Cardiovascular Pharmacology

- Hypertension
- Angina pectoris
- Cardiac Arrhythmias
- Heart Failure
Cardiovascular Pharmacology

- Cardiovascular (=Circulatory) system – heart and blood vessels
- Arteries – transport blood to tissues
- Capillaries – sites of exchange, fluid O2, CO2, nutrients etc.
- Venules – collect blood from capillaries
- Veins – transport blood back to heart
- Blood moves within vessels – higher pressure to lower pressure
  Resistance to flow depends on vessel diameter, length and viscosity of blood
Cardiovascular Pharmacology

Cardiac blood flow

• The mammalian heart is a double pump in which the right side operates as a low-pressure system delivering de-oxygenated blood to the lungs, while the left side is a high pressure system delivering oxygenated blood to the rest of the body.

• The walls of the right ventricle are much thinner than those of the left, because the work load is lower for the right side of the heart.

• The ventricular muscle is relatively stiff, and it would take some time to fill with venous blood during diastole. The thin, flexible atria serve to buffer the incoming venous supply, and their initial contraction at the beginning of each cardiac cycle fills the ventricles efficiently in a short space of time.
Cardiovascular Pharmacology
Regulation of cardiac output

~ 5L /minute; dependent on:
- Heart rate
- Stroke volume
- Preload
- Afterload

Starling’s Law
Ventricular contraction is proportional to muscle fiber stretch
Aortic output pressure rises as the venous filling pressure is increased
Increased venous return – increase cardiac output – up to a point!
Cardiovascular Pharmacology

**Cardiac electrical activity**

- Cardiac muscle does not require any nervous stimulation to contract.
- Each beat is initiated by the spontaneous depolarisation of pacemaker cells in the sino-atrial (SA) node. These cells trigger the neighbouring atrial cells by direct electrical contacts and a wave of depolarisation spreads out over the atria, eventually exciting the atrio-ventricular (AV) node.
- Contraction of the atria precedes that of the ventricles, forcing extra blood into the ventricles and eliciting the Starling response.
- The electrical signal from the AV node is carried to the ventricles by a specialised bundle of conducting tissue (the bundle of His).
- The conducting tissues are derived from modified cardiac muscle cells, the Purkinje fibers. The conducting bundles divide repeatedly through the myocardium to coordinate electrical and contractile activity across the heart.
- Although each cardiac muscle cell is in electrical contact with most of its neighbours, the message normally arrives first via the Purkinje system.
Cardiovascular Pharmacology

Venous return
• Systemic filling pressure
• Auxiliary muscle pump
• Resistance to flow between peripheral vessels and right atrium
• Right atrial pressure - elevation

Regulation of Arterial Pressure
• Arterial pressure = cardiac output + peripheral resistance
• Arterial pressure affected by:
  – the autonomic nervous system (fast)
  – the renin-angiotensin system (hours or days)
  – the kidneys (days or weeks)
Antihypertensive Drugs

Hypertension:
• Usually symptom-free
• Consequences: Heart failure, kidney damage, stroke, blindness …

Potential drug targets:
• CNS, ANS: decrease sympathetic tone
• Heart: decrease cardiac output
• Veins: dilate => decrease preload
• Arterioles: dilate => decrease afterload
• Kidneys: increase diuresis; inhibit RAA system
Antihypertensive Drugs

Four major drug categories

• **Sympathetic nervous system suppressors:**
  – $\alpha_1$ and $\beta_1$ antagonists
  – $\alpha_2$ agonists

• **Direct vasodilators:**
  – Calcium channel antagonists
  – Potassium channel agonists

• **Renin-angiotensin system targeting drugs:**
  – ACE inhibitors
  – Angiotensin II receptor antagonists

• **Diuretics:**
  – Thiazides
  – Loop diuretics
  – K$^+$-sparing diuretics
Antihypertensive Drugs: Vasodilators

Calcium channel blockers (= Calcium antagonists):
- Inhibit calcium entry into cells of the arteries
  => decreased afterload

Dihydropyridines:
- Target specifically L-type channels on vascular smooth muscle cells
- No cardiac effects (“Vasoselective Ca++ antagonists”)
- Can cause peripheral edema
- **Nifedipine**
  - Prototype
  - ![Nifedipine](image)

- **Nicardipine**
- **Nimodipine**
- **Nisoldipine**
- **Amlodipine**
Antihypertensive Drugs: Vasodilators

Potassium channel agonists:

- Minoxidil
  - Increases outward K⁺ current => membrane hyperpolarization, which inhibits Ca²⁺ channel activity
  - Used only for severe, treatment-resistant hypertension
  - Major side effect: Hirsutism => used topically to treat baldness (Rogaine®)
Antihypertensive Drugs: Vasodilators

• Nitroprusside
  – Very unstable (only iv)
  – Metabolized by blood vessels into NO
    => activates cGMP production => vasodilation
  – **Rapid action** (30 sec !), short duration (effect ends after 3 min) => blood pressure “titration”
  – Used only to treat **hypertensive emergencies**
Antihypertensive Drugs: RAAS-targeting drugs

**Renin-angiotensin system**

- Important role in regulating blood volume, arterial pressure, and cardiac and vascular function.
- Most important site for renin release is the kidney: sympathetic stimulation (acting via β1-adrenoceptors), renal artery hypotension (e.g. stenosis), and decreased sodium delivery to the distal tubules stimulate the release of renin by the kidney.
- Renin acts upon a circulating substrate, angiotensinogen (produced mainly by the liver) which undergoes proteolytic cleavage to form the decapeptide angiotensin I (AT I).
- Vascular endothelium, particularly in the lungs, contains angiotensin converting enzyme (ACE), which cleaves off two amino acids to form the octapeptide, angiotensin II (AT II).
Antihypertensive Drugs: RAAS-targeting drugs

Renin-angiotensin system

Angiotensin II

- Constricts vessels thereby increasing vascular resistance and arterial pressure
- Stimulates the adrenal cortex to release aldosterone, which acts upon the kidneys to increase sodium and fluid retention
- Stimulates the release of vasopressin (antidiuretic hormone, ADH) from the pituitary which acts upon the kidneys to increase fluid retention
- Facilitates norepinephrine release and inhibits re-uptake from nerve endings, thereby enhancing sympathetic adrenergic function
- Stimulates cardiac and vascular hypertrophy
Antihypertensive Drugs: RAAS-targeting drugs

ACE - Inhibitors

- Captopril
  - First ACE inhibitor
  - Given po
  - Frequent side effect: cough (reduced inactivation of kinins)
- Enalapril
- Benazepril
- Ramipril
- Lisinopril
- Etc…
Antihypertensive Drugs: RAAS-targeting drugs

AT II Receptor Antagonists

Do not interfere with kinin processing => no cough

- Losartan
- Candesartan
- Eprosartan
- Valsartan
- Irbesartan
- Etc…
Angina pectoris

- Medical term for chest pain or discomfort due to coronary heart disease. Typical angina pectoris (=“tight heart” is uncomfortable pressure, fullness, squeezing or pain in the center of the chest.
- Angina is a symptom of myocardial ischemia, which occurs when the myocardium does not receive sufficient oxygen.
- People with stable angina have episodes of chest discomfort that are usually predictable, such as on exertion or under stress (Treatment: Nitrates, β-blockers).
- In people with unstable angina, the chest pain is unexpected and usually occurs while at rest. The discomfort may be more severe and prolonged than typical angina (Treatment: Nitrates).
- Variant angina is also called Prinzmetal's angina. Unlike typical angina, it nearly always occurs when a person is at rest, and does not follow physical exertion or emotional stress. Variant angina is due to coronary artery spasm (Treatment: Ca++ channel blockers).
Angina pectoris - Nitrates

• **Nitroglycerin**
  - Organic nitrate
  - Acts on vascular smooth muscle to promote vasodilation
  - Primarily works on veins, only modest dilation of arterioles
  - *Decreases oxygen demand by decreasing venous return* => use in stable angina

  It was originally believed that nitrates and nitrites dilated coronary blood vessels, thereby increasing blood flow to the heart. It is now believed that atherosclerosis limits coronary dilation and that the benefits of nitrates and nitrites are due to dilation of arterioles and veins in the periphery. The resultant reduction in preload, and to a lesser extent in afterload, decreases the workload of the heart and lowers myocardial oxygen demand.

  - **Oral, sublingual, IV, buccal and transdermal administration**
  - **Adverse effects** – headache, tachycardia, hypotension
  - Never to be combined with other drugs causing vasodilation (Viagra®) or hypotension
Angina pectoris - Nitrates

- **Isosorbide-dinitrate (ISDN)**
  - More stable than nitroglycerol
  - Longer lasting effect
  - Tolerance can occur – give lowest dose possible

- **Nitroprusside**
Cardiac Arrhythmia

Arrhythmias:
Abnormal rhythms of the heart that cause the heart to pump less effectively

Arrhythmia occurs:
– when the heart’s natural pacemaker develops an abnormal rate or rhythm
– when the normal conduction path is interrupted
– when another part of the heart takes over as pacemaker

Types of arrhythmia:
– Tachycardia: unusually fast heartbeat
– Bradycardia: unusually slow heartbeat
– Atrial fibrillation: the atria quiver rather than contract normally because of rapid and irregular electrical signals in the heart. Beside the abnormal heart beat, there is also a risk that blood will pool in the atria, possibly causing the formation of blood clots.
– Ventricular fibrillation: life threatening condition in which the heart ceases to beat regularly and instead “quivers” or fibrillates very rapidly – sometimes at 350 beats per minute or more (causes 350,000 death/year in the US - “sudden cardiac arrest”)
Cardiac Arrhythmia

Arrhythmias:

Drug Classes:
- Class I: Sodium channel blockers
- Class II: β-blockers
- Class III: Potassium channel blockers
- Class IV: Calcium channel blockers
- Other arrhythmic drugs
Cardiac Arrhythmia

Arrhythmias:
Class I - Sodium channel blockers:
Block Na\(^+\) entry during depolarization phase
For atrial and ventricular arrhythmias ("all-purpose")
  • Procainamide
  • Quinidine
For acute treatment of ventricular arrhythmias
  • Lidocaine
For chronic treatment of ventricular arrhythmias
  • Flecainide
  • Propofenone
Cardiac Arrhythmia

**Arrhythmias:**

**Class II - β-blockers:**
For tachycardia
- Propranolol

**Class III - Potassium channel blockers:**
Prolong repolarization phase by blocking outward potassium flux
For treatment of intractable ventricular arrhythmias
- Bretylium
- Amiodarone

**Class IV - Calcium channel blockers:**
Prolong repolarization phase by blocking inward calcium current
Predominantly for treatment of atrial arrhythmias
- Verapamil
Cardiac Arrhythmia

Arrhythmias:

Other antiarrhythmics:

• Adenosine
  For paroxysmal supraventricular tachycardia
  iv only, extremely short half-life
  used to terminate arrhythmias (blocks reentrant pathway)
  (Paroxysmal = an arrhythmia that suddenly begins and ends)

• Digoxin
  For atrial fibrillation

• Epinephrine, Isoproterenol
  For bradycardia
Congestive Heart Failure

Congestive heart failure:

• characterised by inadequate contractility, so that the ventricles have difficulty in expelling sufficient blood => rise in venous blood pressures
• Raised venous pressures impair fluid drainage from the tissues and produce a variety of serious clinical effects:
  – *Right sided* heart failure causes lower limb oedema. Blood pooling in the lower extremities is associated with intravascular clotting and thromboembolism
  – *Left sided* heart failure produces pulmonary oedema and respiratory distress

  – Causes: Blocked coronary arteries; viral infections; hypertension; MI; leaky heart valves
Congestive Heart Failure

Classification of severity

- I – no limitation of physical activity
- II – slight limitation
- III – marked limitation
- IV – symptoms occur at rest
Congestive Heart Failure

Treatment options:

• Diuretics
  – Loop diuretics
  – Thiazides
  – Spironolactone

• ACE inhibitors & AT II antagonists

• Vasodilators
  – Nitrates

• Cardiac Glycosides
Congestive Heart Failure

**Cardiac Glycosides:**

- Chief active ingredient in several plant families and animals:
Congestive Heart Failure

Cardiac Glycosides:

- **Two main categories:**
  - Cardenolides (Digitalis, Convallaria, Oleandra)
  - Bufadienolides (Helleborus, Poison Arrow Frog)
Congestive Heart Failure

Cardiac Glycosides:

• Cardiac glycosides slow the heart rate and increase the force of contraction
• Extracts of *D. purpurea* have been used clinically for over 200 years to treat heart failure and edema (“dropsy”)
• The cardiac glycosides inhibit the Na\(^+\)/K\(^+\)-ATPase pump, which causes an increase in intracellular Na\(^+\) => slowing of the Na\(^+\)/Ca\(^++\)-exchanger => increase in intracellular Ca\(^++\).
• Low therapeutic index => Associated with an appreciable risk of toxicity
• **Digoxin** is the most widely used preparation of digitalis (half-life = 1-2 days), although **digitoxin** (half-life = 7 days) is used in situations where long half-life may be an advantage.
• Digitalis is the drug of choice for heart failure associated with atrial fibrillation
Congestive Heart Failure

**Cardiac Glycosides:**

- Improve cardiac performance (=positive inotrope)
- Increases cardiac output
- Decreased sympathetic tone
- Increase urine output
- Decreased renin release
- **Does not prolong life** (only symptom relief)

**Toxicity:**

- Overdose; drug interaction; accidental ingestion of plants (children!)
- **Potassium** competes with cardiac glycoside for binding to Na\(^+\)/K\(^+\)-ATPase pump => potassium is an “antidot” for cardiac glycoside poisoning
- Injection of **anti-cardiac glycoside antibodies**