# Drugs in the Cardiovascular System - Part Two

## Learning Outcomes

- Understand the control of blood pressure, cardiac output and total peripheral resistance
- Understand the use of the following antihypertensive drugs (site of action, mechanisms & adverse effects)
    - α1 -adrenoceptor antagonists
    - angiotensin-converting enzyme inhibitors
    - angiotensin AT1 receptor antagonists
    - Ca2+ channel antagonists

## Peripheral Resistance and Blood Pressure

- Anti-hypertensive drugs lower blood pressure by affecting peripheral resistance in blood vessels.
- Poiseuille's Law: resistance is influenced by factors like vessel length, blood viscosity, and vessel diameter

$$Q = \frac{\pi P r^4}{8\eta L} \qquad Q = \frac{P}{R} \qquad R = \frac{8\eta L}{\pi r^4} \qquad R \propto \frac{1}{r^4}$$

## Impact of Vessel Diameter on Resistance

- Resistance is inversely proportional to the fourth power of vessel radius.
- Small changes in vessel radius can significantly impact resistance.
- Smaller arteries have a greater effect on total peripheral resistance than larger arteries.

## Factors Influencing Vascular Tone

- Passive factors like pressure and vessel structure, and active factors like smooth muscle tone influence resistance.
- Sympathetic nerves release noradrenaline which activate α1 - adrenoceptors on SMC to elicit constriction
- Circulating factors such as catecholamines (adrenaline, noradrenaline), angiotensin II and vasopressin.
- Endothelial cells release vasoactive factors that cause vasodialtion (nitric oxide, prostacyclin) or vasoconstriction (endothelin-1)
- The balance between constrictor and vasodilator factors determines vascular tone.

## Hypertension

- TPR is elevated in hypertension and is due to functional imbalance between constriction and relaxation, and structural changes
    - Excessive sympathetic activation, remodelling, or endothelial dysfunction
- As blood pressure rises, blood vessels undergo structural changes (remodelling)
- Vascular remodelling occurs in both primary and secondary hypertension.
- Two major forms of remodelling are inward eutrophic and inward hypertrophic remodelling.
    - Inward eutrophic: rearrangement of smooth muscle cells around a smaller lumen; thicker media; narrower lumen; greater wall thickness:lumen ratio
    - Inward hypertrophy: inward hypertrophy of medial layer encroaches lumen; thicker media, narrower lumen; greater wall thickness:lumen ratio
- Remodelling leads to structural changes that impact vascular resistance and blood pressure regulation.

## Consequences of Vascular Remodelling

- Narrowing of the vessel lumen increases vascular resistance at rest.
- Greater media to lumen ratio results in increased resistance and blood pressure in response to constrictor stimuli.

## HOW CAN WE LOWER TOTAL PERIPHERAL RESISTANCE?

- By inhibiting sympathetic activation of blood vessels
- By inhibiting the renin-angiotensin system
- By inhibiting signalling pathways involved in smooth muscle contraction

## Inhibiting Sympathetic Vasoconstriction

- Targeting vascular alpha one adrenal receptors can inhibit sympathetic vasoconstriction.
- Selective a1 receptor antagonist drugs like prazosin bind to these receptors, leading to vasodilation, decreased peripheral resistance, and lowered blood pressure.
- Adverse effects include:
    - First dose hypotension: excessive fall in BP within 90 min of 1st dose, approx 50% patients
    - Nasal congestion: inhibits α1 -adrenoceptor-mediated constriction of arteries in nasal mucosa; subsequent dilatation leads to nasal congestion.
    - Postural hypotension: fall in BP upon standing, particularly problematic in elderly due to age-related blunting of baroreceptor reflex.
    - Initial reflex tachycardia: baroreceptor reflex - regulates blood pressure by increasing heart rate, contractility, and peripheral resistance when blood pressure falls

## Postural Hypotension

- Changes in posture can lead to postural hypotension due to rapid blood pooling in the lower extremities and decreased venous return
- Elderly patients and those on a1 receptor antagonists may have impaired reflex responses.

## Inhibiting the Renin-Angiotensin System

- Renin-Angiotensin-Aldosterone system: Angiotensinogen (renin) -> Angiotensin I (Angiotensin-converting enzyme [ACE]) -> Angiotensin II
    - Angiotensinogen is released by juxtaglomerular (granular) cells located in walls of afferent arterioles
    - Renin is released from sympathetic activation of β1-adrenoceptors on granular cells, fall in BP sensed by afferent arteriole, or fall in Na+ delivery to distal renal tubules.
    - Angiotensin I is 40% in lung endothelium, 60% elsewhere
- Angiotensin II plays a key role in vasoconstriction, mediated by AT1 receptors; aldosterone release, mediated by AT1 receptors in adrenal cortex; and cardiovascular remodelling (long-term)
    - Aldosterone secretion leads to increased Na+ and H20 reabsorption
- Renin-angiotensin system inhibitors like ACE inhibitors and AT1 receptor antagonists are commonly used for hypertension.

## Comparison of ACE Inhibitors and AT1 Receptor Antagonists

- Both are orally administered
- ACE inhibitors prevent angiotensin II formation and may cause a dry cough due to bradykinin accumulation.
    - Less angiotensin II formation =
        - Less AT1-R mediated vasoconstriction thus lower TPR
        - Less AT1-R mediated aldosterone secretion thus less NA+/H2O retention = lower preload and thus CO leads to lower BP
    - Bradykinin also has minor vasodilative properties = lower TPR and BP
- AT1 receptor antagonists block angiotensin II action and are less likely to cause a cough = higher compliance
- AT1 receptor antagonists are very selective and retain the beneficial effects of angiotensin II on AT2 receptors (counterregulatory role in BP regulation)
- Both classes can reverse pathological cardiovascular changes and have less impact on cardiovascular reflexes.

## Advantages and Disadvantages

- ACE inhibitors and AT1 receptor antagonists can cause first dose hypotension, hyperkalaemia (increased in K+ as aldosterone excretes K+), and acute renal failure
    - Hyperkalemia is problematic for patients on K+-sparing diuretics or with renal impairment.
    - Acute renal failure is more problematic in patients with renal artery stenosis where renal function dependent on angiotensin II to maintain glomerular filtration rate, but is reversible
- RAAS inhibitors have advantages like less postural hypertension and safety in asthmatics.
- They can also inhibit cardiovascular remodelling and have a positive impact on structural changes in the heart and vessels.

## Impact on Blood Pressure

- Beta blockers primarily impact cardiac output, while alpha-1 adrenergic receptor antagonists lower total peripheral resistance.