



Advanced Physiology

Lec.2 Physiology of Cardiovascular system

By: Pro D
muneef Saab Ahmed

Endothelins

A family of peptides acting locally as autacoid or paracrine hormones. Three isoforms of the 21 amino acid peptide have been identified: ET-1, ET-2 and ET-3. They are produced by a variety of cells, including endothelial and epithelial cells, macrophages and fibroblasts. Endothelins are characterised by two intra-chain disulphide rings, leading to a hairpin loop configuration, along with six conserved amino acid residues at the C terminus.

Cardiovascular system

Endothelins are synthesised by the proteolysis of large pre-proendothelins, which are cleaved to big endothelins, and then processed to the mature peptide by endothelin-converting enzyme.

Endothelins induce dose-dependent contraction in vascular smooth muscle, ET-1 being the most potent known endogenous vasoconstrictor. Two high affinity endothelin receptors have been recognised, ETA and ETB. They have been characterised as seven transmembrane domain G-protein receptors coupled to phospholipase C. The ETA receptor is the predominant type of receptor.

Valsalva manoeuvre

The *Valsalva manoeuvre* is a global test of cardiovascular responses. It involves forced expiration against a closed glottis

Effects of the resulting positive intrathoracic pressure include:

- 1- Compression of the lungs
- 2- Blood forced through the pulmonary veins to the left atrium and ventricle
- 3- Increased left ventricular stroke volume
- 4- Transient rise in systemic blood pressure
- 5- Reduced venous return to the heart
- 6- Reduced cardiac output
- 7- Reduced blood pressure

Measurement of arterial blood pressure

Indirect methods

Sphygmomanometer, using palpation and auscultation, the latter making use of the characteristic sequence of Korotkow sounds.

Oscillotonometry, which uses a double cuff system, the proximal cuff occluding the arterial pulsations and the distal cuff sensing pulsations. The pulsations are amplified by a pressure-sensitive aneroid chamber.

Direct methods

Intra-arterial cannula connected to a calibrated pressure transducer.

Renin–angiotensin mechanism

This integrated hormonal cascade system regulates arterial blood pressure, intravascular volume and electrolyte balance. More broadly, it is a complex autocrine system involved in diverse processes of cellular biology and pathophysiology.

Reduced arterial blood pressure



Renin, a proteolytic enzyme that is synthesised and stored as a precursor in granular juxtaglomerular cells in afferent arteriolar wall of glomerulus (specialised myoepithelial cells in the media). The cells respond to changes in transmural pressure gradient between afferent arteriole and interstitium. They are innervated directly by the sympathetic postganglionic unmyelinated fibres. Renin is a carboxyl-peptidase enzyme acting on plasma alpha-2-globulin

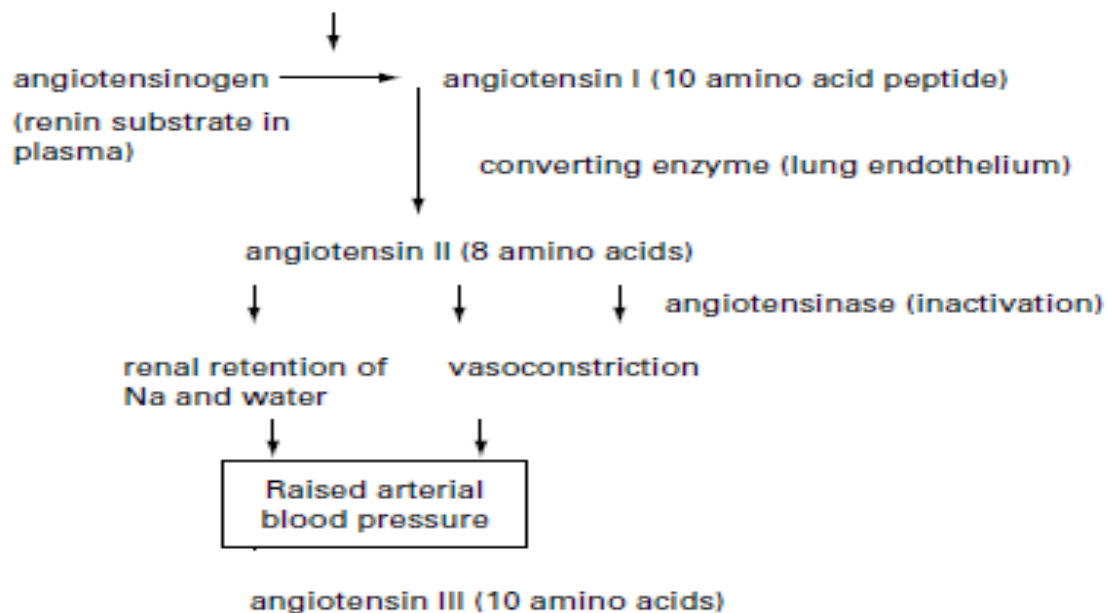


Figure 6.2 Pathway for renin–angiotensin mechanism.

Pathway for renin–angiotensin mechanism

Angiotensin II can also be produced by non-angiotensin-converting enzyme (ACE) pathways, e.g. the chymase pathway.

Angiotensin-converting enzyme is a membrane-bound zinc metallopeptidase

localised on the luminal surface of endothelial cells. Plasma levels of ACE are genetically determined. The ACE gene may manifest insertion (I) or deletion (D) polymorphism, with three possible genotypes (DD, DI, II).

Stimulation of the renin–angiotensin–aldosterone mechanism

This is achieved by:

- 1- Increased renal sympathetic nerve activity (beta 1-adrenoreceptor stimulation).
- 2- Fall in afferent arteriolar perfusion pressure (juxtaglomerular cells) (intrarenal baroreceptors).
- 3- Reduced sodium load delivered to distal renal tubule (macula densa cells: specialised renal tubular epithelial cells located at the transition between the thick segment of the ascending limb of the loop of Henle and the distal convoluted tubule. They function as chemoreceptors and are stimulated by a decreased Na⁺ load).
- 4- Reduction in right atrial pressure.

Renin

This has a circulatory half-life of 40–120 minutes

Release is inhibited by:

- Angiotensin II
- Angiotensin III
- Arginine vasopressin (ADH)
- Hypematraemia
- Hyperkalaemia
- Atrial natriuretic factor

Causes of increased renin secretion:

- Sodium depletion
- Diuretics
- Hypotension
- Haemorrhage
- Upright posture
- Dehydration
- Constriction of renal artery or aorta
- Cardiac failure
- Cirrhosis

Effects of angiotensin II

Vasoconstriction: systemic (preferentially coronary and cerebral) and intrarenal vascular smooth muscle constriction;
Increased proximal tubular reabsorption of sodium;
Stimulation of aldosterone release: increased distal tubular reabsorption of sodium;
Arginine vasopressin (ADH) release: water retention;
Stimulation of thirst;
Stimulation of sympathetic nervous system activity;
Augmentation of adrenal medullary catecholamines;
Direct inhibition of renin release in the kidney;

Positive inotropic action on myocardium;
Increased endothelin secretion;
Stimulation of plasminogen activator inhibitor-1.

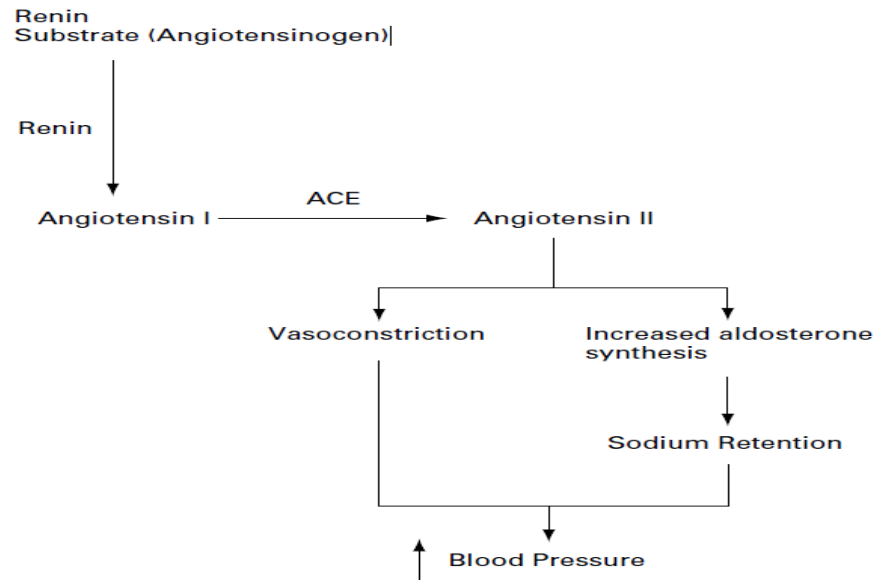


Figure 6.3 Renin-angiotensin mechanism. ACE, angiotensin-converting enzyme.

Mechanisms for the actions of angiotensin II

Neural mechanisms

Increased central sympathetic outflow;
Presynaptic augmentation of neuronal noradrenaline release;
Augmentation of adrenal adrenaline;
Postsynaptic augmentation of other pressors;
Baroreflex blunting.

Vascular mechanisms

Direct vasoconstriction;
Cellular hypertrophy and hyperplasia (chronic).

Other volume-related mechanisms

Aldosterone release modulation;
Arginine vasopressin (ADH) release modulation;
Increased thirst;
Increased dietary salt intake.

Pharmacological manipulation of the renin-angiotensin mechanism

This can be achieved by the use of angiotensin-converting enzyme inhibitors and angiotensin II-receptor antagonists. Angiotensin-converting enzyme inhibitors have disadvantages relating to the facts that:

Angiotensin-converting enzyme is not a specific enzyme and is involved in the breakdown of other substances, e.g. bradykinin, which results in cough and angio-oedema. Secondary increase in angiotensin I levels due to loss of negative feedback can overcome the ACE blockade, leading to a return of angiotensin II levels to normal with chronic ACE inhibitor use.

Angiotensin II-receptor blockers

Angiotensin II acts on AT1 and AT2 receptors. Angiotensin I receptor stimulation causes vasoconstriction and synthesis and release of aldosterone. Non-peptide angiotensin II antagonists generally act as specific competitive antagonists at the AT1 receptor. They have no intrinsic agonist activity and do not influence pathways outside the renin-angiotensin system such as bradykinin metabolism. The role of the AT2 receptor is yet to be fully elucidated, but it may be involved in the control of growth and differentiation during embryogenic development.

AT2-receptor blockers

Biphenyl tetrazoles

Losartan

Candesartan

Irbesartan

Tasosartan

Non-biphenyl tetrazoles

Eprosartan

Telmisartan

Non-heterocyclic

Valsartan

Classification of antihypertensive agents

Diuretics:

Thiazides

Loop diuretics

Beta-adrenergic blockers

Non-selective: nadolol, propranolol, timolol

Selective: atenolol, metoprolol

Partial agonist: acebutolol, oxprenolol

Alpha blockade: non-selective: labetalol

Non-selective: partial agonist: pindolol

Angiotensin-converting enzyme inhibitors: captopril, enalapril, lisinopril, ramipril

Calcium channel blockers: amlodipine, diltiazem, nifedipine, verapamil

Angiotensin II antagonists: losartan, valsartan

Alpha 1-adrenergic blockers: doxazosin, prazosin, terazosin

Central and peripheral sympatholytics: clonidine, methyldopa, reserpine

Direct vasodilators: hydralazine, minoxidil

Adrenergic neuron blockers: guanethidine

Antihypertensive effects of beta blockers

These are achieved by:

Blockade of beta receptors on the renal juxtaglomerular cells, leading to renin blockade and decreased angiotensin II concentrations.

Blockade of myocardial beta receptors, leading to reduced cardiac contractility and heart rate.

Blockade of central nervous system (CNS) beta receptors, leading to reduced sympathetic output from the CNS, and blockade of peripheral beta receptors, reducing noradrenaline concentrations.

Angiotensin II antagonists lower blood pressure by reducing systemic possible vascular resistance, while maintaining cardiac output.

Cardiac output.

Determinants of cardiac output

The cardiac output is the amount of blood pumped to the peripheral circulation per minute. It depends upon:

Heart rate, which is primarily determined by the rate of spontaneous phase 4 depolarisation of the sino-atrial node pacemaker cells

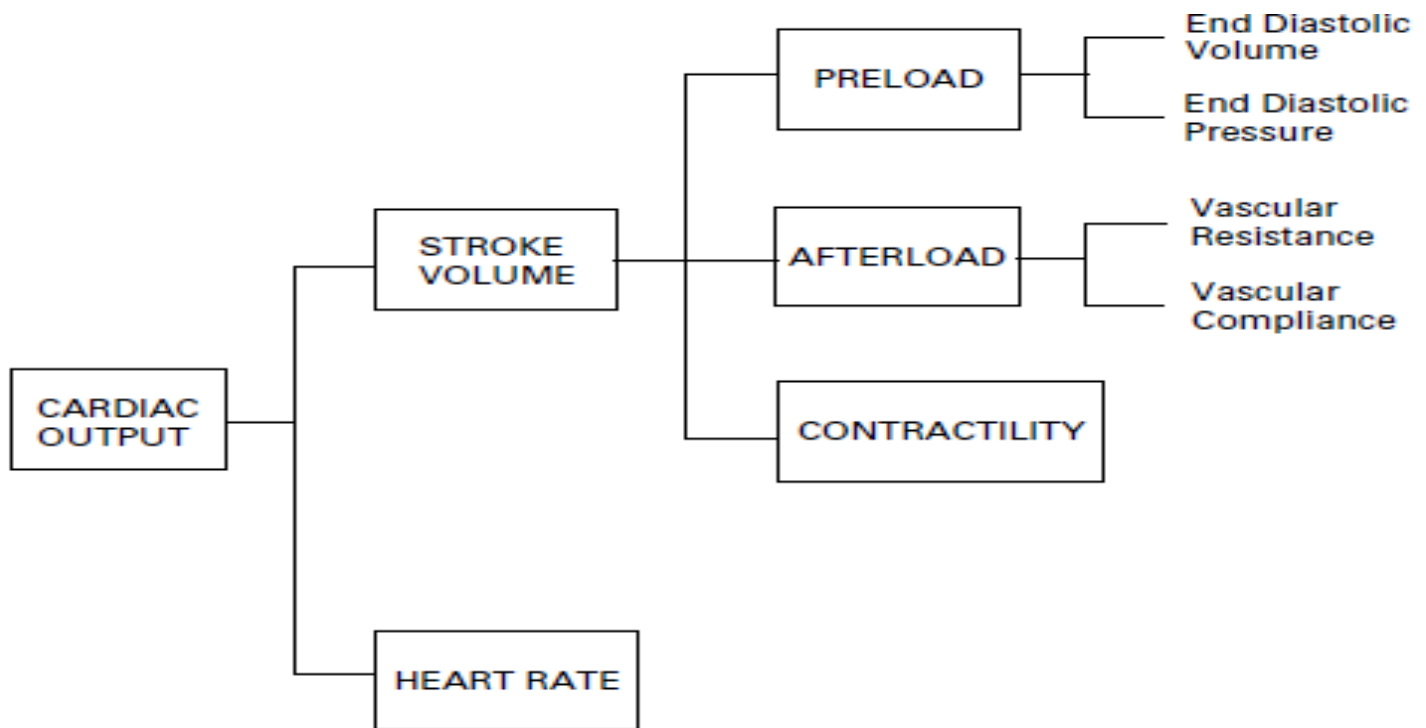


Figure 6.4 Cardiac output.

Stroke volume (end-diastolic volume–end-systolic volume), the amount of blood ejected by the ventricle with each contraction, in turn dependent upon:

- 1- **Preload** (filling pressure) (diastolic myocardial tension or left ventricular (LV) end-diastolic volume) (diastolic stretch), which depends on the initial amount of stretch placed upon LV fibres. End-diastolic volume depends on filling volume, and on factors that impede cavity dilatation (myocardial elasticity and viscoelasticity, wall thickness, and intramyocardial blood volume). Preload is increased by volume loading when LV function is normal, and decreased by diuresis and venodilatation.

- 2- **Afterload** (resistance imposed by the systemic circulation) (systolic myocardial wall tension). Afterload is increased with high intraventricular pressures, increased aortic impedance/systemic vascular resistance, increased ventricular radius and negative intrathoracic pressure, and increased blood viscosity. It is decreased with reduced aortic impedance/systemic vascular resistance, reduced intraventricular pressure, positive intrathoracic pressure and increased ventricular wall thickness.

- 3- **Myocardial contractility** (force of LV contraction independent of preload and afterload) (increased contractility shifts Frank–Starling curve to left). Contractility is increased by inotropic drugs and by the relief of ischaemia and hypoxia. It is decreased by ischaemia, hypoxia and negatively inotropic drugs.

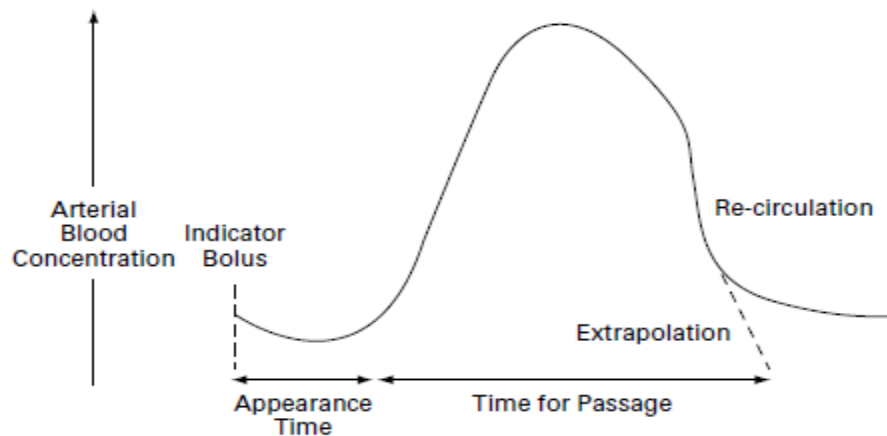


Figure 6.5 Indicator-dilution curve.

Cardiac reserve

Cardiac reserve mechanisms that increase cardiac output in the face of increased demand primarily involve an increase in the heart rate and/or an increase in stroke volume. Other mechanisms that may operate include:

Redistribution of the cardiac output, with differential perfusion of organs;
Cardiac dilatation and hypertrophy, within limits.

Increases in heart rate produce the following effects:

Shortening of systole;

Shortening of diastole, with reduced coronary perfusion time, reduction in ventricular filling and a rate-dependent alteration in stroke volume;

A rate-dependent positive inotropic effect.

