



Ischemic heart disease.
Cardiac arrhythmias

December 2, 2004

Myocardial ischaemia

- occurs when there is an imbalance between the supply of oxygen (and other essential myocardial nutrients) and the myocardial demand for these substances. The causes are as follows:
 - Coronary blood flow to a region of the myocardium may be reduced by a mechanical obstruction that is due to:
 - There can be a decrease in the flow of oxygenated blood to the myocardium that is due to:
 - ✓ An increased demand for oxygen may occur owing to an increase in cardiac output (e.g. thyrotoxicosis) or myocardial hypertrophy (e.g. from aortic stenosis or hypertension).
 - ✓ Myocardial ischaemia most commonly occurs as a result of obstructive coronary artery disease (CAD) in the form of coronary atherosclerosis. In addition to this fixed obstruction, variations in the tone of smooth muscle in the wall of a coronary artery may add another element of dynamic or variable obstruction.

The process of coronary atherosclerosis

- Coronary atherosclerosis is a complex inflammatory process characterized by the accumulation of lipid, macrophages and smooth muscle cells in intimal plaques in the large and medium-sized epicardial coronary arteries.
- The vascular endothelium plays a critical role in maintaining vascular integrity and homeostasis. ***Mechanical shear stresses*** (e.g. from morbid hypertension), ***biochemical abnormalities*** (e.g. elevated and modified LDL, diabetes mellitus, elevated plasma homocysteine), ***immunological factors*** (e.g. free radicals from smoking), ***inflammation*** (e.g. infection such as *Chlamydia pneumoniae* and *Helicobacter pylori*) and ***genetic alteration*** may contribute to the initial endothelial 'injury' or dysfunction, which is believed to trigger atherogenesis.

The process of coronary atherosclerosis

- The development of atherosclerosis follows the endothelial dysfunction, with *increased permeability to and accumulation of oxidized lipoproteins*, which are taken up by macrophages at focal sites within the endothelium to produce *lipid-laden foam cells*. Macroscopically, these lesions are seen as flat yellow dots or lines on the endothelium of the artery and are known as '*fatty streaks*'. The 'fatty streak' progresses with the appearance of extracellular lipid within the endothelium ('*transitional plaque*').

The process of coronary atherosclerosis

- Release of cytokines such as *platelet-derived growth factor and transforming growth factor- β (TGF- β)* by monocytes, macrophages or the damaged endothelium promotes further accumulation of macrophages as well as smooth muscle cell migration and proliferation.
- *The proliferation of smooth muscle* with the formation of a layer of cells covering the extracellular lipid, separates it from the adaptive smooth muscle thickening in the endothelium. *Collagen* is produced in larger and larger quantities by the smooth muscle and the whole sequence of events cumulates as an '*advanced or raised fibrolipid plaque*'. The 'advanced plaque' may grow slowly and encroach on the lumen or become unstable, undergo thrombosis and produce an obstruction ('*complicated plaque*').

The process of coronary atherosclerosis

- Two different mechanisms are responsible for thrombosis on the plaques
- ***The first*** process is superficial endothelial injury, which involves denudation of the endothelial covering over the plaque. Subendocardial connective tissue matrix is then exposed and platelet adhesion occurs because of reaction with collagen. The thrombus is adherent to the surface of the plaque.

The process of coronary atherosclerosis

- ***The second*** process is deep endothelial fissuring, which involves an advanced plaque with a lipid core. The plaque cap tears (ulcerates, fissures or ruptures), allowing blood from the lumen to enter the inside of the plaque itself. The core with lamellar lipid surfaces, tissue factor (which triggers platelet adhesion and activation) produced by macrophages and exposed collagen, is highly thrombogenic. Thrombus forms within the plaque, expanding its volume and distorting its shape. Thrombosis may then extend into the lumen. A 50% reduction in luminal diameter (producing a reduction in luminal cross-sectional area of approximately 70%) causes a haemodynamically significant stenosis. At this point the smaller distal intramyocardial arteries and arterioles are maximally dilated (coronary flow reserve is near zero), and any increase in myocardial oxygen demand provokes ischaemia.

Superficial intimal injury
Endothelial denudation

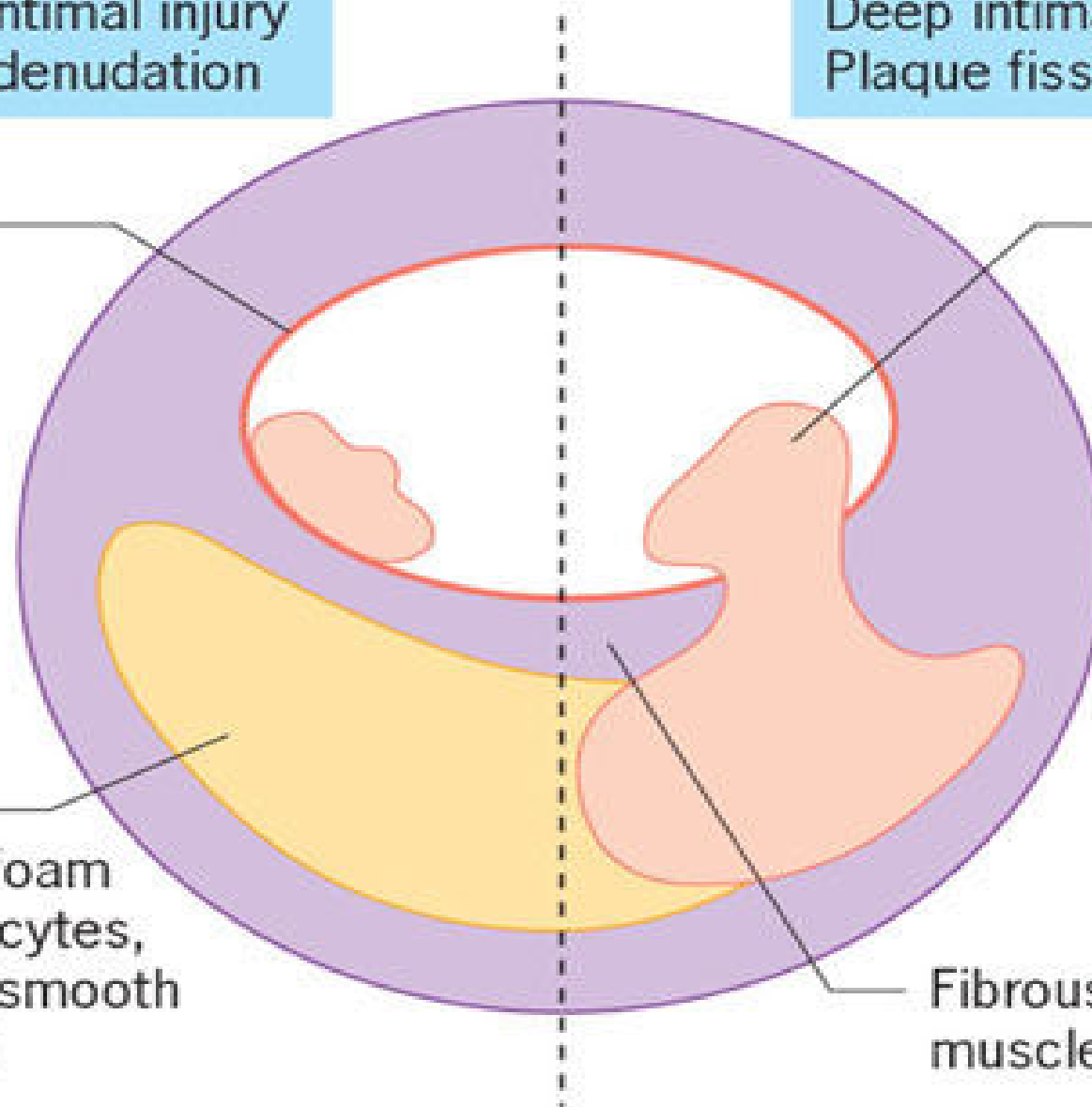
Deep intimal injury
Plaque fissuring

Endothelium

Thrombus

Plaque core
(fat deposit, foam
cells, lymphocytes,
phagocytes, smooth
muscle cells)

Fibrous cap (smooth
muscle and collagen)



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The mechanisms for the development of thrombosis on plaques

Table 13.25

Risk factors for coronary disease

Fixed

Age
Male sex
Positive family history
Deletion polymorphism in the ACE gene (DD)

Potentially changeable with treatment

Hyperlipidaemia
Cigarette smoking
Hypertension
Diabetes mellitus
Lack of exercise
Blood coagulation factors – high fibrinogen, factor VII
C-reactive protein
Homocysteinaemia
Personality
Obesity
Gout
Soft water
Contraceptive pill
Heavy alcohol consumption

ACE, angiotensin-converting enzyme

Coronary artery disease (CAD)

- The aetiology of CAD is multifactorial, and a number of 'risk' factors are known to predispose to the condition.
- Some of these - such as *age, gender, race and family history* - cannot be changed, whereas other major risk factors, such as *serum cholesterol, smoking habits, diabetes and hypertension*, can be modified.
- However, not all patients with myocardial infarction are identified by these risk factors.

Angina

- The diagnosis of angina is largely based on the clinical history. The chest pain is generally described as 'heavy', 'tight' or 'gripping'. Typically, the pain is central/retrosternal and may radiate to the jaw and/or arms. Angina can range from a mild ache to a most severe pain that provokes sweating and fear. There may be associated breathlessness.
- ***Classical or exertional angina pectoris*** is provoked by physical exertion, especially after meals and in cold, windy weather, and is commonly aggravated by anger or excitement. The pain fades quickly (usually within minutes) with rest. Occasionally it disappears with continued exertion ('walking through the pain'). Whilst in some patients the pain occurs predictably at a certain level of exertion, in most patients the threshold for developing pain is variable.
- ***Decubitus angina*** is that occurring on lying down. It usually occurs in association with impaired left ventricular function, as a result of severe coronary artery disease.
- ***Nocturnal angina*** occurs at night and may wake the patient from sleep. It can be provoked by vivid dreams. It tends to occur in patients with critical coronary artery disease and may be the result of vasospasm.

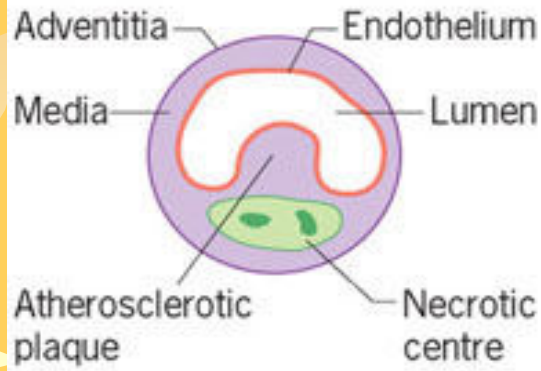
Angina

- ***Variant (Prinzmetal's) angina*** refers to an angina that occurs without provocation, usually at rest, as a result of coronary artery spasm. It occurs more frequently in women. Characteristically, there is ST segment elevation on the ECG during the pain. Specialist investigation using provocation tests (e.g. hyperventilation, cold-pressor testing or ergometrine challenge) may be required to establish the diagnosis. Arrhythmias, both ventricular tachyarrhythmias and heart block, can occur during the ischaemic episode.
- ***Cardiac syndrome X*** refers to those patients with a good history of angina, a positive exercise test and angiographically normal coronary arteries. They form a heterogeneous group and the syndrome is much more common in women than in men. Whilst they have a good prognosis, they are often highly symptomatic and can be difficult to treat. A recent study using phosphorus-31 nuclear magnetic resonance spectroscopy of the anterior left ventricular myocardium in women with this syndrome showed an abnormal metabolic response to stress consistent with the suggestion of myocardial ischaemia probably resulting from abnormal dilator responses of the coronary microvasculature to stress. The prognostic and therapeutic implications are not known.
- ***Unstable angina*** refers to angina of recent onset (less than 1 month), worsening angina or angina at rest.

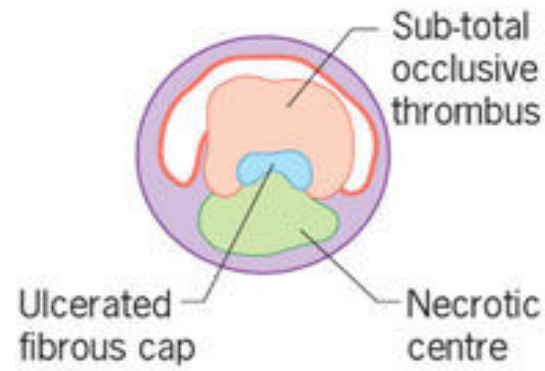
Acute coronary syndrome (ACS)

ACS (also called *unstable angina*) and *myocardial infarction without ST segment elevation* are clinical features of coronary artery disease which lie between stable angina and myocardial infarction with ST elevation or sudden death.

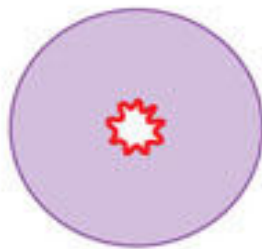
Stable angina pectoris



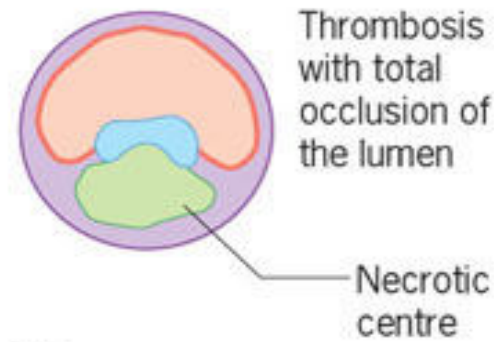
Unstable angina pectoris



Prinzmetal's angina



Myocardial infarction



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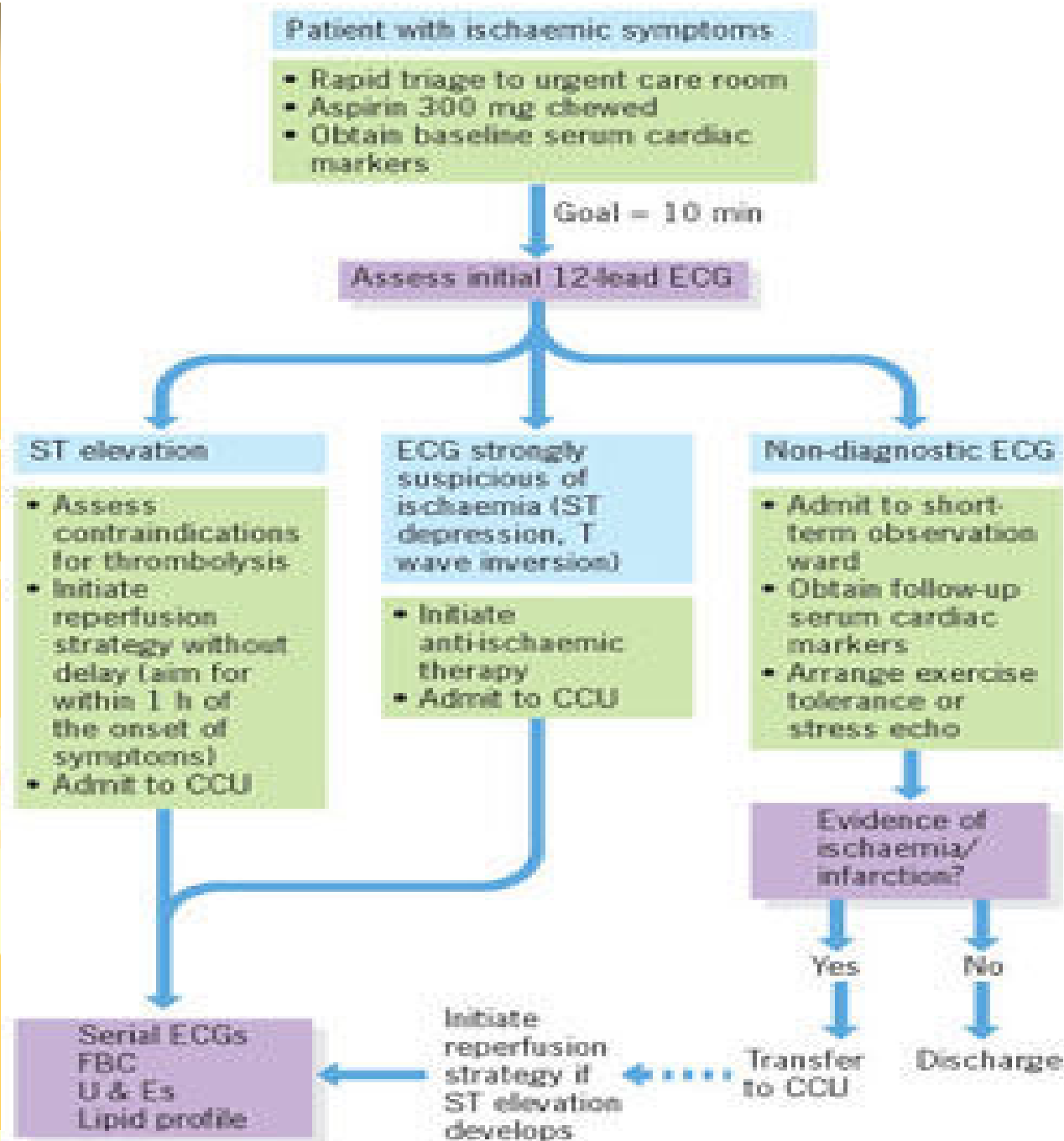
Relationship between the state of coronary artery vessel wall and clinical syndrome.

Myocardial infarction

- Myocardial infarction (MI) is the most common cause of death.
- MI almost always occurs in patients with coronary atheroma as a result of plaque rupture with superadded thrombus. This occlusive thrombus consists of a platelet-rich core ('white clot') and a bulkier surrounding fibrin-rich ('red') clot. About 6 hours after the onset of infarction, the myocardium is swollen and pale, and at 24 hours the necrotic tissue appears deep red owing to haemorrhage. In the next few weeks, an inflammatory reaction develops and the infarcted tissue turns grey and gradually forms a thin, fibrous scar. Remodelling refers to the alteration in size, shape and thickness of both the infarcted myocardium (which thins and expands) and the compensatory hypertrophy that occurs in other areas of the myocardium. The resultant global ventricular dilatation may help maintain the stroke volume of the heart.

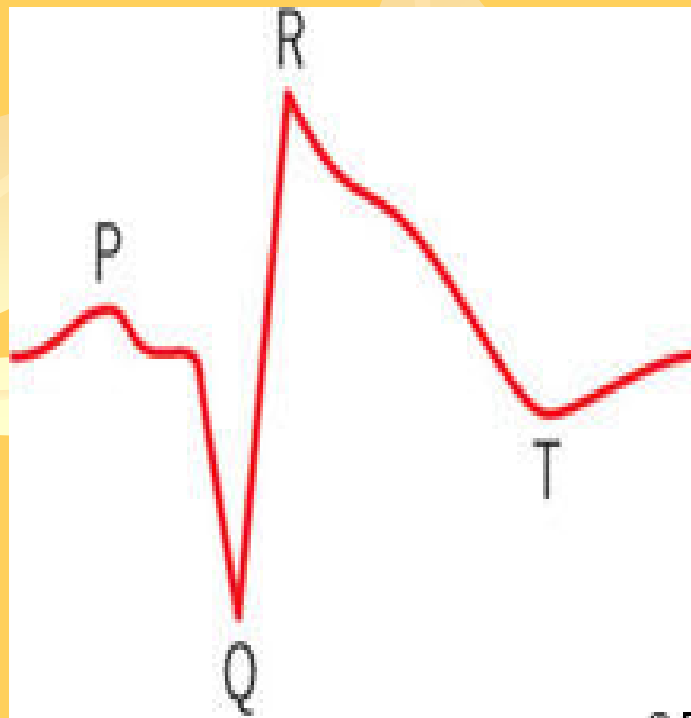
Myocardial infarction

- **Clinical features:**
- **Severe chest pain**, similar in character to exertional angina. The onset is usually sudden, often occurring at rest, and persists fairly constantly for some hours. Whilst the pain may be so severe that the patient fears imminent death, it can be less severe, and as many as 20% of patients with MI have no pain. So-called 'silent' myocardial infarctions are more common in diabetics and the elderly.
- MI is often accompanied by **sweating, breathlessness, nausea, vomiting and restlessness**.
- Patients with acute MI appear **pale, sweaty and grey**. There may be no specific physical signs unless complications develop
- A **sinus tachycardia** and fourth heart sound are common.
- A **modest fever** (up to 38°C) due to myocardial necrosis often occurs over the course of the first 5 days.



MI diagnosis

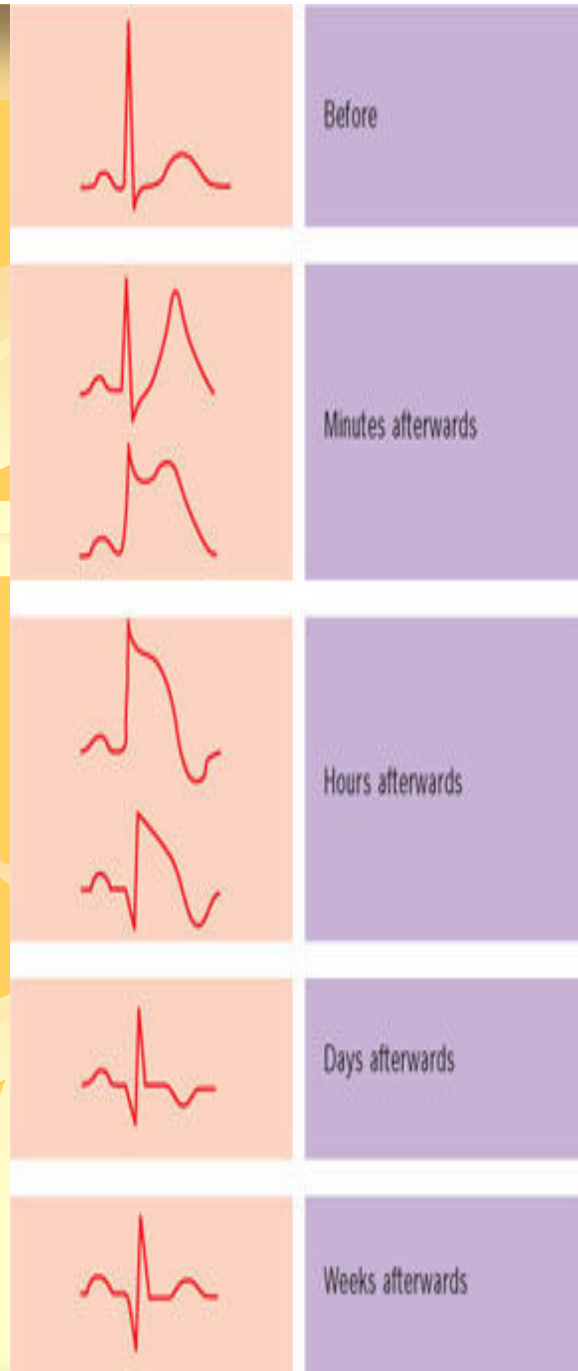
- Diagnosis requires at least two of the following:
 - a history of ischaemic-type chest pain
 - evolving ECG changes
 - a rise in cardiac enzymes or troponins.



$Q \geq 1\text{ mm wide (0.04 s)}$
and/or
 $Q \geq 2\text{ mm deep (0.2 mV)}$

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Electrocardiographic features of myocardial infarction, showing a Q wave, ST elevation and T wave inversion.



Electrocardiographic evolution of myocardial infarction.

After the first few minutes the T waves become tall, pointed and upright and ST segment elevation develops. After the first few hours the T waves invert, the R wave voltage is decreased and Q waves develop.

After a few days the ST segment returns to normal. After weeks or months the T wave may return to upright but the Q wave remains.

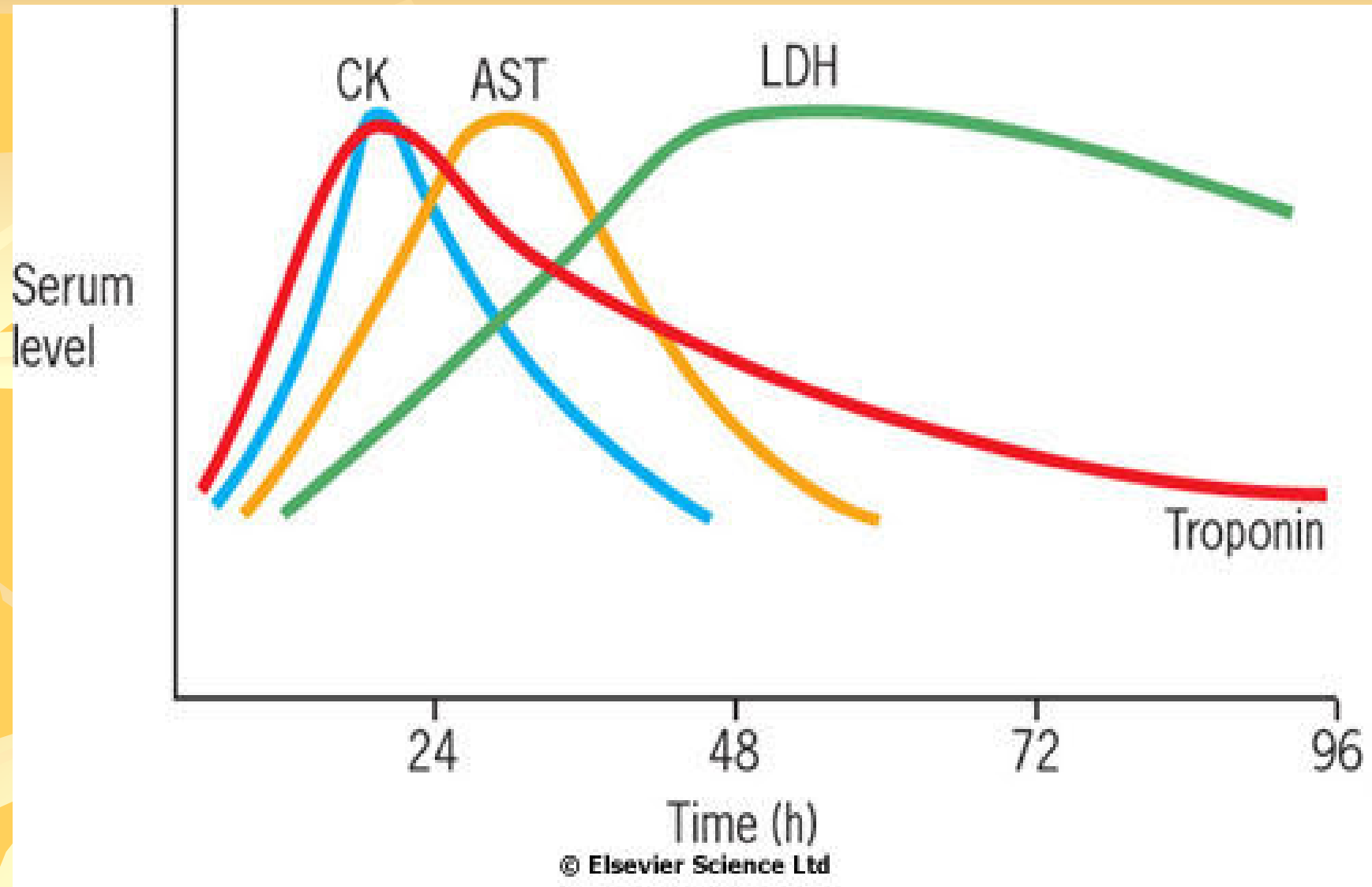
Table 13.29

Typical ECG changes in myocardial infarction

Infarct site	Leads showing main changes
Anterior	
Small	V_3-V_4
Extensive	V_2-V_5
Anteroseptal	V_1-V_3
Anterolateral	V_4-V_6, I, AVL
Lateral	I, II, AVL
Inferior	II, III, AVF
Posterior	V_1, V_2 (reciprocal)
Subendocardial	Any lead
Right ventricle	VR_4

Myocardial ischemia

- is the most common cause of death in the industrialized countries and, as a consequence, its early diagnosis and treatment is of great importance.
- In the electrocardiographic (ECG) signal ischemia is expressed as slow dynamic changes of the ST segment and/or the T wave.
- Long-duration ECG (e.g., Holter recordings, continuous ECG monitoring in the coronary care unit), is a simple and noninvasive method which observes such alterations.
- The development of suitable automated analysis techniques can make this method very effective in supporting the physician's diagnosis and in guiding clinical management.



Cardiac markers in acute myocardial infarction. CK, creatine kinase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

Cardiac markers

- Ischemic cardiac tissue releases several enzymes and proteins into the serum:
- *Creatine kinase* (CK). This peaks within 24 hours and is usually back to normal by 48 hours. It is also produced by damaged skeletal muscle and brain. Cardiac-specific isoforms can be measured (CK-MB) allowing greater diagnostic accuracy. The size of the enzyme rise is broadly proportional to the infarct size.
- *Aspartate aminotransferase* (AST) and *lactate dehydrogenase* (LDH). These non-specific enzymes are rarely used now for the diagnosis of MI. LDH peaks at 3-4 days and remains elevated for up to 10 days and can be useful in confirming myocardial infarction in patients presenting several days after an episode of chest pain.

Cardiac markers

Troponin products Troponin complex is a heteromeric protein playing an important role in the regulation of skeletal and cardiac muscle contraction. It consists of three subunits, troponin I (TnI), troponin T (TnT) and troponin C (TnC).

Each subunit is responsible for part of troponin complex function. E.g. TnI inhibits ATP-ase activity of acto-myosin. TnT and TnI are presented in cardiac muscles in different forms than in skeletal muscles. Only one tissue-specific isoform of TnI is described for cardiac muscle tissue (cTnI).

It is considered to be more sensitive and significantly more specific in diagnosis of myocardial infarction than the golden marker of last decade – CK-MB, as well as myoglobin and LDH isoenzymes. cTnI can be detected in patient's blood 3 – 6 hours after onset of the chest pain, reaching peak level within 16 – 30 hours. cTnI is also useful for the late diagnosis of AMI, because elevated concentrations can be detected from blood even 5 – 8 days after onset.

Cardiac markers

High sensitivity C-reactive protein (hsCRP)

CRP – “acute phase serum protein” is known for several decades as a non-specific inflammation marker. High CRP levels are detected in human blood during bacterial, viral and other infections, as well as in noninfectious diseases such as rheumatic disorders and malignancies. Among other markers of inflammation, CRP and IL-6 show *the strongest association with cardiovascular events*. In acute coronary syndromes raised concentrations of CRP may be a response to myocardial necrosis. Only high-sensitivity (hsCRP) or ultra-sensitive tests for CRP are useful for predicting heart attacks, since the elevation in the CRP level in those cases require CRP quantification.

Cardiac markers

- **Fatty Acid Binding Protein (FABP)**FABP is a small cytosolic protein responsible for the transport and deposition of fatty acids inside the cell. Cardiac isoform of FABP (cFABP) is expressed mainly in cardiac muscle tissue and in significantly lower concentration in skeletal muscles. cFABP can be used as an early marker of myocardial infarction. It has the same kinetics of liberation into the patient's blood as myoglobin, but is more reliable and sensitive marker of myocardial cell death. That is due to the fact that cFABP concentration in skeletal muscle is significantly lower than myoglobin concentration.
- **Glycogen Phosphorylase isoenzyme BB (GPBB)**GPBB is an enzyme playing an important role in the glycogen turnover. GPBB is a homodimer consisting of two subunits with GPBB can be useful in diagnosis of myocardial tissue damage in the patients with bypass surgery, unstable angina and some other cases.

Cardiac markers

- **Brain S-100 protein** S-100 protein derived from brain tissue is an acidic calcium-binding protein. In brain it is predominantly synthesised by astroglial cells and is mainly presented by two isoforms alpha-beta heterodimer (S-100a) or beta-beta homodimer (S-100b). S-100 protein can be used as a sensitive and reliable marker of central nervous system damage. Structural damage of glial cells causes leakage of S-100 protein into the extracellular matrix and into cerebrospinal fluid, further releasing into the bloodstream. S-100 appears to be a promising marker of brain injury and neuronal damage. Measurements of S-100 protein could be very useful in diagnosis and prognosis of clinical outcome in acute stroke and in the estimation of the ischemic brain damage during cardiac surgery. Elevated serum levels of S-100 correlate with duration of circulatory arrest.
- **Urinary albumin** Microalbuminuria (an increased urinary albumin excretion greater or equal to 15 µg/min, that is not detectable by the usual dipstick methods for macroproteinuria) predicts cardiovascular events in essential hypertensive patients, yet the pathophysiological mechanisms underlying this association remain to be elucidated.
- **NT-proBNP/proBNP** The cardiac ventricles are the major source of plasma brain natriuretic peptide. BNP is synthesized as prohormone (proBNP) that is cleaved upon its release into two fragments, a C-terminal, biologically active fragment (BNP) and a N-terminal, biologically inactive fragment (NT-proBNP). Furthermore, BNP and NT-proBNP have been shown to independently predict prognosis in patients early after myocardial infarction as well as in patients with acute and chronic heart failure.

Complications

- In the acute phase - the first 2 or 3 days following MI - ***cardiac arrhythmias, cardiac failure and pericarditis*** are the most common complications.
- Later, ***recurrent infarction, angina, thromboembolism, mitral valve regurgitation and ventricular septal or free wall rupture*** may occur.
- Late complications include the ***post-MI syndrome (Dressler's syndrome), ventricular aneurysm, and recurrent cardiac arrhythmias***.

Complications

- **Ventricular extrasystoles** These commonly occur after MI. Their occurrence may precede the development of ventricular fibrillation, particularly if they are frequent (more than five per minute), multiform (different shapes) or R-on-T (falling on the upstroke or peak of the preceding T wave).
- **Sustained ventricular tachycardia** This may degenerate into ventricular fibrillation or may itself produce serious haemodynamic consequences.
- **Ventricular fibrillation** This may occur in the first few hours or days following an MI in the absence of severe cardiac failure or cardiogenic shock. It is treated with prompt defibrillation (200-360 J). Recurrences of ventricular fibrillation can be treated with lidocaine (lignocaine) infusion or, in cases of poor left ventricular function, amiodarone. When ventricular fibrillation occurs in the setting of heart failure, shock or aneurysm (so-called 'secondary ventricular fibrillation'), the prognosis is very poor unless the underlying haemodynamic or mechanical cause can be corrected.
- **Atrial fibrillation** This occurs in about 10% of patients with MI. It is due to atrial irritation caused by heart failure, pericarditis and atrial ischaemia or infarction. It is not usually a long-standing problem, but it is a risk factor for subsequent mortality.

Complications

- ***Sinus bradycardia*** This is especially associated with acute inferior wall MI. Symptoms emerge only when the bradycardia is severe. When symptomatic, the treatment consists of elevating the foot of the bed and giving intravenous atropine, 600 μg if no improvement. When sinus bradycardia occurs, an escape rhythm such as idioventricular rhythm (wide QRS complexes with a regular rhythm at 50-100 b.p.m.) or idiojunctional rhythm (narrow QRS complexes) may occur. Usually no specific treatment is required. It has been suggested that sinus bradycardia following MI may predispose to the emergence of ventricular fibrillation. Severe sinus bradycardia associated with unresponsive symptoms or the emergence of unstable rhythms may need treatment with temporary pacing.
- ***Sinus tachycardia*** This is produced by heart failure, fever and anxiety. Usually, no specific treatment is required.

Complications - conduction disturbances

AV nodal delay (first-degree AV block) or higher degrees of block may occur during acute MI, especially of the inferior wall (the right coronary artery usually supplies the SA and AV nodes).

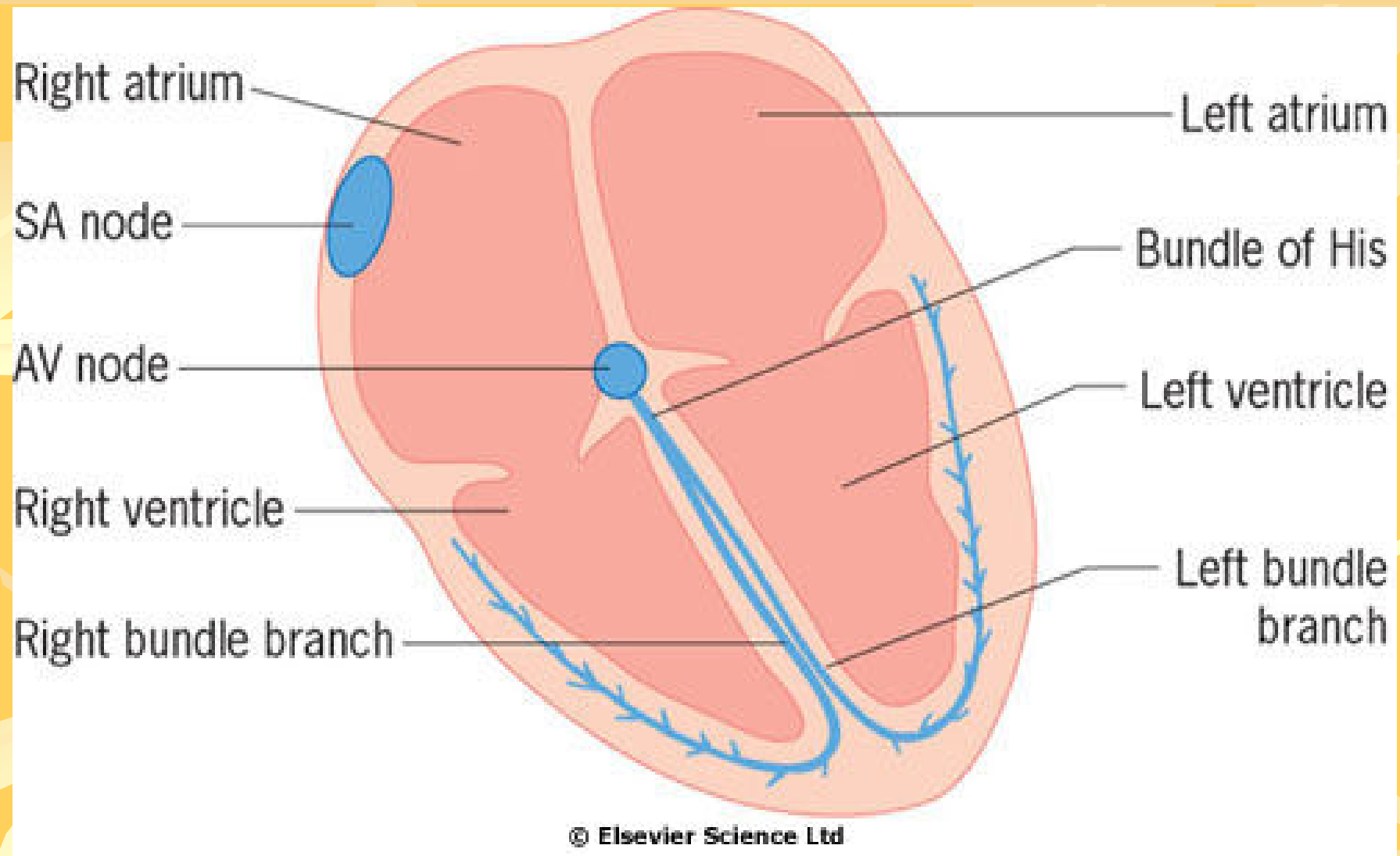
Complete heart block, when associated with haemodynamic compromise, may need treatment with atropine or a temporary pacemaker. Such blocks may last for only a few minutes, but frequently continue for several days. Permanent pacing may need to be considered if complete heart block persists for over 2 weeks. Acute anterior wall MI may also produce damage to the distal conduction system (the His bundle or bundle branches). The development of complete heart block usually implies a large MI and a poor prognosis. The ventricular escape rhythm is slow and unreliable, and a temporary pacemaker is necessary. This form of block is often permanent.

Cardiac arrhythmias

- An abnormality of the cardiac rhythm is called a cardiac arrhythmia. Such a disturbance of rhythm may cause sudden death, syncope, heart failure, dizziness, palpitations or no symptoms at all. There are two main types of arrhythmia:
- *Bradycardia*: the heart rate is slow (<60 b.p.m.)
- *Tachycardia*: the heart rate is fast (>100 b.p.m.).
- Tachycardias are subdivided into *supraventricular tachycardias*, which arise from the atrium or the atrioventricular junction, and *ventricular tachycardias*, which arise from the ventricles. Some arrhythmias occur in patients with apparently normal hearts, and in others arrhythmias originate from scar tissue as a result of underlying structural heart disease. When myocardial function is poor, arrhythmias tend to be more symptomatic and are potentially life-threatening.

Cardiac arrhythmias

- Some arrhythmias occur in patients with apparently normal hearts, and in others arrhythmias originate from scar tissue as a result of underlying structural heart disease. When myocardial function is poor, arrhythmias tend to be more symptomatic and are potentially life-threatening.



The normal cardiac conduction system. AV, atrioventricular; SA, sinoatrial.

The conduction system of the heart

- Each natural heartbeat begins in the heart's pacemaker - the sinoatrial (SA) node. This is a crescent-shaped structure that is located around the medial and anterior aspect of the junction between the superior vena cava and the right atrium.
- Progressive loss of the diastolic resting membrane potential is followed, when the threshold potential has been reached, by a more rapid depolarization of the sinus node tissue. This depolarization triggers depolarization of the atrial myocardium. The atrial tissue is activated like a 'forest fire', but the activation peters out when the insulating layer between the atrium and the ventricle - the annulus fibrosus - is reached.
- The depolarization continues to conduct slowly through the atrioventricular (AV) node. This is a small, bean-shaped structure that lies beneath the right atrial endocardium within the lower interatrial septum. The AV node continues as the His bundle, which penetrates the annulus fibrosus and conducts the cardiac impulse rapidly towards the ventricle. The His bundle reaches the crest of the interventricular septum and divides into the right bundle branch and the main left bundle branch.

Nerve supply of the cardiovascular system

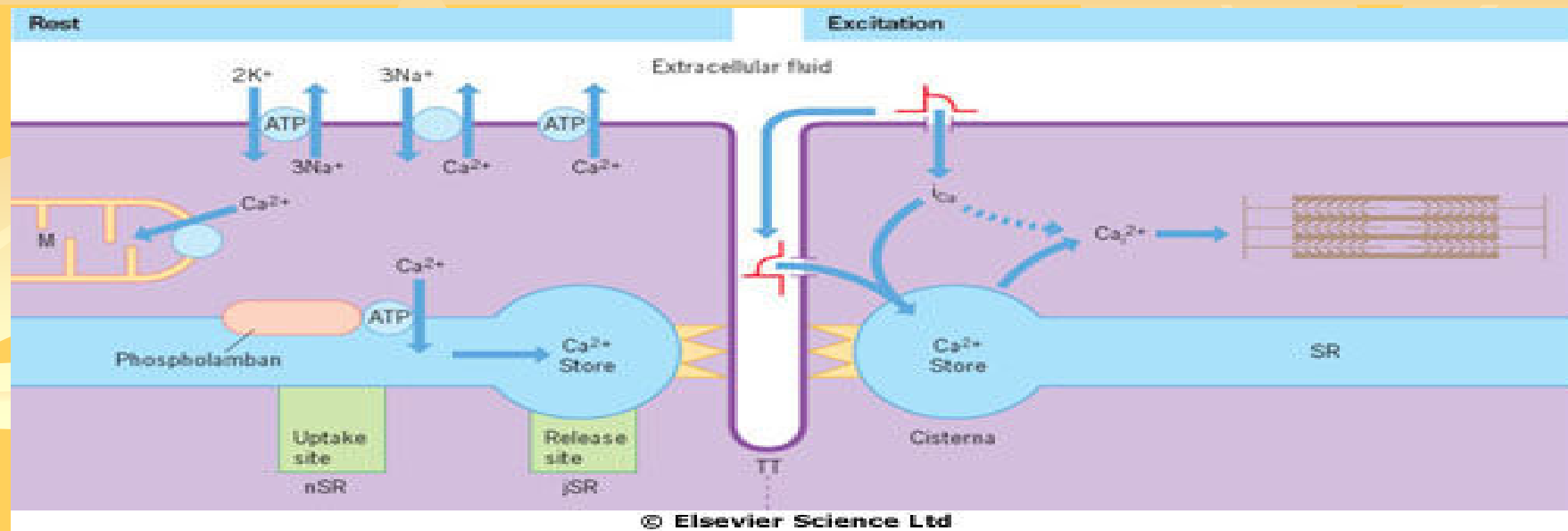
- Adrenergic nerves supply atrial and ventricular muscle fibres as well as the conduction system.
- ***β1-Receptors*** predominate in the heart with both epinephrine (adrenaline) and norepinephrine (noradrenaline) having positive inotropic and chronotropic effects.
- ***β2-Receptors*** predominate in the vascular smooth muscle and cause vasoconstriction.
- Cholinergic nerves from the vagus supply mainly the SA and AV nodes via ***M2 muscarinic receptors***. The ventricular myocardium is sparsely innervated by the vagus. Under basal conditions, vagal inhibitory effects predominate over the sympathetic excitatory effects, resulting in a slow heart rate.

β -Adrenergic stimulation and cellular signalling

- β -Adrenergic stimulation enhances Ca^{2+} flux in the myocyte and thereby strengthens the force of contraction. Binding of catecholamines (e.g. norepinephrine (noradrenaline)) to the myocyte β_1 -adrenergic receptor stimulates membrane-bound adenylate kinases. These enzymes enhance production of cyclic AMP that activates intracellular protein kinases, which in turn phosphorylate cellular proteins, including L-type calcium channels within the cell membrane. β -Adrenergic stimulation of the myocyte also enhances myocyte relaxation. The return of calcium from the cytosol to the sarcoplasmic reticulum (SR) is regulated by phospholamban (PL), a low-molecular-weight protein in the SR membrane. In its dephosphorylated state, PL inhibits Ca^{2+} uptake by the SR ATPase pump.

β -Adrenergic stimulation and cellular signalling

- However, β 1-adrenergic activation of protein kinase phosphorylates PL, and blunts its inhibitory effect. The subsequently greater uptake of calcium ions by the SR hastens Ca^{2+} removal from the cytosol and promotes myocyte relaxation. The increased cAMP activity also results in phosphorylation of troponin-I, an action that inhibits actin-myosin interaction, and further enhances myocyte relaxation. Production of SR proteins Ca^{2+} ATPase and phospholamban is also regulated by the thyroid hormone T3 acting through changes in gene transcription.



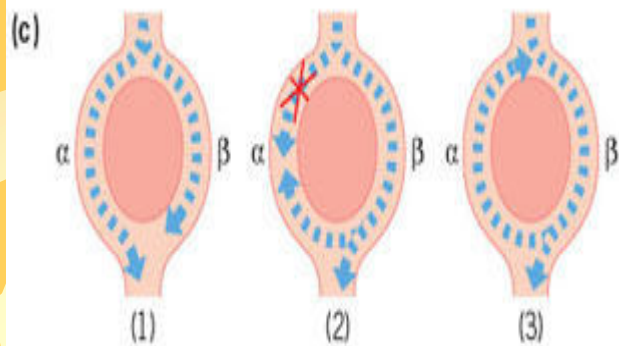
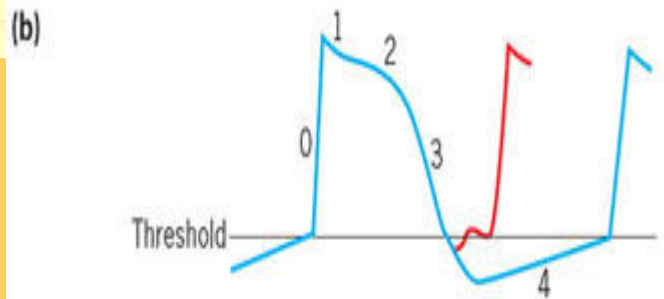
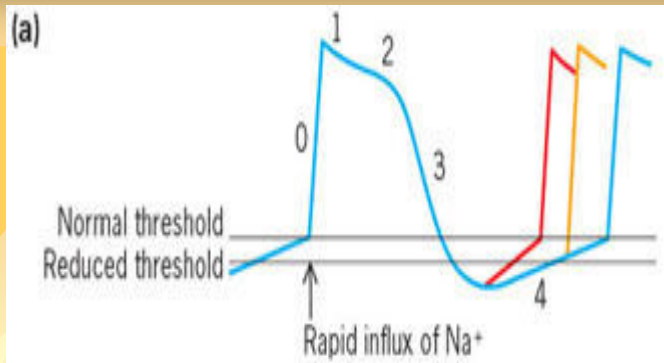
The calcium cycle.

Right side - excitation.

Early plateau current i_{Ca} passes through L (long-lasting)-type, dihydropyridine-sensitive calcium channels in the surface and transverse tubule (TT) membrane. This Ca^{2+} activates nearby calcium-induced calcium-release channels, which form the 'feet' on the junctional sarcoplasmic reticulum (jSR). Release of stored Ca^{2+} follows.

Left side - rest.

Calcium pumps in network sarcoplasmic reticulum (nSR) restock the store, and are regulated by phospholamban. Na-Ca exchangers in the surface expel Ca^{2+} . Mitochondria (M) contribute to long-term buffering of intracellular Ca^{2+} .



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Mechanisms of arrhythmogenesis.

(a) and (b) Action potentials (i.e. the potential difference between intracellular and extracellular fluid) of ventricular myocardium after stimulation.

(a) Increased (accelerated) automaticity due to reduced threshold potential or an increased slope of phase 4 depolarization.

(b) Triggered activity due to 'after' depolarizations reaching threshold potential.

(c) Mechanism of circus movement or re-entry.

In panel (1) the impulse passes down both limbs of the potential tachycardia circuit.

In panel (2) the impulse is blocked in one pathway (α) but proceeds slowly down pathway β , returning along pathway α until it collides with refractory tissue.

In panel (3) the impulse travels so slowly along pathway β that it can return along pathway α and complete the re-entry circuit, producing a circus movement tachycardia.

Mechanisms of arrhythmogenesis

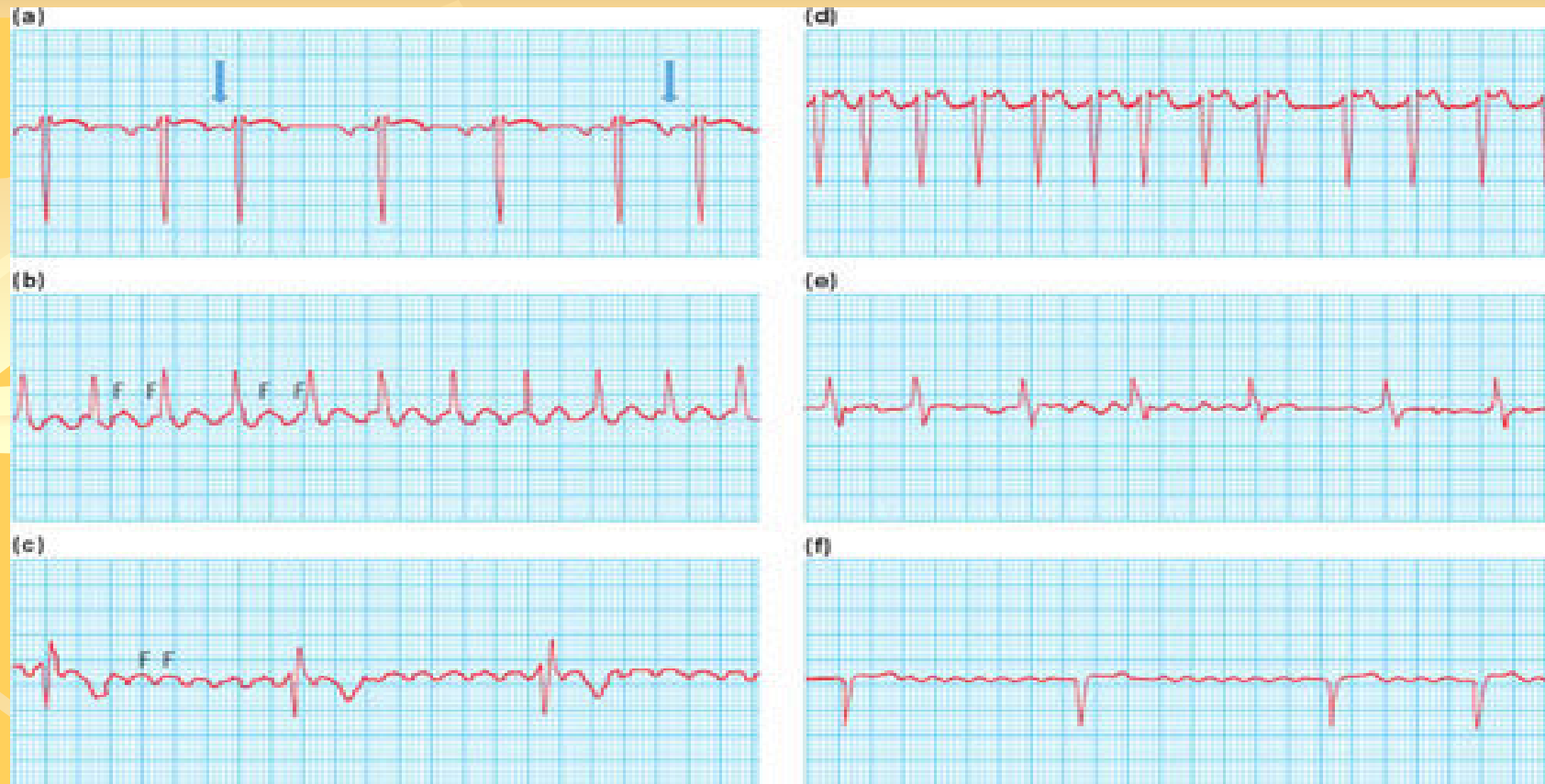
- ***Accelerated automaticity*** The normal mechanism of cardiac rhythmicity is slow depolarization of the transmembrane voltage during diastole until the threshold potential is reached and the action potential of the pacemaker cells takes off. This mechanism may be accelerated by increasing the rate of diastolic depolarization or changing the threshold potential. Such changes are thought to produce sinus tachycardia, escape rhythms and accelerated AV nodal (junctional) rhythms.
- ***Triggered activity*** Myocardial damage can result in oscillations of the transmembrane potential at the end of the action potential. These oscillations may reach threshold potential and produce an arrhythmia. The abnormal oscillations can be exaggerated by pacing and by catecholamines and these stimuli can be used to trigger this abnormal form of automaticity. The atrial tachycardias produced by digoxin toxicity are due to triggered activity. The initiation of ventricular arrhythmia in the long QT syndrome may be caused by this mechanism.

Mechanisms of arrhythmogenesis

- ***Re-entry (or circus movements)*** The mechanism of re-entry occurs when a 'ring' of cardiac tissue surrounds an inexcitable core (e.g. in a region of scarred myocardium). Tachycardia is initiated if an ectopic beat finds one limb refractory (α) resulting in unidirectional block and the other limb excitable. Provided conduction through the excitable limb (β) is slow enough, the other limb (α) will have recovered and will allow retrograde activation to complete the re-entry loop. If the time to conduct around the ring is longer than the recovery times (refractory periods) of the tissue within the ring, circus movement will be maintained, producing a run of tachycardia. The majority of regular paroxysmal tachycardias are produced by this mechanism.

Sinus arrhythmia

- Fluctuations of autonomic tone result in phasic changes of the sinus discharge rate. Thus, during inspiration, parasympathetic tone falls and the heart rate quickens, and on expiration the heart rate falls. This variation is normal, particularly in children and young adults. Typically sinus arrhythmia results in a regularly irregular pulse.
- Sinus bradycardia A sinus rate of less than 60 b.p.m. during the day or less than 50 b.p.m. at night is known as sinus bradycardia. It is usually asymptomatic unless the rate is very slow. It is normal in athletes (owing to increased vagal tone).
- Sinus tachycardia Sinus rate acceleration to more than 100 b.p.m. is known as sinus tachycardia.
- Mechanisms of arrhythmia production Abnormalities of automaticity, which could arise from a single cell, and abnormalities of conduction, which require abnormal interaction between cells, account for both bradycardia and tachycardia. Sinus bradycardia is a result of abnormally slow automaticity while bradycardia due to AV block is caused by abnormal conduction within the AV node or the distal AV conduction system.



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ECGs of a variety of atrial arrhythmias.

- (a) Atrial premature beats (arrows).
- (b) Atrial flutter.
- (c) Atrial flutter at a frequency of 305 per minute.
- (d) Irregular ventricular response.
- (e) Moderate conduction of atrial fibrillation.
- (f) So-called 'slow' atrial fibrillation.