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Hemodynamics

M1 – Cardiovascular/Respiratory Sequence
Louis D’Alecy, Ph.D.
Monday 11/03/08, 9:00
Hemodynamics
26 slides, 50 min

1. Pressure & pressure pulses
2. Pressure gradient (perfusion pressure)
3. Determinants of Blood Flow
4. Resistance in series and in parallel
Hemodynamics

"Hemodynamics is concerned with the forces generated by the heart and the motion of blood through the cardiovascular system."

from ucdavis.edu

Blood Pressures and Blood Flow
Flow out

Flow in


LV end-diastolic Volume
**** LVEDV ****
Pressures in right ventricle/pulmonary artery

1 = Ventricular filling
2 = Isovolumetric ventricular contraction
3 = Ventricular ejection
4 = Isovolumetric ventricular relaxation

Pulmonary artery pressure
Right ventricular pressure
Pressure different
SV same
i.e.
Flow same
Veins are more compliant than arteries.
SV = Loads the spring, i.e. increased volume increases pressure

Aortic flow = unloads the spring
Arterial pressure

MAP = \( P_d + \frac{1}{3}P_p \)

Pulse Pressure = (Systolic - Diastolic)
Pulse Pressure Increases with age
Flow = \frac{P_{\text{artery}} - P_{\text{vein}}}{R}

Flow is directly proportional to the pressure difference.

“pressure gradient” or $\Delta P$
Flow between two points

\[ P_1 = 100 \text{ mmHg} \]
\[ P_2 = 10 \text{ mmHg} \]
Flow rate = 10 ml/min

\[ P_1 = 500 \text{ mmHg} \]
\[ P_2 = 410 \text{ mmHg} \]
Flow rate = 10 ml/min
Arterial Determinants of Perfusion Pressure

NORMAL PERFUSION PRESSURE (mmHg)

<table>
<thead>
<tr>
<th>90</th>
<th>85</th>
<th>Artery</th>
<th>80</th>
</tr>
</thead>
</table>

HYPOTENSIVE PERFUSION PRESSURE (mmHg)

| 75 | 70 | Artery | 65 |

Yein

<table>
<thead>
<tr>
<th>5</th>
<th>0</th>
<th></th>
</tr>
</thead>
</table>
Or Laparoscopic Surgery?

Abdominal Compartment Syndrome

Both can compress great veins and reduce visceral perfusion pressure.

e.g. due to excessive hydration
DETERMINANTS OF PERFUSION PRESSURE

NORMAL PERFUSION PRESSURE (mmHg)

Artery | 90 | 85 | 5 | 0

HYPOTENSIVE PERFUSION PRESSURE (mmHg)

Artery | 75 | 70 | 5 | 0

INCREASED VENOUS PRESSURE (mmHg)

Artery | 90 | 85 | 20 | 15

HYPOTENSION & ↑ VENOUS PRESSURE (mmHg)

Artery | 75 | 70 | 20 | 15
Flow is directly proportional to $\Delta P$ and inversely proportional to $R$

$R = \text{resistance}$
Resistance ~ hindrance to flow

**Series Resistance Add**

\[ R_s = R_1 + R_2 + R_3 \]

\[ \dot{Q} = \frac{\Delta P}{R_s} \]

Q = flow

**Measure flow and pressure drop and calculate resistance.**

$R = \text{Resistance} \quad r = \text{radius}$

$$R = \frac{8\eta L}{\pi r^4}$$

L = length  
$\eta$ = viscosity  
r = radius

Flow = $\frac{\text{Perfusion Pressure}}{\text{Resistance}}$

Thus 2X $r$ produces 16X flow!!
Flow is directly proportional to $\Delta P$

and

directly proportional to $r^4$

i.e. the 4th power of the radius
<table>
<thead>
<tr>
<th></th>
<th>Arteries</th>
<th>Arterioles</th>
<th>Capillaries</th>
<th>Venules</th>
<th>Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>internal diameter</strong></td>
<td>2.5 cm</td>
<td>0.4 cm</td>
<td>30 μm</td>
<td>5 μm</td>
<td>70 μm</td>
</tr>
<tr>
<td></td>
<td>2 mm</td>
<td>1 mm</td>
<td>20 μm</td>
<td>1 μm</td>
<td>2 μm</td>
</tr>
<tr>
<td><strong>number</strong></td>
<td>1</td>
<td>160</td>
<td>5 × 10⁷</td>
<td>10¹⁰</td>
<td>10⁸</td>
</tr>
<tr>
<td><strong>total cross-sectional area</strong></td>
<td>4.5 cm²</td>
<td>20 cm²</td>
<td>400 cm²</td>
<td>4500 cm²</td>
<td>4000 cm²</td>
</tr>
</tbody>
</table>

Effect of tube radius

Radius of A ($r_A$) = 2
Radius of B ($r_B$) = 1

\[ R_A \propto \frac{1}{r_A^4} = \frac{1}{2^4} = \frac{1}{16} = 0.0625 \]

\[ R_B \propto \frac{1}{r_B^4} = \frac{1}{1^4} = \frac{1}{1} = 1.0 \]

Therefore $R_B = 16 \times R_A$

Flow = \( \frac{\Delta P}{R} \)

Therefore flow in B = \( \frac{1}{16} \) th of flow in A

Same $\Delta P$
Parallel Resistance Network
With different individual resistances

\[ \frac{1}{R_p} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} \]

\[ \dot{Q}_{\text{total}} = \dot{Q}_1 + \dot{Q}_2 + \dot{Q}_3 \]

\[ \Delta P = P_i - P_0 \]

Another example:

Parallel Resistance Network
With identical individual resistances

Assume you have four vessel paths in parallel and each has the same individual resistance of 4.

What is the overall resistance of this parallel network?
\[
\frac{1}{R_t} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4}
\]

\[
\frac{1}{R_t} = 1 + \frac{1}{4} + \frac{1}{4} + \frac{1}{4}
\]

\[
R_t = 1
\]

COMBINED (Total)
The parallel resistance network has less resistance than any individual component.
Parallel Resistance Network

More checkout lines means that there is less resistance to “flowing” out of the store.

Parallel resistances add as reciprocals.
Tissue Blood Flow and Tissue Vascular Resistance

(**Assume Perfusion Pressure is Constant**) 

• Vasoconstriction
  \[ \Rightarrow \downarrow r \Rightarrow \uparrow R_{\text{tissue}} \Rightarrow \downarrow F_{\text{tissue}} \]

• Vasodilation
  \[ \Rightarrow \uparrow r \Rightarrow \downarrow R_{\text{tissue}} \Rightarrow \uparrow F_{\text{tissue}} \]

\[ F_{\text{tissue}} = \dfrac{\text{Perfusion Pressure}}{R_{\text{tissue}}} \]
1. Vasoconstrictors and Vasodilators
2. Neural control of resistance
3. Humoral control of resistance
4. Local control of resistance
5. Nitric oxide, Nitric oxide synthase (NOS)
6. Asymmetrical dimethylarginine
BLOOD

endothelial cell

prostacyclin

Epi

endothelial cell

β₂

NO

contract

vascular smooth muscle

histamine

adenosine

endothelial cell

endothelial cell

endothelin

endothelial cell

cardiac muscle

mast cell

α₁

NE

sympathetic nerve

relax

relax

relax

relax

relax

relax

NO

NO

NO

NO

NO

NO

NO

NO
VSM can change tension without action potentials

A change in VSM tension causes vasodilation or vasoconstriction
ELECTROMECHANICAL COUPLING

Membrane depolarization

sarcolemma

\[ \text{Ca}^{2+} \]

\[ \uparrow [\text{Ca}^{2+}]_i \]

Contraction

PHARMACOMECHANICAL COUPLING

Vasoconstrictor agonist

[Image of pharmacological pathways]

Calmodulin binds to the myosin light chain kinase upon Ca++ binding.

The myosin light chain kinase converts ATP to ADP, releasing a phosphate group (PO₄).

The regulatory light chain is phosphorylated by the kinase, activating the myosin for contraction.

D'Alecy
At rest
myosin can not bind to actin in absence of light chain phosphorylation

Cycling bridges
myosin rapidly dissociates from actin upon binding ATP during each cycle
initial rise in muscle tension

Latch bridges
dephosphorylated myosin dissociates from actin very slowly producing slow bridge cycling
maintained tension tonic contraction
Sympathetic nerves/plasma epinephrine

Sympathetic postganglionic neurons to skeletal muscle arterioles:
- Release norepinephrine
- Tends to cause vasoconstriction
  - $\alpha_1$

Adrenal medulla:
- Secretes epinephrine into blood
- Tends to cause vasodilation
  - $\beta_2$

Norepinephrine in extracellular fluid
Smooth muscle in skeletal muscle arterioles
Altered arteriolar radius
Arteriolar radius

Neural controls
- Vasoconstrictors: Sympathetic nerves
- Vasodilators: Neurons that release nitric oxide

Hormonal controls
- Vasoconstrictors: Epinephrine, Angiotensin II, Vasopressin
- Vasodilators: Epinephrine, Atrial natriuretic hormone

Local controls
- Vasoconstrictors: Internal blood pressure (myogenic response), Endothelin-1
- Vasodilators: Oxygen, $K^+$, $CO_2$, $H^+$, Osmolarity, Adenosine, Eicosanoids, Bradykinin, Substances released during injury, Nitric oxide

Arteriolar smooth muscle
Altered arteriolar radius
Local Influences on Arterioles
(Local = no neural or humoral control)

Active Hyperemia

Reactive Hyperemia

Autoregulation
Think of accumulation of vasodilator metabolites.

Active hyperemia
= increased blood flow in response to increased metabolic demand

Reactive Hyperemia
= increased blood flow following a period of no flow

Conclusions—Thus, lower reactive hyperemia is associated with increased cardiovascular risk in patients with peripheral arterial disease. Furthermore, flow-mediated dilation and reactive hyperemia incrementally relate to cardiovascular risk, although impaired flow-mediated dilation was the stronger predictor in this population. These findings further support
Autoregulation = relatively constant blood flow in the face of changed perfusion pressure

Think of vasodilator metabolite washout.

Local controls

Vasoconstrictors
- Internal blood pressure (myogenic response)
- Endothelin-1

Vasodilators
- ↓ Oxygen
- K⁺, CO₂, H⁺
- Osmolarity
- Adenosine
- Eicosanoids
- Bradykinin
- Substances released during injury
- Nitric oxide

Source: Undetermined
Other Smooth Muscles

Vascular

arteries, arterioles, venuoles, veins, lymphatic

Gastrointestinal

longitudinal vs circular, esophageal, gastric, intestinal
sphincter smooth muscles, gallbladder
bile and pancreatic ducts

Pulmonary

tracheal, bronchial, bronchiolar

Urinary System

bladder, ureters, urethra

Reproductive System

uterus, vagina, oviducts, vas deferens, prostate capsule

Miscellaneous

iris of eye
capsule of spleen
piloerector muscles of skin hairs
myoepithelial cells of glands
Spiral cut vessel strip

Vessel Ring

Tension measurement
Historical Response to Ach = contraction!!

Direct action on VSM

Source Undetermined
Vessel with intact endothelium relaxes to Ach !!!!!!
Via NO release from EC

Intact endothelium

Without endothelium

1 g

5.10^-7
5.10^-6

Artery wall tension

10^-7

10 min

5.10^-7 5.10^-6 5.10^-5 5.10^-4 5.10^-3

Acetylcholine

Prostacyclin

Source Undetermined
Fig 6.2

ENDOTHELIAL CELL

SMOOTH MUSCLE CELL

Endothelial-dependent vasodilators (e.g., ACh, serotonin, thrombin, shear stress)

Prostacyclin, EDRF-NO

↑ cAMP, ↑ cGMP

RELAXATION

Thrombin, Angiotensin II, Epinephrine

Endothelin-1

CONTRACTION
Sheer or Flow Mediated Dilation

* FMD *

NOS

NOS Isoforms, Activity and Inhibition

• Three isoforms: endothelial, neuronal and inducible

• Catalyze formation of NO and citrulline from L-arg

• NO production in endothelium produces------
  – Vasodilation, inhibition of platelet aggregation & inhibition of pro-inflammatory response

• Inhibit NOS $\Rightarrow$ ↓NO $\Rightarrow$ endothelial dysfunction $\Rightarrow$
  – vasoconstriction
  – atherogenesis
  – cardiovascular disease
ADMA the newest “bad guy”; maybe?

Asymmetrical Dimethylarginine = ADMA
Asymmetrical Dimethylarginine (ADMA)

• What is it?
• What can it do?
• Where does it come from?
• Where does it go?
• What does it really do?
• Can we mimic or block it to therapeutic advantage?
The Cast of Players

ADMA = Asymmetrical dimethylarginine
       (more abundant NOS inhibitor)

SDMA = Symmetrical dimethylarginine
       (?? Inactive on NOS)

L-NMMA = Monomethylarginine
         (less abundant NOS inhibitor)

DDAH = Dimethylarginine dimethylaminohydrolase
       (hydrolyzes ADMA)

PRMT = Protein arginine methyltransferase
       (makes ADMA and SDMA)
What is ADMA?

Arginine and endogenous derivatives

<table>
<thead>
<tr>
<th>ADMA</th>
<th>SDMA</th>
<th>NMMA</th>
<th>L-Arginine</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOS Inhibitor</td>
<td>NOS-Inactive</td>
<td>NOS Inhibitor</td>
<td>NOS Substrate</td>
</tr>
<tr>
<td>DDAH Substrate</td>
<td>Regioisomer</td>
<td>DDAH Substrate</td>
<td></td>
</tr>
</tbody>
</table>

Source Undetermined
Major control for NO??

PRMT           DDAH        all in WB

L-arginine → NO synthase → NO

ADMA

Vasodilation
Platelet aggregation
Monocyte adhesion
Release of superoxide radicals
Proliferation of vascular smooth muscle cells
Oxidation of LDL

ADMA: Formation/Release

- Protein-incorporated arginine residues are dimethylated by protein arginine methyltransferases (PRMTs)
  - No methylation of free arginine reported
- Free ADMA released via “normal protein turnover”

Questions: Where does free plasma ADMA originate and how is it released in WB ex vivo?
Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study
_Lancet_ 2001; 358: 2113–17

Zoccali C. et al tested the predictive power of ADMA for mortality and cardiovascular outcomes and concluded “ADMA is a stronger independent predictor of all-cause mortality and cardiovascular outcomes… in patients with CRF…”

“Predictor”
Where does ADMA come from?

- Elevated plasma ADMA in:
  - Hypercholesterolemia
  - Hypertension
  - Hyperhomocyst(e)inemia
  - Tobacco exposure
  - Peripheral arterial occlusive disease
  - Experimental hemorrhage (acute)
  - Pre-eclampsia
  - Hyperglycemia
  - Insulin resistance in patients --- and so on
Methods

• Incubation of rat whole blood (WB) and WB fractions
  – Sample placed in vial and incubated at 37°C

• HPLC analysis of blood ADMA/SDMA

• Acid hydrolysis of blood components
  – Liberates free amino acids for their quantification
Summary

• **WB plasma** contains free ADMA at < 1 μM

• WB contains > 40 μM protein-incorporated ADMA with the majority (>95%) in RBCs

• WB possesses the proteolytic machinery necessary for ADMA release into the plasma

• Inhibition of protease activity attenuates ADMA release from blood *ex vivo*
Conclusion

• WB can be considered a 5 kg “liquid organ” in intimate contact with the vascular endothelium.

• WB has the capacity to release physiologically and pathophysiologically relevant amounts of ADMA \textit{ex vivo}.

• WB is an independent source of ADMA and as such may play an etiological role in vascular disease.
ADMA-NOS-NO pathway the newest drug target?

PRMT       DDAH

+          -

L-arginine

NO synthase → NO

Vasodilatation
Platelet aggregation
Monocyte adhesion
Release of superoxide radicals
Proliferation of vascular smooth muscle cells
Oxidation of LDL

all in WB

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