TRANSFUSION TRIGGER IN THE
PERI-OPERATIVE SURGICAL
PATIENT

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WHY GIVE BLOOD? WHAT IS OUR GOAL?

• 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
BIG PROBLEM NUMBER 1

- Red cell volume ≠ Hemoglobin, Hct
- Tissue perfusion parameters:
  
  **Global parameters:** lactic, ScvO2, SVO2,
  
  **Tissue parameters:** PtcO2, Perfusion index, StO2, tonometers
  
  **GOAL:** cellular bioenergetics

*Argument with no end:* we are not measuring what we need to measure.
One guideline suits all: NOT!!

Protocol driven: NOT!!

Regressing: improving the individual components which help to achieve our goal of getting oxygen to the cells
HCT: RED CELL VOLUME TO BV (PV + RBCV)

Normal RBCV + Normal PV
Euvolemic Anemia: Low RBCV + High PV = Hct 30% (well tolerated)
Hypovolemic Anemia: Low RBCV + High PV = Hct 30% (killer)
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”.

WE MEASURE RED CELL VOLUME, PLASMA VOLUME = BLOOD VOLUME (SINCE 2004)

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

Normally, albumin transudates from the circulation into the interstitial fluid at a rate of approximately 0.25% per minute. BV measurements performed by Feldshuh in unpublished studies have found the rate of transudation to normally range between approximately 0.05% per minute to 0.45% per minute, although an exact normal range has not been established.
RED CELL VOLUME, AVOID HEMO-CONCENTRATION, HEMODILUTION

Measure PV (I-131), Measure Hct, Calculate RBCV
HYPOVOLEMIC ANEMIA
- IN OUR HANDS??? 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 sicu
  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.

• Takanishi DM et al, Anesth Analg 2008;106:1808
• Valeri RC et al, Transfusion 2006;46:365
PROBLEMS IN TRANSFUSION MEDICINE.

- 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

- Hebert PC et al NEJM 1999;340:409
- Deans KJ et al, CCM 2007; 35:1509
BLOOD IS BAD...

• Too many articles (majority are retrospective)
• Patients dying of anemic hypoxia
I GUESS ITS PHYSIOLOGY

- \(1 \text{ g Hb} \rightarrow 9\% \text{ CO; } 50\% \downarrow\text{Hb} \rightarrow \text{double CO}\)
- Euvolemic anemia well tolerated in healthier specimens
- Best Hct & best viscosity for all organs in terms of \(\text{O}_2\) transport in euvolemic animals for all organ perfusion: Hct 40 (Crowell 1967, Fan 1980)
- 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

- Case RB et al Am J Med March 1955;397
- Fan FC et al Am J Physiol 1980;238:H545
THE OLD, BROKEN HEARTS (RETROSPECTIVE STUDIES, NOT CAUSE AND EFFECT)

• 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

• Rady MY et al Crit Care Med 1998;26:225
• Wu WC et al, NEJM 2001;345:1230
• Wu WC et al JAMA 2007;297:2481
RED CELLS AND MORTALITY: SEVERE SEPSIS, SEPTIC SHOCK. BLOOD IS GOOD

- Severe sepsis, septic shock: Transfused patients had a lower risk of 7-day mortality (9 vs 27%), 28 day mortality (24 vs 38%), and hospital mortality (31 vs 42%), all p<.05)
- Sakr et al : Crit Care 2010:14:R92. transfusion are independent risk factors to lower mortality in SICU, especially in patients 66-80 years of age
- Vincent JL et al (Anesthesiology 2008, 108:31) Sepsis study, propensity score case matching, patients with blood transfusions had a lower mortality. Multivariate analysis of all patients, red cell transfusion is not associated with mortality.
LIBERAL OR RESTRICTIVE AFTER CARDIAC SURGERY (MURPHY G ET AL, NEJM 2015:372:997), 17 CENTERS UNITED KINGDOM

- Multicenter parallel group trial
- 7.5 g/dL vs 9.0 g/dL
- Average age 70 and similar co-morbidities
- More deaths in the restrictive group 4.2% vs liberal group 2.6% (p=.045)
PRT USING RED CELL VOLUME AND BLOOD VOLUME AS A GUIDE TO RED CELLS AND FLUID. (Yu, m et al, Shock 2011,35:220)

<table>
<thead>
<tr>
<th></th>
<th>Control (n=50)</th>
<th>Blood volume (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>APACH 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,

Fluids given to Blood volume measurement and transfused for red cell volume >20% deficit
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Blood volume group</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>
<tr>
<td>Units of red cells given</td>
<td>133</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>Units of red cell/patient</td>
<td>2.66</td>
<td>3.16</td>
<td></td>
</tr>
<tr>
<td>Favorable response</td>
<td>87/198 (44%)</td>
<td>150/254 (59%)</td>
<td>.002</td>
</tr>
<tr>
<td>Unfavorable response</td>
<td>49/198 (25%)</td>
<td>46/254 (18%)</td>
<td>.10</td>
</tr>
<tr>
<td>Neutral response</td>
<td>62/198 (31%)</td>
<td>58/254 (23%)</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

(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)
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>BV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC days</td>
<td>9.3 ± 5.2</td>
<td>8.3 ± 5.1</td>
</tr>
<tr>
<td>(n=50)</td>
<td>(n=50)</td>
<td>.57</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>29.2 ± 33.5</td>
<td>23.8 ± 23.9</td>
</tr>
<tr>
<td>(n=50)</td>
<td>(n=50)</td>
<td>.38</td>
</tr>
<tr>
<td>ICU days</td>
<td>28.0 ± 24.6</td>
<td>8.7 ± 27.0</td>
</tr>
<tr>
<td>(n=50)</td>
<td>(n=50)</td>
<td>.90</td>
</tr>
<tr>
<td>Hospital days</td>
<td>54.7 ± 41.0</td>
<td>43.7 ± 31.3</td>
</tr>
<tr>
<td>(n=50)</td>
<td>(n=50)</td>
<td>.14</td>
</tr>
<tr>
<td>Mortality</td>
<td>13/50 (26%)</td>
<td>4/50 (8%)</td>
</tr>
<tr>
<td>(n=50)</td>
<td>(n=50)</td>
<td>.02</td>
</tr>
<tr>
<td>Mortality from MSOF</td>
<td>12/50 (24%)</td>
<td>4/50 (8%)</td>
</tr>
<tr>
<td>(n=50)</td>
<td>(n=50)</td>
<td>.03</td>
</tr>
</tbody>
</table>
RISKS  (ANN INTERN MED 2012;E-429)

• 1:100 fever, TACO (transfusion associated circulatory overload)
• 1:1000 (death from clerical error)
• 1:10,000 TRALI (transfusion related acute lung injury)
• 1:100,000 Life threatening reaction
• 1:1,000,000: HIV, HCV, fatal hemolysis
CONTROVERSY REGARDING BLOOD STORAGE?

• Lacroix et al, NEJM 2015: multicenter trial critically ill patients. N=1200 into each arm. Blood <8 days vs standard blood. No difference in 90 day mortality

• Steiner ME et al (NEJM 2015). Multicenter trial, Cardiac surgery patients. Red cells <7 days vs 28 days. No difference in 28 day mortality

• Is blood getting safer?
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.

• There are no tissue perfusion goals

• Level I – RBC transfusion is maybe indicated with inadequate DO2,- guidelines are general. (Napolitano CCM 2009).

• Not one transfusion trigger!
Clinical recommendations about hemoglobin concentration thresholds and other clinical variables that trigger RBC transfusions in HEMODYNAMICALLY STABLE adults and children.
TRANSFUSION TRIGGER IN CARDIOVASCULAR SURGERY: META-ANALYSIS (CURLEY GF ET AL, CRIT CARE MED 2014;42:2611)

• UNABLE TO ARRIVE AT A CONCLUSION
RED CELL TRANSFUSION: TOO COMPLEX TO BASE ON A SINGLE NUMBER, JL VINCENT

- We are not measuring what we need to measure: red cell volume
- Hemoglobin/hematocrit as therapeutic endpoint assumes EUVOLEMIA, i.e. plasma volume has expanded to compensate for the lower red cell
- Problem with red cells is the mechanism of storage: immunosuppression, metabolic load, red cell malleability.
- Blood is not bad for you. The way we store blood is bad.
- We need to get better red cells, rather than not give red cells
OUR MONITORING SYSTEM IS INADEQUATE FOR ORGAN SPECIFIC ISCHEMIA: BASE EXCESS, LACTIC ACID

• Skin as a early marker for tissue perfusion: first to vasoconstrict in shock and last to perfuse

• Organ specific anemia tolerance. More sensitive markers for kidneys, gastrointestinal tract, liver, skeletal muscle (heart, brain- protected): kidney are less tolerant (Lauscher P et al, Crit Care Med 2013;41:1037)
HOW DO I DO IT IN OUR SICU?

• Poor Cardiac function and not meeting tissue perfusion goals: Lactic acid, vasopressor requirements not going down, SvO2, Transcutaneous oxygen PO2, Perfusion index (Masimo), StO2 (near infra-red)

• Give red cells to a hemoglobin of 14 g/dL or normal red cell volume in severely compromised cardiac function and inadequate tissue perfusion

• Measure red cell volume in selected patients to guide red cell or volume management. Mitigates the problem of hemoconcentration and hemodilution.

• Younger patients with normal heart: hemoglobin 7 g/dL if no signs of hypoperfusion.

• Optimum hemoglobin varies according to time of disease
LEVEL 1 EVIDENCE

• Give blood if patient is bleeding
• Don’t give blood to a hemoglobin of 7 if the patient is fine (cardiovascular, symptoms, perfusion parameters)

• We need a better assessment of blood volume so we can use Hb/Hct in context to plasma volume (hemoconcentration/hemodilution).
• We need better studies using tissue perfusion endpoints, or early biomarkers of organ injury.