Hemodynamics: Optimizing Oxygen Delivery

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Introduction

• Background on oxygen delivery
• Why measure oxygen delivery
• Does affecting oxygen delivery matter?
• How to make sense of this:
  Recommendations
Background on Oxygen Delivery

- Terms
- Formulas
- How to measure oxygen delivery
- How to measure oxygen consumption
- How to measure CO/CI
Terms

- **Oxygen Delivery (DO₂)** - amount of oxygen delivered to the body tissues in one minute
  - \( DO₂ = \text{CO} \cdot \text{O}_2\text{Content} \) (CaO₂)

- **Oxygen Consumption (VO₂)** - rate oxygen removed from blood for use by tissues.
  - \( VO₂ \) is measured by calorimetry
  - \( VO₂ \) (ml/Kg-min) = \( \text{CO} \cdot (\text{CaO}_2 - \text{CvO}_2) \) (Fick)

- **Oxygen Extraction (EO₂)** - slope of \( DO₂/VO₂ \) relationship
  - Often expressed as O₂ extraction ratio \( \frac{(\text{CaO}_2 - \text{CvO}_2)}{\text{CaO}_2} \) Normally 0.25-0.3
Oxygen Delivery

- Oxygen delivery not measured directly.
- $\text{DO}_2 = \text{CO} \cdot \text{CaO}_2$
- $\text{CaO}_2 = (\text{Hgb} \cdot 1.36 \cdot \text{SaO}_2) + (0.0031 \cdot \text{PaO}_2)$
- Normal Values: 1000 mL/min or 500 mL/min-m$^2$
Oxygen Consumption

• Measured by “Reverse Fick”
  – $\text{VO}_2 \ (\text{ml/Kg-min}) = \text{CO} \cdot (\text{CaO}_2 - \text{CvO}_2$
• More practically by indirect calorimetry
• Normal values at rest approximately 3mL/Kg-min or 250 mL/min
**DO2/VO2 Relationship**

- Critical DO2: Point below which VO2 is limited by delivered oxygen amount
- Slope of line is O2 extraction ratio
- Similar relationship to VO2 max graph

![Graph showing DO2/VO2 relationship](image)
What is involved in O$_2$ Delivery

- CO/Cl
- O$_2$ Content
How to Control DO$_2$/VO$_2$

- Increase O$_2$ Content
  - Increase Hemoglobin
  - Increase FiO$_2$
- Increase CI
- Decrease “regional” VO$_2$
  - Control fever
  - Control work of breathing
    - Adequate sedation
    - Paralysis
How to Measure CI

• Non Invasive
  – Thoracic Electrical Bio-impedance

• Minimally Invasive
  – Lithium Dilution Cardiac Output
  – Pulse Contour Analysis
  – FloTrac System

• Invasive
  – Esophageal Doppler Monitoring
  – Transpulmonary Cardiac Output
  – Pulmonary Artery Catheter
  – ScVO$_2$ Monitoring

Increasing Invasiveness

Decreasing Invasiveness
Why Measure Oxygen Delivery

- Shock states / shock physiology
- Cycle of dysoxia
- Early observations of shock (critical illness) survivors

- What is it that we care about in shock?
  - Blood pressure
  - Oxygen delivery
Shock Physiology

• Lack of adequate perfusion
• Leading to cycle of cell dysfunction
• Leads to decreased ability of cell VO$_2$
• Leading to cell death
• Eventual death of organism
Cycle of Dysoxia

↓ VO₂

Cell Dysfunction

↓ Cl

↓ DO₂
Early Observations of Survivors

• Shoemaker and others published multiple observational studies looking at shock survivors
• Findings:
  • Survivors achieve higher values of CI, oxygen delivery, oxygen consumption, lower oxygen extraction levels
  • Underlying assumption that maximizing DO₂ would increase VO₂ and reduce tissue hypoxia
Does Shoemaker make sense?

- Seems intuitive that improving tissue oxygenation beneficial
- What level of DO$_2$ should be targeted
- Perhaps timing of intervention is important
- Patient selection may be important
Does Affecting Oxygen Delivery Matter?

- Many varied and conflicting studies
- Cover wide variety of ICU patients
- Instituted at various times
- Data is a methodological quagmire
Essentially 2 difficult studies in one
Significant methodology issues
Critically-ill non-cardiac high-risk surgical patients
2 groups (control/protocol) each with own hemodynamic goals
- Control: CI 2.8-3.5 DO₂ 400-550 VO₂ 120-140
- Protocol: CI > 4.5 DO₂ > 600 VO₂ >120
All groups received fluids, inotropes, vasopressors, vasodilators as needed

Shoemaker Chest 1988
Shoemake 1st Series

- 252 Patients randomized control vs protocol and when started study period (pre-op vs post-op)
- Analyzed patient mortality by subgroup
  - Early vs late, control vs protocol, Cl nl at baseline vs elevated at baseline
- In all groups combined
  - Control (57/168) 34% mortality
  - Protocol (21/108) 19% (p<0.01)
- Patients with normal pre-op hemodynamics
  - Control (33/118) 28% mortality
  - Protocol (7/67) 10% (p<0.05)

Shoemaker Chest 1988
Shoemaker 2nd Series

- 146 patients met criteria for study
- 58 not randomized (45 not ill enough)
- Split remaining 88 patients into 3 groups
  - CVC control group (normal HD targets)
  - PAC control group (normal HD targets)
  - PAC protocol group (supraphysiologic targets)
- Analyzed for mortality
  - CVC control 7/30 deaths (23%)
  - PA control 10/30 deaths (33%)
  - PA protocol 1/28 deaths (4%)
  - Non randomized 17/45 deaths (38%)

Shoemaker Chest 1988
70 pts w/ suspected sepsis randomized to end point of resuscitation only
- Resuscitative goals maintained 72 hrs
- Control group: CI > 3 L/min-m²
- Protocol group: CI > 6L/min-m², SBP > 90
- 19 Patients excluded for various reasons
- 51 eligible patients
Tuchschmidt

- Mortality rate 72% control and 50% protocol (p=0.14)
- Hospital mortality correlated with DO2 levels (p=0.016)
- Note cross-over:
  - 27% protocol CI < 4.5
  - 24% control CI > 4.5

Tuchschmidt  Chest 1992
• 107 high-risk surgical patients
  – 54 control / 53 protocol
• Goal to increase DO$_2$ > 600 with dopexamine (dopamine analog)
• End-point: Overall mortality & complications out to 28 days
• Results: Protocol group had better outcomes
  – higher DO$_2$ (597 vs 399) (p<0.001)
  – Lower mortality (6 vs 22%) (p=0.15)
• Note: Very short ICU times 40 hrs control, 46 hours protocol
Boyd

• Intervention initiated pre-op in 76% patients
• Intra-op management was not controlled
  – Peri-op management at the discretion of the surgeon and anesthesiologist
• Very short ICU times…perhaps patients were not that sick

Boyd  JAMA 1993
• 2 Studies looking at effect of maximizing \( \text{DO}_2 \) on mortality rates in ICU

• Broad patient inclusion spectrum
  – Sepsis, septic shock, ARDS, hypovolemic shock

• Fluids, blood, inotropes as necessary to keep
  – \( \text{DO}_2 = 450-550 \) Control group
  – \( \text{DO}_2 > 600 \) Treatment group

• Comparable patient groups in both studies
Yu #1

- 67 patients
- Control: $DO_2 = 604 \pm 169$
  - 44 % achieved treatment goals
- Treatment $DO_2 = 617 \pm 202$
  - 40 % did not achieve treatment goals
- No difference in $VO_2$ values between groups
- Considerable cross-over in study
- No mortality benefit overall
- Note: Comparing patients who met goals vs those who did not mortality rate much lower in supranormal group (14% vs 56% p=0.01)

Yu Crit Care Med 1993
89 patients

Control group
- \( \text{DO}_2 = 600 \pm 153 \)
- \( \text{VO}_2 = 137 \pm 35 \)
  - 43% achieved treatment goals

Treatment group
- \( \text{DO}_2 = 615 \pm 184 \)
- \( \text{VO}_2 = 134 \pm 35 \)
  - 40% did not achieve treatment goals

Considerable cross-over in study
No mortality benefit overall

Yu Crit Care Med 1994
109 “high-risk” ICU patients assigned to control or treatment group:
- $\text{CI} > 4.5 \text{ L/min-m}^2$
- $\text{DO}_2 > 600 \text{ mL/min-m}^2$
- $\text{VO}_2 > 170 \text{ mL/min-m}^2$

- Dobutamine used to achieve goals (up to 200 mcg/Kg-min)
- Dobutamine given to control group to keep $\text{CI} > 2.8 \text{ L/min-m}^2$

Hayes NEJM 1994
Hayes

- Oxygen consumption similar between groups (p=0.12)
- Treatment group
  - Higher CI (p<0.0.001)
  - Higher DO$_2$ (p<0.001)
  - Lower EO$_2$ (p=0.045)
- Large doses of dobutamine given to treatment group
- Higher mortality in treatment group (54% vs. 34% p=0.04)

Hayes NEJM 1994
• Large multi-center RCT 762 pts w/ acute physiology scores 11 or higher.
• Randomly assigned to 3 groups: Control, Cardiac Index, and O₂-Saturation groups.
  – Cardiac Index group tgt CI ≥ 4.5 L/min-m²
  – O₂-Sat group tgt SvO₂ ≥ 70% (or < 20% btwn SpO₂ and SvO₂ in severe hypoxemia)
• Patients treated with volume, inotropic, vasopressor, and vasodilator agents as necessary to achieve goal
• Target values mandatory for 5 days

Gattinoni NEJM 1995
• 505 patients achieved target values, 230 did not (94% control, 45 % CI, 67% SvO₂)
• Found younger, healthier patients achieved targets
• No difference in mortality among 3 patient groups up to discharge from ICU
Heyland Meta-Analysis

- Independent review 64 articles (1980-1994)
- Identified 7 relevant studies
- Overall patients targeted to supraphysiologic values of C Index, DO$_2$ and VO$_2$
- Non-significant trend towards lower mortality (rr 0.86, 95% CI 0.62-1.2)
- Average ICU LOS shorter
  - Mean change of -2.5 days (95% CI -4.8 to -0.1)

Heyland Crit Care Med 1996
Heyland Meta-Analysis

- **Subgroup analysis**
  - Studies that initiated protocol pre-op
    - \( rr \) 0.20 (95% CI 0.07-0.55)
  - Studies that initiated after ICU admission
    - \( Rr \) 0.98 (95% CI 0.79-1.22)

Heyland Crit Care Med 1996
Kern/Shoemaker Meta-Analysis

- Reviewed 21 RCT concerning supra-physiologic goal therapy
- Stratified studies into 4 different groups
  - Severity of illness (high vs low mortality)
    - Studies with mortality > 20% (12 studies)
    - Studies with mortality < 15% (9 studies)
  - "High" mortality group further sub-divided into time of goal implementation
    - Early therapy (8-12 hours post-op or before onset of organ failure) 9 studies
    - Late therapy (after onset of organ failure) 6 studies

Kern Crit Care Med 2002
<table>
<thead>
<tr>
<th>Kern/Shoemakers Meta-Analysis</th>
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1. Control Groups with Mortality Rates Greater than 20%  

- **A. Goals to Supranormal Values After Organ Failure**  
  - Ali, 1999; n=63 31.32, Surg/Med, [0.74 - 0.96 = 0.09]  
  - Yu, 1998; n=67 43.53, Surgical, [-0.62 = 0.31]  
  - Yu, 1998; n=59 27.28, Surgical, [0.57 - 0.62 = -0.05]  
  - Gattinoni, 1995; n=762 2523, Tra/Surg/Med, [0.09 - 0.48 = 0.01]  
  - Hayes, 1994; n=109 50.58, Surg/Med, [0.50 - 0.30 = 0.2]  
  - Yu, 1993; n=70 56.22, Surgical, [0.34 - 0.34 = 0.0]  

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

- **B. Goals to Supranormal Values Before Organ Failure**  
  - Lobo, 2000; n=42 19.12, Surgical, [0.16 - 0.33 = -0.17]  
  - Wilson, 1999; n=138 46.46, Surgical, [0.04 - 0.32 = 0.32]  
  - Bishop, 1995; n=115 60.53, Trauma, [0.18 - 0.37 = 0.19]  
  - Boyd, 1993; n=107 55.56, Surgical, [0.06 - 0.22 = -0.17]  
  - Tuchschmidt, 1992; n=70 26.25, Medical, [0.50 - 0.72 = -0.22]  
  - Shoemaker, 1988; n=70 28.30, Tra/Surg, [0.04 - 0.30 = -0.26]  
  - Schultz, 1985; n=70 35.35, Trauma, [0.03 - 0.29 = -0.26]  

  **Subtotal:** -0.23 (+/- 0.07), p < 0.05

2. Control Groups with Mortality Rates Less than 15%  

- **A. Goals to Supranormal Values**  
  - Velmahos, 2000; n=153 40.35, Trauma, [0.15 - 0.31 = 0.16]  
  - Usoro, 1995; n=134 16.18, Circulatory, [0.05 - 0.11 = -0.06]  
  - Durbin, 1996; n=60 23.27, Tra/Med, [0.11 - 0.10 = 0.01]  

- **B. Goals to Normal Values**  
  - Valenine, 1998; n=136 60.60, Acute Surg, [0.05 - 0.02 = 0.03]  
  - Bender, 1997; n=104 51.53, Acute/Limb Salvage, [0.02 - 0.02 = 0.0]  
  - Ziegler, 1997; n=72 32.40, Acute/Limb Salvage, [0.00 - 0.05 = 0.04]  
  - Myers, 1995; n=60 30.30, CABG/Valve Repl, [0.00 - 0.03 = -0.03]  
  - Bertani, 1993; n=89 28.31, Periph Vasc, [0.01 - 0.10 = -0.09]  

  **Subtotal:** -0.01 (+/- 0.03), p > 0.05

**Overall:** -0.04 (+/- 0.025), p < 0.05

- **Overall mortality rate decrease of 0.04 ± 0.025**
- **No difference in any group except high mortality group with early onset to therapy**  
  - Mortality rate decrease  
    - -0.23 ± 0.07

Kern Crit Care Med 2002
Remaining Questions

• Does targeting increased oxygen delivery improve outcome?
• Clear that survivors are able to increase CI and DO2 values significantly above normal
  – Is this an association of benefit or cause of benefit
• Perhaps targeting supra-normal hemodynamic values causes harm
• Survivors are able to do it on their own
• Any other evidence
What about early goal directed therapy?

Rivers, et al devised a protocol for sepsis:
- Utilized fluid replacement incl. blood
- Vasoactive agents
- Inotropic agents
- Oxygen utilization (delivery) monitoring

Significant mortality benefit
- 30.5% vs. 46.5% in-hospital mortality

Sounds similar to earlier studies

Rivers NEJM 2001
Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP

<8 mm Hg

Crystalloid

Colloid

8–12 mm Hg

MAP

<65 mm Hg

Vasoactive agents

>90 mm Hg

Transfusion of red cells until hematocrit >30%

>70% ScvO₂

Transfusion of red cells until hematocrit >30%

<70% ScvO₂

Inotropic agents

<70%

Goals achieved

No

Yes

Hospital admission

Rivers NEJM 2001
Validating ER EGDT

- ED patients with suspected infection or SIRS with SBP < 90 after fluid loading or lactate $\geq 4$ mol/L
- 79 patients pre-intervention compared with 77 patients post-intervention
- Intervention EGDT similar to Rivers study
- In hospital mortality 27% pre-intervention vs. 18% post-intervention
  - 9% absolute and 33% relative mortality reduction
  - Non-significant Kaplan-Meier survival estimate

Jones, CHEST 2007
Goal-directed resuscitation algorithm

Kaplan-Meier survival curve comparing survival of patients in the pre-EGDT intervention (before phase) and post-EGDT intervention (after group)

Survival (%)

Hospital Days

Log-rank test $P = 0.13$

Validating Early Therapy

- 135 pre-operative patient for major abdominal surgery
- Randomized to control group
  - MAP > 80, UOP > 0.5 mL/Kg-hr, CVP 8-12
- Or protocol group
  - Control parameters PLUS O₂ER < 27%
    - From Shoemaker 1988 data
- No mortality benefit
- Fewer organ failures
  - 27 total organ failures control vs 9 protocol (p<0.001)
- Shorter hospital LOS
  - 11.3±3.8 days vs 13.4±6.1 days (p<0.05)

Donati, CHEST 2007
Therapeutic protocol

Preop (T0):
Arterial and central venous line
Check SaO2 – ScvO2 – calculate O2ERe

Group A

Intra-op (T1): O2ERe (hourly)

≤ 27% → No change (or decrease Dobe)
> 27% → CVP

< 10 cm H2O → Fluid challenge
- Colloids (when Hb > 10 g/dl)
- PBC (when Hb < 10 g/dl)
If O2ERe still > 27%

> 10 cm H2O → Dobutamine

Group B

Standard management (MAP, urine output, CVP)

Postop (T2): Similar management than intra-op.
Checks of O2ERe at the end of anesthesia, 0.5, 1, 2 and 6 hours and day +1
Time Course of Variables

Number and type of organ failures observed in group A (O2ERe group, dotted column) and in group B (standard management group, black column)

![Chart showing the number and type of organ failures observed in group A and group B.]

Conclusions

• What patient characteristics are important
  – Too old, too sick, heart failure or other cardiac patients?
• What actual hemodynamic and oxygen delivery goals should be targeted?
  – Is CI > 4.5 and DO2 > 600 too high?
• Does increased monitoring and associated hemodynamic variables help or hurt
  – Shoemaker CVC equivalence with PAC
  – Rivers evidence with ScVO2 use only
• Seems clear that pushing patients who do not meet goals may indeed be harmful
Conclusions

• No clear perfect study showing increased oxygen delivery ALONE improves outcome
• Good evidence that early therapy has significant mortality benefit
  – Also good evidence that late therapy does not help much
• Good evidence that optimizing hemodynamics and improving DO2 before VO2 changes negatively is beneficial
• Probably don’t need to target the (unrealistic) values of earlier studies

• For now we have the Rivers (and others) version of EGDT to follow.