Index |
| SVO2 (<70) | SVO2 |
| Unable to get PEEP to 5 | PEEP |
| On vasopressors – list name & dose | On vasopressors – list name & dose |
| On inotropes – list name & dose | On inotropes – list name & dose |
| Increasing/hi BUN 25% | BUN |
| Increasing/hi Creatinine 25% | Creatinine |
| Base deficit (> -5) w/o renal dysfunction | Base deficit |
| Other reason | Other |
| ALBUMIN level | ALBUMIN level |
| BNP | BNP |
| O2 challenge test | O2 challenge test |

### PARAMETERS AFTER BV RESULTS & TXMENT

| Blood vol | High | Low | Euvolemic | Blood vol |
| Plasma vol | High | Low | Euvolemic | Plasma vol |
| Red cell vol | High | Low | Euvolemic | Red cell vol |

### CLINICAL DECISION RE: PT VOLUME STATUS PRE-BV

| Blood vol | High | Low | Euvolemic | Blood vol |
| Plasma vol | High | Low | Euvolemic | Plasma vol |
| Red cell vol | High | Low | Euvolemic | Red cell vol |

### ACTUAL BV RESULTS (for pts in BV arm)

| Blood vol | +/- mL | +/- % | H/L/Eu |
| Plasma vol | +/- mL | +/- % | H/L/Eu |
| Red cell vol | +/- mL | +/- % | H/L/Eu |

### TREATMENT AFTER BV RESULTS

| Treatment decision before BV (or in Control) | FLUID |
| Fluid | FLUID |
| BLOOD | BLOOD |
| DIURESIS/less fluid | DIURESIS/less fluid |

RN TO DO: Print waveforms (EKG, RR, Arterial; EKG, RR, CVP). AMPLIFY THE SCALE. No waveforms needed if EKG and RR only.
• Obtain ALL hemodynamic values at time of BV (right before, during, or right after) including vigileo flotrac variables, REF pulmonary artery catheter variables including EF and EDVI. If heart rate is irregular or respiratory efforts are variable, put in comment section for SVV since that will introduce inaccuracies for the SVV number.
• Remind SICU team to obtain OFF PEEP PCWP (wedge) at time of BV if pt is on PEEP >15.
<table>
<thead>
<tr>
<th></th>
<th>Control (n=50)</th>
<th>BV (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63 ± 16</td>
<td>60 ± 17</td>
</tr>
<tr>
<td>Female:Male</td>
<td>18:32</td>
<td>23:27</td>
</tr>
<tr>
<td>APACHE II</td>
<td>24 ± 3</td>
<td>25 ± 4</td>
</tr>
<tr>
<td>Septic shock</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>ARDS</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>CV failure</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

CVP, PAOP, SvO, DO2, CI, Hct, BV, RBCV
40% with cardiac history, 40% elevated troponin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control (50)</th>
<th>BV (50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Cardiac history</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>COPD</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes m</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>4.1 ± 3.1</td>
<td>4.0 ± 2.8</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.7 ± 1.0</td>
<td>1.9 ± 1.7</td>
</tr>
<tr>
<td>Creatine Cl</td>
<td>48 ± 25</td>
<td>52 ± 30</td>
</tr>
<tr>
<td>Elevated trop</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Platelet count</td>
<td>149 ±190</td>
<td>191 ±190</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>2.6 ± 2</td>
<td>4.0 ± 4.8</td>
</tr>
</tbody>
</table>
## Treatment changes based on BVA in first 7 days

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Blood Volume Group</th>
</tr>
</thead>
<tbody>
<tr>
<td># of BVA</td>
<td>198</td>
<td>254</td>
</tr>
<tr>
<td># BVA w/ Rx change</td>
<td>121/198 (61%)</td>
<td>112/254 (44%)</td>
</tr>
<tr>
<td>More fluid</td>
<td>21/198 (11%)</td>
<td>34/254 (13%)</td>
</tr>
<tr>
<td>Less fluid/diuresis</td>
<td>62/198 (31%)</td>
<td>56/254 (22%)</td>
</tr>
<tr>
<td>More red cell</td>
<td>53/198 (27%)</td>
<td>32/254 (13%)</td>
</tr>
<tr>
<td>Less or no red cell</td>
<td>21/198 (11%)</td>
<td>16/254 (6%)</td>
</tr>
</tbody>
</table>

Better at guessing in the BV group, see previous results. Diuresed earlier, gave blood earlier in the course by 1.5 ± 2 days.
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>BV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># times RBCV deficit &gt;20%</td>
<td>66/198 (33%)</td>
<td>40/254 (16%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td># times BV &lt;0%</td>
<td>39/198 (18%)</td>
<td>49/254 (19%)</td>
<td>.86</td>
</tr>
<tr>
<td># times BV&gt;16%</td>
<td>96/198 (48%)</td>
<td>94/254 (37%)</td>
<td>.02</td>
</tr>
<tr>
<td># times PV&lt;0%</td>
<td>12/198 (6%)</td>
<td>24/254 (9%)</td>
<td>.25</td>
</tr>
<tr>
<td># times PV&gt;16%</td>
<td>152/198 (76%)</td>
<td>165/254 (65%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Units of red cells given: 133 vs 158
Units of red cell/patient: 2.66 vs 3.16

Favorable response: 87/198 (44%) vs 150/254 (59%) p = .002
Unfavorable response: 49/198 (25%) vs 46/254 (18%) p = .10
Neutral response: 62/198 (31%) vs 58/254 (23%) p = <.05

(Response: change of: 10 mm Hg in BP, 10 beats per minute in HR, 15% in CI or SVI (michard), 25% on vasoactive agents, 20 points in PaO2/FiO2, (jochberger), 25% in BUN or Creat)
Hawaii SICU Shock bundle (beale o8)

- Glutamine 10 mg tid through GI tract asap (enterocytes)
- Early enteral feeding to 25% kcals needed (mesenteric perfusion)
- Vitamine A 10,000U
- Vitamine E 800 units
- Selenium 200 mcg. Ascorbic acid 3 grams in 0.9% NaCl at 20 mL/hr
- Hydrocortisone 50 q6 if BP is <100 and cortisol tests are low (Marik)
- BS 80-110 mg/dL (van de berghe)
- Treat to DO2 to meet tissue perfusion
- APC for microcirculatory failure (PtcO2) – (chapital o8)
<table>
<thead>
<tr>
<th></th>
<th>Control (n=50)</th>
<th>BV (n=50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC days</td>
<td>9.3 ± 5.2</td>
<td>8.3 ± 5.1</td>
<td>.57</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>29.2 ± 33.5</td>
<td>23.8 ± 23.9</td>
<td>.38</td>
</tr>
<tr>
<td>ICU days</td>
<td>28.0 ± 24.6</td>
<td>28.7 ± 27.0</td>
<td>.90</td>
</tr>
<tr>
<td>Hospital days</td>
<td>54.7 ± 41.0</td>
<td>43.7 ± 31.3</td>
<td>.14</td>
</tr>
<tr>
<td>Mortality</td>
<td>13/50 (26%)</td>
<td>4/50 (8%)</td>
<td>.02</td>
</tr>
<tr>
<td>Mortality from MSOF</td>
<td>12/50 (24%)</td>
<td>4/50 (8%)</td>
<td>.03</td>
</tr>
</tbody>
</table>
CHF patients EF<35% Androne et al,04

- PE: (VS, JVD, S3, rales, hepatomegaly), Na+, BUN, Creat, BNP vs BV (no relationship)

- Majority of patients had hypervolemia, the degree of volume overload was not determined by clinical exam from cardiologists including an S3

- No clear relationship between BNP and BV at baseline or after treatment, which may reflect multiple factors affecting BNP levels. (Androne, Katz)

- SBP lower and BUN higher, GFR lower in hypervolemic patients!!!!!!!

- There was a relationship between hypervolemia (both recognized and unrecognized) with mortality rate median follow up of 719 days.
SVV and BV in 18 ventilated patients with no spontaneous respiration, 74 data points

- $r = .11$, $R^2 = .012$

- 8/54 (15%) instances hypovolemia with SVV <9.5%
PPV

Domingo, S et al 2008 (abstract)

- 29 patients, 84 data points
- PP = SBP – DBP (1 respiratory cycle)
- \(100 \times \frac{(PP_{\text{max}} - PP_{\text{min}})}{(PP_{\text{max}} + PP_{\text{min}})/2}\)
- 14/69 (20%) hypovolemic when PPV was <13% (imply adequate preload)
- 13/15 (86%) hypervolemic when PPV ≥13% (imply inadequate preload)
- 57/84 (68%) = congruent information
IVC collapsibility during respiratory cycle, estimate CVP

IVC collapsibility <50% (adequate volume), vs >50% (hypovolemic)

<50%: 5 (eu or hypevolemic)  2 (hypovolemic)

>50%: 1 (eu or hyper)  4 (hypo)
In CHF, no correlation between BNP and BV (Androne 2004)

Change in BV correlate better with hemodynamics than changes in BNP (James KB 2005)

For BNP >500 pg/mL, 11% associated with hypovolemia (Takahashi et al, J Trauma Acute Care Surg 2013: 75:813)
Let's think among 2 levels

- **CARDIAC PRELOAD:**
  Volume for the heart

- **VASCULAR PRELOAD:**
  Volume for the vascular system

The two volumes may not agree
Anemia: deficiency of RBC mass

- 1972: (Biron, Altschule, Valeri)
  n=300, 18-45 yo males, orthopedic injuries
- Cardiac arrest with induction
- Circulating RBC mass deficits up to 40%, not reflected in HEMATOCRIT >30%
- "this may support life, but not health".

"MISSING BLOOD SYNDROME"
Hypovolemic anemia
- in our hands, nowadays???
Valeri 06, Takanishi 08

- Valeri et al 06: postop pts – vascular (n=40) and cardiac surgery (n=20). Postoperative Hct and transfusions correlated best with preoperative red cell volume. All hypovolemic, anemic. Real Hct lower by 4-6%

- Takanishi et al (Anesth Analg 08); n=40 with 86 data points in icu
  41/86 (48%): Lab Hct lower than normalized Hct (PV excess)
  15/86 (17%): Lab Hct is higher than normalized Hct (PV deficit)
  30/86 (35%): equivalent

22/86 had >24% deficit in RBCV.
Missing blood syndrome.. In our patients

Edwards K et al 06 (abstract)

- Retrospective analysis of 690 BV on 351 SICU patients (simultaneous Hct)
- 69/690 (10%) >40% deficit RBCV, 33/69 demonstrated Hct >30% (missing blood syndrome)
I guess its physiology

- 1 g Hb $\rightarrow$ 9% CO; 50% ↓Hb $\rightarrow$ double CO
- Euvolemic anemia well tolerated in healthier specimens
- Many animal studies coronary artery constriction, decompensate at higher Hb as Hb is lowered. (Case 1955)
- Problem with blood: transformation with storage solution and with time
- ONE VALUE CANNOT SUIT ALL
Problems in transfusion medicine: RBCV vs H/H, goal directed transfusion to tissue perfusion.

- Hb 7 - 9 g/dL vs 10 - 12 g/dL (Hebert 99)
- 838/2039 enrolled after being consented
- Enrolled in first 72 hrs ICU admission
- LA normal, 20% CV, APACHE II 21
- Re-analysis of TRICC trial shows that pts with ischemic heart disease had higher mortality in the red cell restricted group (Deans 2007). – 21 vs 26% mortality
The old, broken hearts (large retrospective studies)

- Cardiac surgery in elderly ≥75 yo (retrospective), found hemoglobin <13 to be associated with mortality on day 2. (Rady-1998). N= 1157

- Wu-2001- (Retrospective) age ≥65 with acute MI, found mortality lower with transfusion to >30%. N=78,974

- Wu 2007- retrospective study of age ≥65 undergoing non-cardiac surgery, and for every 1% lower Hct from normal, see an increase of 1.6% mortality. N=310,311
Guidelines for transfusion

- All studies when discussing Hb/Hct levels are assuming a normal BV, i.e. that the PV has increased appropriately to low RBCV resulting in a normal BV, a potentially erroneous assumption in hospitalized patients.

- Level I – RBC transfusion is maybe indicated with inadequate DO$_2$, guidelines are general. (Napolitano CCM 2009).

- Not one transfusion trigger!
Controversy: fluids, blood

- We are not measuring what we need to measure
- RBCV to guide Red cell transfusion (not Hct)
- Blood volume to guide Fluid infusion (not central pressures)
- Pressure ≠ Volume
- Better/easier Method of Tissue/cellular oxygenation state or bioenergetics.
Issues with BVA

- Still cumbersome, 5 blood draws, technician at bedside
- Buy-in from hospital personnel (lab, nuclear medicine department)
- Cost
- Intermittent test
- Other dye – rather than radio-isotope
There are no good surrogate markers for Blood Volume.

Measurement of BV impacts endpoint of resuscitation for both fluids and blood. First prospective randomized trial using BV vs PAC.

We need to find an easier method (non-invasive, continuous): ICG dye, saline as dye using US.

Only then, can we rest the controversy of HOW MUCH FLUIDS, HOW MUCH BLOOD

FLUID MANAGEMENT AS USUAL
THANK YOU, MAHALO
Future research

- Single center trial in a very specific group of patients
- Multi-center trial
- Optimum goals may vary with disease and timing of disease process
- Red cell transfusion: tissue or metabolic parameter of perfusion. Some patients may tolerate RBCV deficit 20-30%
- Sodium abnormality
- Albumin leak
G.H. is a 42 y/o single male with longstanding HTN and ESRD S/P renal trx (Brother) at age 29. Baseline creatinine 2-3; Post Trx diabetes mellitus. On immunosuppressants.

Admitted following a high velocity MVA; sustained LOC; c/o right abdominal pain

CT scans revealed:
- laceration of transplanted kidney in RLQ with surrounding hematoma
- subarachnoid hemorrhage; compression fx L2, transverse process (L4, L5), rt humerus, rt radius
Admission labs:

1) Hgb 10.7  Hct 32.5

2) creatinine 3.3  Bun 34

3) Na 137  K 3.4  Cl 105  CO2 21
1st 3 hospital days:

- Fluids, 2U PRBC (H/H 8.4/25) for low UO of <30 mL/hr. Normal VS.
- ORIF of humerus and radial fx

- Intake 16,235  Output 4,530
  - (Net +11,700 ml)

4th hospital day, HR 130, low PaO2, intubation.
- edema up to flanks
- creatinine 3.3 → 4.0, BUN 35
- Hgb 9.9  Hct 29.0
Loop diuretics
More fluids + blood
Schizoid treatment: both fluid + diuresis
Lasix bolus, drip started
Intake 2075: output 3210
hospital day 5, normal VS:

- Creatinine 5.3 (3.3 → 4.0).
- **BUN 60 (34).**
- Hgb 10.1  Hct 31.8

- **Echo:** normal LV size, EF 70%
- Lasix drip continued
Patient’s BVA

Blood volume deficit 1992 ml. (-32%)
- Red cell volume deficit 1429 ml. (-56%)
  Hemoglobin was 10 g/dL
- Plasma volume deficit 562 ml. (-15%)
- Normalized HCT 29 → 19.6%

(what the Hct would be if patient’s plasma volume was adjusted to maintain a normal BV)

- HYPOVOLEMIC ANEMIA, misleadingly high Hct
Happy ending

- Received blood, fluids
- Creatinine 5.3 → 4.6 (within 12 hours)
- 9th hospital day:
  - Creatinine 3.3, Bun 62
  - Hgb 12.8 Hct 39.1
  - CXR: improved.
- No loss of transplanted kidney function