BP REGULATION

- Short-term BP regulation is controlled by **neural reflexes** involving the ANS, which buffers large fluctuations during activities like standing or moving
- **Baroreceptors** are mechanoreceptors located in high-pressure sites, specifically the **aortic arch** and the **carotid sinus**
  - These receptors detect changes in stretch which is an indirect measure of BP
- Increased BP causes increased stretch and baroreceptor firing. Signals are transmitted via afferent sensory nerves to the cardiovascular control centre in the medulla
- The **medulla** (the autonomic centre of the brainstem) integrates this information and adjusts autonomic outflow through efferent nerves to the heart, blood vessels, and adrenal medulla
- A fall in BP leads to:
  - Decreased baroreceptor firing and activation of the SNS
  - Withdrawal of PSNS activity to the SA node to increase HR
  - Increased SNS activation of the left ventricle to increase contractility
  - Vasoconstriction of arteries and veins to increase TPR and venous return

CARDIAC PARAMETERS

- **CO** is the volume of blood pumped per minute, calculated as HR × SV
- The intrinsic rate of the SA node is 60–100 beats per minute, but resting HR is typically 60–80 bpm due to dominant PSNS tone acting on M2 receptors via acetylcholine
- SNS activation increases HR through noradrenaline or adrenaline binding to β1 adrenoceptors
- **SV** is determined by preload and contractility
- **Preload** is the load placed on the heart muscle before contraction, determined by venous return
  - According to the **Frank-Starling relationship**, increasing the length of muscle fibers (ventricular filling) increases the force of contraction
- **Contractility** is the intrinsic strength of the contraction, increased by SNS activation of β1 receptors on ventricular myocytes
- **Afterload** is the resistance the heart must pump against to eject blood into the systemic circulation

HYPERTENSION

- **Hypertension** is defined by consistently elevated BP, often categorized as Grade 1 when systolic is around 140–159 mmHg or diastolic is 90–99 mmHg
- **Primary** (ie essential) **hypertension** accounts for 90–95% of cases and has no single identified cause, though risk factors include high salt intake, obesity, and physical inactivity
- Secondary hypertension (5–10%) results from identifiable conditions like renal disease, endocrine disorders (eg adrenal tumours), or pregnancy (preeclampsia)
- Elevated BP causes pathological remodelling:
  - Inward eutrophic remodelling involves the rearrangement of existing vessel wall material around a smaller lumen
  - Inward hypertrophic remodelling involves the growth of the smooth muscle layer (media) towards the lumen, increasing the wall-to-lumen ratio
- These structural changes increase baseline resistance and exaggerate the response to vasoconstrictor stimuli

BETA BLOCKERS

- **Beta blockers** act as antagonists at β1 receptors to lower BP by reducing CO
- Mechanism of action:
  - Inhibition of β1 receptors on the SA node reduces HR
  - Inhibition of β1 receptors on ventricular myocytes reduces contractility and SV
  - Blockade of β1 receptors in the juxtaglomerular apparatus of the kidney reduces renin secretion, leading to decreased RAAS activity and lower blood volume
- Adverse effects include bradycardia, decreased exercise capacity, and fatigue due to reduced blood flow to skeletal muscle
- Non-selective beta blockers can also inhibit β2 receptors, causing bronchoconstriction (dangerous for asthmatics) and cold extremities due to impaired peripheral vasodilation
- **Lipophilic beta blockers** (eg propranolol) can cross the blood-brain barrier, causing insomnia and vivid dreams
- Newer generations are hydrophilic or β1-selective (cardio-selective) to minimise CNS and respiratory side effects

VASCULAR RESISTANCE

- **Resistance** is determined by vessel length, blood viscosity, and internal radius
- Resistance is inversely proportional to the fourth power of the radius

$$R \propto \frac{1}{r^4}$$

  - *This means that if an artery gets blocked reducing its diameter by half, blood flow is reduced by a factor of 16x*
- Arterioles have a much higher capacity to affect TPR than large conduit arteries like the aorta
- Vascular tone is a balance between vasoconstrictors (noradrenaline, angiotensin II, endothelin-1) and vasodilators (**nitric oxide**, **prostacyclin**)
- SNS nerves release noradrenaline to activate α1 receptors on concentric smooth muscle, causing contraction and narrowing the vessel

ALPHA 1 ADRENOCEPTOR ANTAGONISTS

- **Selective α1 antagonists** (eg prazosin) block noradrenaline from binding to vascular smooth muscle, leading to vasodilation and reduced TPR
- First-dose hypotension is a common side effect where BP drops excessively within 90 minutes of the initial dose, requiring slow titration
- Postural (orthostatic) hypotension occurs when the reflex increase in SNS activity upon standing is blocked, causing blood to pool in the legs and reducing cerebral perfusion
- Reflex tachycardia may occur as the baroreceptor reflex attempts to compensate for the sudden fall in TPR by increasing HR
- Nasal congestion is caused by the vasodilation of arteries in the nasal mucosa

RAAS INHIBITORS

- Renin is released from the kidney in response to low BP, low sodium delivery, or SNS activation of β1 receptors
- Renin converts angiotensinogen to angiotensin I, which is then converted to the potent vasoconstrictor angiotensin II by ACE
- Angiotensin II increases BP by:
  - Directly constricting systemic blood vessels via AT1 receptors
  - Stimulating the release of aldosterone from the adrenal cortex, which increases sodium and water reabsorption
  - Promoting pathological **cardiovascular remodelling**
- **ACE inhibitors** (eg captopril, enalapril) block the production of angiotensin II and the breakdown of bradykinin
  - Elevated **bradykinin** promotes vasodilation but often causes a dry, persistent cough
- **AT1 receptor antagonists** (ARBs, eg losartan) block angiotensin II from binding to its receptor, offering similar BP-lowering effects without the dry cough
- Adverse effects of RAAS inhibitors include hyperkalaemia (due to decreased aldosterone-mediated potassium excretion) and potential acute renal failure in patients with bilateral renal artery stenosis

CALCIUM CHANNEL BLOCKERS

- **CCBs** inhibit **L-type (CAV 1.2) voltage-operated calcium channels** in vascular smooth muscle and cardiac tissue
- Reduced calcium influx limits the formation of the Ca2+-calmodulin complex, which is necessary to activate MLCK and initiate muscle contraction
- Selectivity varies by class:
  - Dihydropyridines (eg nifedipine, amlodipine) are vascular-selective, primarily reducing TPR
  - Phenylalkylamines (eg verapamil) and Benzothiazepines (eg diltiazem) have more significant effects on cardiac rate, rhythm, and contractility
- CCBs have minimal effect on veins and skeletal muscle
- Side effects of vascular CCBs include flushing, headache (due to meningeal vasodilation), and reflex tachycardia
- Non-dihydropyridines are contraindicated in heart failure because they can excessively decrease heart rate and contractility