BLOOD FLOW DISTRIBUTION AND MICROCIRCULATION IN CRITICALLY ILL

Dr Sau Yee Lam
The Concept of Ventriculo-Arterial Coupling

Why do warm-blooded animals have a high systemic blood pressure?
Why do warm-blooded animals have a high systemic blood pressure?

Very “Expensive” Trait

- Requires increased muscular pumping
  - myocardial at risk of ischemia and infarction
- Stresses arterial conduits
  - stress degeneration
    - Atherosclerosis
    - Aneurysms
      - Rupture of congenital aneurysms
- End-organ dysfunction
  - Heart, brain, kidneys
Regulation of Organ Blood Flow

- High intra-organ input resistance
  - Arteriolar tone, precapillary sphincter
  - Tissue interstitial pressure
- High input pressure
- Primary method to increase organ blood flow
  - Local vasodilation in metabolically active tissues
  - Passive increase in arterial inflow

Cardiac output important only to maintain pressure
Rationale for defense of arterial pressure

Allows autoregulation of blood flow distribution
Cardiac Output is Proportional to Global Oxygen Uptake

\[ \text{VO}_2 \]

Cardiac Output
Regional Blood Flow is Proportional to Regional Metabolic Demand

Regional VO$_2$

Regional Metabolic Demand
Global autonomic control important in optimizing TO₂

Vasoconstrictor tone alters the dysxia threshold in hypoxic hypoxia


Adrenergic vasoconstriction augments tissue O₂ extraction during reduction in O₂ delivery

Loss of Autonomic Tone Impairs O₂ Distribution

Increased Autonomic Tone *(global decrease in TO2)*
Improves O2 Extraction

Maginniss et al/ J Appl Physiol 76:1451-64, 1994
Vascular Pressure-Flow Relations

Effect of Decreasing Vasomotor tone on Pressure-Flow Coupling

- Mean Arterial Pressure
- Aortic Blood Flow
- Normal tone
- Decreased vasomotor tone

Graph showing the relationship between mean arterial pressure and aortic blood flow under normal and decreased vasomotor tone conditions.
Control of Regional Blood Flow Distribution

Different vascular beds have different O$_2$ extraction capacities (Regional VO$_2$/DO$_2$)


Different vascular beds have different passive pressure-flow relations (regional P/Q)


The absolute amount of blood flow redistribution is limited in stress states

Blood flow is diverted away from vascular bed that can most avidly extract O2

- Marked decrease in muscle and liver blood flow
- Lesser decrease in kidney and gut blood flow
- If perfusion pressure is maintained

No decrease in brain blood flow
- If perfusion pressure is maintained


A lower DO2 crit than predicted, if proportional flow to all organs remained the same as global flow decreased
Active blood flow redistribution among organs during hemorrhage improves O2 extraction efficiency

Blood flow tends to be distributed away from organs with better O2 extraction capacities

Maximizing DO2crit as global DO2 declines

Liver ➔ Gut ➔ Kidney

Passive Pressure-Flow Relations

Arterial Pressure

Organ blood flow

Kidney

Gut

Liver

Phenobarbital-aneasthetized, canine, n=8
Organ Specific Autoregulation

Blood Flow

Perfusion Pressure (mmHg)

dilated

autoregulating

constricted
Mean Arterial Pressure is NOT Organ Perfusion Pressure

Relation Between MAP & Perfusion Pressure

- MAP = Diastolic pressure + 1/3 pulse pressure
- Perfusion pressure = Input – Output Pressure

<table>
<thead>
<tr>
<th>Organ</th>
<th>Input Pressure</th>
<th>Output Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>MAP</td>
<td>CVP (ITP) or ICP</td>
</tr>
<tr>
<td>Heart</td>
<td>Diastolic arterial pressure</td>
<td>CVP (ITP)</td>
</tr>
<tr>
<td>Kidney, Gut</td>
<td>MAP</td>
<td>CVP or Intra-abd pressure</td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>MAP</td>
<td>CVP or Interstitial Pressure</td>
</tr>
</tbody>
</table>

Perfusion Pressure and Organ Flow

Coronary PP = DAP – LVEDP

Renal PP = MAP – Tissue Pressure

Organ Perfusion Pressure (mmHg)
Input Arterial Pressure Varies Across Vascular Circuits

Perfusion Pressure

Aorta

Length of Vessel
Perfusion Pressure is the Primary Determinants of Local Blood Flow

Blood flow redistribution is limited

- Active blood flow redistribution occurs early in hemorrhage and is limited
- Once established, further reductions in blood flow decrease organ blood flow only if perfusion pressure also decreases

Arterial Pressure is the primary determinate of visceral organ blood flow following hemorrhage during remote exercise.

- **Δ Arterial Pressure**
- **Δ Organ Blood Flow**

* splanchnic blood flow
* o renal blood flow

Romand et al. AJRCCM 153:203-210, 1996
Regional blood flow distribution in sepsis

- Dissociation between blood flow and metabolic demand
- Dissociation between nutrient flow and cellular uptake and utilization
Sepsis alters vasomotor tone

- Decreased adrenergic responsiveness
- Pathologic vasoconstriction
  - PGF$_2$
  - Thromboxane A$_2$
  - Platelet activating factor
  - Leukotrienes
- Pathologic vasodilation
  - Nitric oxide synthase
  - Leukotrienes, 20-HETE
Sepsis alters arteriolar tone

Acute endotoxemia decreases critical closing pressure (Pzf) but does not alter the slope of the pressure-flow (P/Q) relation (<6h)


Sustained sepsis and endotoxemia decreases both Pzf and the slope of P/Q relation (arterial resistance) via systemic iNOS expression

Effect of endotoxin of arterial pressure-flow relations

- Initial decrease in Pzf
- Subsequent decrease in slope once iNOS upregulated

Sepsis alters the pressure-flow relations among organs

- Blood flow redistribution varies in a non-uniform fashion among visceral organs
  

- Blood flow redistribution not altered by Norepinephrine
  
  Belloma et al. AJRCCM 159:1186-92, 1999
Effect of endotoxin on visceral arterial pressure-flow relations

Endotoxin and renal blood flow

Mean pressure-flow data

Flow (ml/min)

Pressure (mm Hg)

Control
Norepinephrine
Endotoxin
Norepi & Endo

n=9

Belloma et al. AJRCCM 159:1186-92, 1999
Lactate flux across various organ beds

Lactate release by the lung

Lung lactate and lung injury

Lung is a source of lactate

- Experimental endotoxemia
  - Sayeed. Circ Shock 9:335-41, 1982

- Clinical studies of sepsis
Change in Anion Flux following Endotoxin Infusion

Kellum et al: J Appl Physiol 78:2212-9, 1995
Metabolic acidosis

Lactate may reflect either ischemic lactate release, aerobic lactate production, or normal metabolism by anaerobic WBCs.

Metabolic acidosis may reflect dilutional acidosis, anionic protein release or true lactic acidosis.
Does resuscitation restore organ blood flow in sepsis?

**NO**

Within organ blood flow redistribution

- Mucosal tissue hypoxia not improved by resuscitation, despite restoration of mesenteric blood flow to basal levels
- Serosal surface oxygenation restored

Determinants of Capillary Blood Flow

- **Fahraeus Effect (30% reduction in Hct)**
  - Obligatroy Film of plasma over endothelium


- **Heterogeneity of flow distribution**
  - Streaming and branch point effects


- **Retardation of plasma flow**


Fahraeus Effect

Obligatory Film of Plasma on Capillary Endothelial Surface

Whole Blood Hematocrit 45%
Tube Hematocrit 30%

As cross-sectional area of vessel gets smaller, the effect of this PLASMA layer increases

Outflow Hematocrit 45%
Capillary Streaming at Branch Points

Gut microvilli supplied by side capillaries

Muscles supplied by end capillaries

End-arteriole
Flow

Side capillary

End capillary
Capillary Hematocrit

RBC gating into capillary and increased RBC velocity relative to plasma

Whole Blood Hematocrit 45%

Capillary Hematocrit 10%

Although RBC flux higher than plasma
Ischemia risk from RBC-free plasma space depleted of $O_2$

Outflow Hematocrit 45%
Capillary Hct as RBC (Cars) & Plasma (Trunks) Traversing a Tunnel

2 cars and 5 trucks are in the tunnel at any time but one truck and car enter and leave together.
Capillary Hematocrit and Tissue oxygenation
Beyond global oxygen supply-demand relations in search of measures of dysoxia

- Global measures of VO₂/DO₂ do not reflect regional blood flow
- Regional markers have yet to be shown superior to global markers in defining therapeutic effectiveness

Gastric-arterial PCO2 gradients do not reflect systemic and splanchnic hemodynamics or DO2

- Prospective study of 30 post-cardiac surgery patients

No relationship between change in ΔPg-aCO2 and Δ splanchnic DO2

Uusaro et al. Shock 14:13-7, 2000
Do macro-circulatory parameters reflect organ perfusion?

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Dobutamine</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>93 (84-108)</td>
<td>108 (97-122)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>71 (68-80)</td>
<td>69 (65-75)</td>
<td>0.52</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>13 (11-16)</td>
<td>11 (9-14)</td>
<td>0.13</td>
</tr>
<tr>
<td>Pulmonary Artery Occlusion P</td>
<td>13 (10-15)</td>
<td>12 (10-15)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>3.7 (3.2-4.1)</td>
<td>4.2 (3.5-5.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>63 (58-72)</td>
<td>74 (64-78)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pulse pressure variation (%)</td>
<td>6 (2-8)</td>
<td>6 (3-8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Urine output (ml)</td>
<td>90 (51-119)</td>
<td>52 (25-220)</td>
<td>0.39</td>
</tr>
<tr>
<td>Norepi dose (mcg/kg/min)</td>
<td>0.15 (0.07-0.33)</td>
<td>0.16 (0.06-0.42)</td>
<td>0.39</td>
</tr>
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Identifying Cardiovascular Reserve: StO2 during an vascular occlusion test
Do macro-circulatory parameters reflect organ perfusion?

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<tr>
<td>Capillary Refill Time (s)</td>
<td>3 (2-4)</td>
<td>3 (2-5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Central-to-Toe Temp (°C)</td>
<td>3.3 (1.5-3.8)</td>
<td>3.6 (0.4-4.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>Thenar muscle O₂ saturation (%)</td>
<td>82 (74-88)</td>
<td>84 (75-88)</td>
<td>0.10</td>
</tr>
<tr>
<td>StO₂ recovery slope after VOT (%/s)</td>
<td>2.5 (1.2-3.4)</td>
<td>2.1 (1.1-3.1)</td>
<td>0.01</td>
</tr>
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Do macro-circulatory parameters reflect organ perfusion?

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<tr>
<td>Mixed venous O₂ saturation (%)</td>
<td>77 (72-81)</td>
<td>78 (75-81)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mixed venous-arterial pCO₂ gradient (mm Hg)</td>
<td>3.3 (1.5-3.8)</td>
<td>3.6 (0.4-4.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>Arterial lactate (mmol/l)</td>
<td>2.8 (2.4-3.9)</td>
<td>2.8 (2.4-4.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>O₂ Delivery (ml/min/m²)</td>
<td>566 (374-722)</td>
<td>717 (419-771)</td>
<td>0.02</td>
</tr>
<tr>
<td>O₂ Consumption (ml/min/m²)</td>
<td>129 (100-156)</td>
<td>140 (106-167)</td>
<td>0.35</td>
</tr>
<tr>
<td>ICG plasma disappearance rate*</td>
<td>18.8 (11.7-24.6)</td>
<td>14.4 (9.5-25.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>ICG retention rate at 15 min (%)</td>
<td>6.0 (2.8-17.4)</td>
<td>11.5 (2.3-24.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Gastric-arterial pCO₂ (mmHg)</td>
<td>13 (7-18)</td>
<td>13 (7-29)</td>
<td>0.52</td>
</tr>
<tr>
<td>Intraabdominal pressure (mmHg)</td>
<td>12 (8-16)</td>
<td>12 (9-17)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*(%/min)

Do macro-circulatory parameters reflect organ perfusion?

Sublingual microcirculatory parameters

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<tbody>
<tr>
<td>Total microcirculatory density (n/mn)</td>
<td>11.8 (10.2-12.5)</td>
<td>11.9 (9.7-12.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>Perfused vessel density (n/mn)</td>
<td>9.1 (7.9-9.9)</td>
<td>9.1 (7.9-10.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Proportion of perfused microvessels (%)</td>
<td>75 (69-79)</td>
<td>79 (72-84)</td>
<td>0.09</td>
</tr>
<tr>
<td>Microvascular flow index</td>
<td>2.1 (1.9-2.5)</td>
<td>2.1 (1.8-2.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>Heterogeneity of microvascular flow</td>
<td>0.58 (0.46-0.73)</td>
<td>0.47 (0.40-0.86)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Organ Perfusion Pressure is important

- Increasing MAP > 65mmHg with noradrenaline improves tissue perfusion in septic shock
- Increasing MAP further, >75 or 85 mmHg does not increase tissue perfusion further

High Blood Pressure (80-85 mmHg) vs Low Blood Pressure (65-75 mmHg) Targets in Septic Shock

Asfar et al NEJM 370:1583-93, 2014
High Blood Pressure (80-85 mmHg) vs Low Blood Pressure (65-75 mmHg) Targets in Septic Shock

Asfar et al NEJM 370:1583-93, 2014
Noradrenaline improves outcome from septic shock

- Prospective observational study n=97
- Use of norepinephrine strongly associated with a favorable outcome when controlled for MAP

Comparison of Norepinephrine to Dopamine in Patients in Shock

Kaplan-Meier Curves for 28-day Survival in the ITT Population

Comparison of Norepinephrine to Dopamine in Patients in Shock

Forest Plot for Predefined Subgroup Analysis According to Type of Shock

The way in which organ perfusion pressure is maintained is important

- Increasing MAP >65mmHg improves outcome in patients in septic shock better if vasopressor is norepinephrine

- Evidence of pre-existent organ injury (low uo), inflammation (serum lactate) also determine outcome

Recommendations

➢ Monitoring
   • Measure real perfusion performance variables
     ✓ Uo, MAP, capillary refill, sensorium
   • Measure surrogates variables for collaboration not confirmation
     ✓ Gut tonometry, serum lactate, ScvO2, v-aPCO2
   • Trends may be more important than absolute values

➢ Management
   • Fluids and vasopressor to keep MAP >65mmHg
   • Norepinephrine is the drug of choice
   • Consider increasing inotropy if cardiac output remains low and evidence of tissue hypoperfusion