Cardiovascular Physiology

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Curriculum

- Cardiac muscle contraction
- The cardiac cycle: pressure and volume relationships
- Rhythmicity of the heart
- Regulation of cardiac function; general and cellular
- Control of cardiac output (including the Starling relationship)
- Fluid challenge and heart failure
- Electrocardiogram and arrhythmias
Curriculum

- Neurological and humoral control of systemic blood pressures, blood volume and blood flow (at rest and during physiological disturbances e.g. exercise, haemorrhage and Valsalva manoeuvre)
- Peripheral circulation: capillaries, vascular endothelium and arteriolar smooth muscle
- Characteristics of special circulations including: pulmonary, coronary, cerebral, renal, portal and foetal
Lecture

- Anatomy stuff
- Electrical stuff
- Mechanical stuff
- Regulation stuff
- Microcirculation
Functions of CVS

- Transport – oxygen, glucose, AAs, FFAs, vitamins, drugs, water
- Control – hormone delivery and production (ANP)
- Temperature regulation
- Reproduction – hydraulics of penile erection
Anatomy Stuff

- **Diffusion**
  - NMJ (0.1µm) – 5 millionths second
  - LV wall (1cm) – 12 hours
  - Capillary to cell (10µm) – 50ms

- **Two circulations in series**
  - High pressure
  - Low pressure
CO vs tissue
Oxygen vs tissue

- Skin: 20%
- Other: 2%
- Liver & GIT: 10%
- Kidneys: 10%
- Brain: 10%
- Heart: 10%
- Muscle: 10%
a, CT coronary angiogram and corresponding conventional angiogram of the right coronary artery (RCA) in a patient presenting with stable angina pectoris and a calcium (Agatston) score of 79

Left anterior oblique (A) and right anterior oblique (B) view of 3D fused image

Characteristics of blood vessels
Myocyte anatomy

- Myocyte: 50 – 100µm long
  - Desmosomes & gap junctions
  - Sarcoplasmic reticulum
  - T-tubules
  - Myofibrils 1µm diameter
    - Sarcomeres 1.8 – 2 µm long
    - Z-lines, A-bands and I-bands
    - Actin & myosin
Myocyte anatomy

- I-bands shorten; A-bands do not
  - Sliding filament mechanism
  - Ca binds Troponin C; tropomyosin moves; myosin head binds to actin, moves, then disengages
  - 400 myosin heads per filament
Sarcomere anatomy

- One sarcomere
- A band
- H zone
- Z line
- Thick filament (myosin)
- Thin filament (actin)

I-band
Pressure changes in the circulation

[Graph showing pressure changes in systemic and pulmonary circulation, with blood pressure values labeled.]
# Mean Pressures

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
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</thead>
<tbody>
<tr>
<td>Atrium</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Ventricle – End diastole</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Ventricle – Peak systole</td>
<td>25</td>
<td>120</td>
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</table>
Electrical Stuff

- Resting potential
- Pacemaker cells
- Things that affect electrical stuff
$E_i \equiv V_{in} - V_{out} = \frac{RT}{zF} \ln \frac{[C]_{out}}{[C]_{in}}$
Electrical stuff

- Nernst equation:

\[ E_i \equiv V_{in} - V_{out} = \frac{RT}{zF} \ln \frac{[C]_{out}}{[C]_{in}} \]

- \( E_{Na} = +70\text{mV} \)
- \( E_K = -94\text{mV} \)

\( E_i \) = equilibrium potential; \( R \) = universal gas constant; \( T \) = temperature (K); 
\( z \) = valency; \( F \) = Faraday’s constant; \( \ln \) = natural logarithm
Electrical stuff

- **Currents:**
  - $I_b$ – inward background current (Na)
  - $I_k$ – outward background current (K and Na/K pump)

- **Ohm’s Law:** $i = g \Delta V$
  - $I_b = g_Na (V_m - E_{Na})$
  - $I_k = g_K (V_m - E_K)$

- At equilibrium the currents are equal…
Goldman constant field equation is obtained by rearranging for $V_m$

- $V_m$ is the resting potassium potential modified by a fraction of the resting sodium potential
- The fraction is the ratio of sodium to potassium conductance. i.e. 1/10
- $V_m$ is -79mV
Ion pumps

- 3 Na – 2 K ATPase
  - (ouabain/digoxin blocks)
- Na-Ca exchanger: 1 Ca out: 3 Na in
  - Accounts for $\frac{3}{4}$ calcium expulsion
- Ca-ATP pumps – $\frac{1}{4}$ calcium expulsion
  - especially on sarcoplasmic reticulum
Myocyte ion pumps
Cardiac action potential
Electrical stuff
Normal myocyte

- 4 - resting potential is relatively flat

- 0 - rapid depolarisation due to opening of voltage gated sodium channel \( m \) gates (tetrodotoxin blocks) triggered by charge being drawn by adjacent depolarised cell. Occurs about -70 to -60mV. Overshoot to +20 to +30mV
Normal myocyte

1 – Rapid inactivation of Na channel $h$ gate

2 – voltage operated slow (L-type) calcium channels open at -35mV stabilising membrane at 0 to -20mV. Potassium permeability decreases during the 200-400ms plateau (conservation). VOCs inactivate at 1/10 000$^{th}$ rate of sodium channels. Contraction only lasts about 200ms and is weakening by end of plateau.
Normal myocyte

- 2 – Calcium concentration rises from 0.1µM to 1-10µM. Usually around 2µM which partially activates contractile proteins

- *Calcium-induced calcium release from the SR accounts for 80-90% calcium rise in the cell. It is blocked by ryanodine.*
Normal myocyte

- 3 – Repolarisation due to inactivation of VOC Ca channels allowing increased conductance of K channels. At -50mV the sodium channels change from inactive to closed. ($m$ closed and $h$ open) This marks the change from the absolute refractory period to the relative refractory period.
Sinus node pacemaker

- Resting potential -60mV (Na channels are inactive)
- $I_f$ – “funny” inward current (Na)
- Decreasing K conductance
- At -40mV T-type Ca VOCs open and contribute to final third of action potential

(At A-V node only Ca VOCs contribute to action potential.)
Things that affect electrical activity

- **Hyperkalaemia** – 7.5mM can arrest the heart (8mM in severe exercise!)

  Resting potential increases

  Action potential is sluggish as Na gates remain “inactivated” leading to heart block and arrhythmias; it is shorter resulting in less Ca and weaker contraction
Things that affect electrical activity

- **Beta receptor stimulation**
  - Increases cAMP
  - Increases calcium current
  - Increases “funny” Na current (blocked by Caesium)
  - Activates phospholamban-Ca pumps on SR shortening AP

- **Muscarinic receptor stimulation**
  - Decreases cAMP
  - Opens $K_{ACh}$ channels causing hyperpolarisation
alpha-adrenergic receptors
Troponin release after myocardial injury

A ACUTE MYOCARDIAL INFARCTION

B MINOR MYOCARDIAL INJURY

C MYOCARDITIS

Mechanical Stuff

- $BP = CO \times TPR$
- $CO = SV \times HR$
- SV depends on pre-load, afterload and contractility.

“Preload, afterload and contractility are physiological concepts that have originated in the laboratory, for which it is difficult to find good clinical correlates.”
The cardiac cycle

Electrocardiogram
Heart sounds phonocardiogram

Aortic pressure (at o, the aortic valve opens; at c, it closes)
Left ventricular pressure (—)
Left atrial pressure (---) (right is similar)
Left ventricular volume (at c', the mitral valve closes; at o', it opens)

Jugular venous pressure, showing a,c, and v waves

Carotid pressure (n=dicrotic notch)
Radial pressure
Pulmonary arterial pressure
Right ventricular pressure

Phases of cardiac cycle
Length-strength

- Preload is sarcomere length prior to contraction and is reflected in the force generated during isovolaemic contraction.
  - Increased stretch *immediately* increases force of contraction by increasing number of actin/myosin binding sites.
  - Seems to increase sensitivity of contractile apparatus.
  - *Later* force of contraction increases due to increase in intracellular Ca (about 40% of increase) possibly due to stretch-sensitive calcium channels.
In humans there is no tailing-off of the “Starling curve”
Contractility

- “A change in contractile energy that is not due to a change in fibre-length is called a change in contractility.”
- $dP/dt$ is affected by fibre-length
- End-systolic volume curves from families of LV pressure-volume loops are the best measure of contractility
- Bowditch effect (increase heart rate increases contractility)
Normal pressure-volume loop and one in heart failure
Afterload

\[ S = \frac{(P_2 - P_1) \cdot r}{w} \]
Afterload

- Wall stress (S) in systole is afterload.
- Tension is stress times wall thickness.
- Laplace’s Law rearranged gives us an insight into afterload.
Metabolism

- 15% gross efficiency
  - Most energy spent on isovolumetric contraction (raising pressure) therefore lowering blood pressure helps failing heart

- 2/3 to ¾ energy from FFAs. Rest from glucose and lactate.
An 84-year-old man with coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, and congestive heart failure was admitted to the hospital because of a decrease in mental status.
Regulation Stuff

- Blood volume
- Blood pressure
Blood Volume - renin ("reenin")
Renin-Aldosterone system

- Decreased blood volume
- Decreased blood pressure
- Decreased NaCl and K+ at distal tubule
- β-adrenergic stimulation

- Increased blood volume
- Increased blood pressure

- Distal tubule: Na+ and bicarbonate reabsorption, K+ excretion

- Angiotensinogen (renin substrate) → Renin → Angiotensin I → Angiotensin II
  - ACE (lung)

- Aldosterone
  - ACTH
  - Adrenal gland

- Na+
- K+

- Sodium reabsorption
Arginine vasopressin secretion, plasma osmolality, and blood pressure/volume

![Graph showing the relationship between plasma vasopressin, blood pressure/volume, and plasma osmolality. The graph illustrates how plasma vasopressin levels change with percent change in blood pressure/volume and plasma osmolality.]
Brain pathways that mediate arginine vasopressin secretion
Receptors and reflexes

- **Pressors** - tachycardia and peripheral vasoconstriction
- **Depressors** - bradycadidia and peripheral vasodilatation.
Receptors and reflexes

- **Afferents**
  - Veno-atrial stretch receptors – large myelinated nerves via X. Cause tachycardia (no change in contractility) and moderate diuresis
  - Unmyelinated mechanoreceptors – 80% vagal afferents generally depressor response to atrial and ventricular stretch
Receptors and reflexes

**Afferents**

- **Chemosensitive fibres** – both vagal and sympathetic. Latter respond to bradykinin and other substances released by ischaemic myocardium (lactate, K ions) and are thought to mediate pain of angina (they ascend in spinothalamic tracts with somatic afferents – hence referred pain). Cause a pressor response.
Receptors and reflexes

- Afferents
  - Carotid and aortic bodies respond to hypoxia and acidosis
  - With low blood pressure ‘stagnant hypoxia’ in the bodies is a powerful stimulus; causes rapid breathing seen in severe shock.
  - Lung stretch receptors - reduce vagal outflow and sympathetic tone
  - Skeletal muscle – mechano- and metabolo-receptors (small myelinated (Group III) and non-myelinated (Group IV) but not spindle afferents (Group I))
Long term blood pressure control

- Renin-angiotensin-aldosterone

- Vasopressin

- Atrial natriuretic peptide (secreted directly by certain atrial cells in response to stretch)
Efferent autonomic nerve supply to the heart
**NTS** - nucleus tractus solitarius

**CVM** - caudal ventro-lateral medulla

**RVM** - rostral ventro-lateral medulla

**IMN** - intermedio-lateral column
Baroreflex

- Carotid sinus – via IX, petrous ganglion to NTS
- Aortic arch – via X, nodose ganglion to NTS
- Stimulation leads to bradycardia and reduced sympathetic outflow
- Tonic firing rate - offloading results in the opposite. Fibres are silent below 70mmHg.
- Sympathetics to skin are unaffected; vasoconstriction lowers capillary pressure leading to absorption of tissue fluid; renal sympathetic nerve increases renin-angiotensin-aldosterone secretion; ADH secretion is increased.
Baroreceptor control of the circulation

<table>
<thead>
<tr>
<th>Arterial Pressure</th>
<th>Carotid sinus nerve impulses</th>
<th>Normal</th>
<th>Vagus nerve impulses</th>
<th>Accelerated</th>
<th>Heart Rate</th>
<th>Slowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower</td>
<td></td>
<td></td>
<td>Sympathetic cardiac nerve</td>
<td>Increased</td>
<td>Contractility</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sympathetic vasoconstrictor nerves</td>
<td>Increased</td>
<td>Vasoconstriction</td>
<td>Decreased</td>
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</table>
Baroreflex

- For the rapid stabilisation of blood pressure
- Set-point is moveable
- Responsiveness decreases in hypertensives and with age
Decline in baroreceptor responsiveness
Aortic distensibility

The diagram illustrates the comparison between aortic pressure and flow in a normotensive (56 y) and isolated systolic hypertension (61 y).
The Valsalva

- 18th century Italian physiologist
- Four phases:
  1. Rise in pressure due to pressure on aorta
  2. Fall in pressure and pulse-pressure due to impedance of venous return (Frank-Starling). Pressure stabilises due to baro-reflex of tachycardia and vasoconstriction
  3. Release of intra-thoracic pressure causes immediate drop in pressure as peri-aortic pressure returns to normal
  4. Sudden rush of blood back to heart causes distension and increased stroke volume which increases pressure. Baro-reflex causes decrease in heart rate and vasodilatation.
Microcirculation

- Starling forces
  - Fluid is not constantly reabsorbed at the venous end. This would only occur transiently
  - Fluid is constantly filtered, decreasing exponentially from the arterial to venous end
  - Filtration fraction 0.2-0.3% in most tissues
  - 20% in renal glomerular capillaries, salivary glands, dependent foot
Microcirculation

- Starling forces
  - Net filtration pressure

\[(P_c - P_i) - \delta(\pi_p - \pi_i)\]
Microcirculation

- Autoregulation
  - Myogenic response: increased pressure leads to vasoconstriction (to smaller diameter)
  - Vasodilator washout – increased pressure increases flow and washes out metabolites which leads to vasoconstriction

Venous back-pressure elucidates which is more important (former in brain, intestine, colon, spleen)
Microcirculation

- Myogenic response is probably due to stretch sensitive Ca channels, although in some large arteries endothelial stripping abolishes it, suggesting a role for NO
Nitric oxide: its source, release, and function
Special Circulations

- Pulmonary
- Coronary
- Cerebral
- Renal
- Portal
- Foetal
  - Covered in different lectures...
The transplanted heart.

- Loss of afferent cardiac innervation may interfere with several reflex cardiac mechanisms including salt and water regulation via the renin-angiotensin-aldosterone system, reflex control of the peripheral vasculature, and the sensation of cardiac pain.

- Loss of efferent vagal tone to the sinus node results in a 30% higher resting heart rate than the normally innervated heart. Reflex increases in heart rate and contractility normally brought about by exercise, hemorrhage, or vasodilation are also attenuated by the loss of efferent sympathetic impulses.

- Denervation may produce hypersensitivity to catecholamines due to a lack of adrenergic neuronal uptake.

- Heart transplant recipients rely primarily on a rapid increase in stroke volume via the Starling mechanism to maintain cardiac output in the face of exercise. Cardiac output after transplantation is therefore highly preload dependent and adequate intravascular volume must be maintained during subsequent surgical procedures, especially if spinal or epidural anesthesia is employed. In addition, the heart rate response to indirect acting pharmacologic agents such as atropine, glycopyrrolate, pancuronium, digoxin, phenylephrine, and anticholinesterases will be absent or markedly attenuated.
A 34-year-old woman with a 3-year history of systemic lupus erythematosus was admitted to the hospital with sore throat and headache that had lasted for 3 weeks
Further reading

- E-Learning (www.e-LA.org.uk)
- An Introduction to Cardiovascular Physiology – Levick