Pathophysiology

Changes in the definition of terms relating to the diagnosis of myocardial infarction (MI) have evolved by better understanding of the pathophysiology culminating in the new term of acute coronary syndrome (ACS). Figure 1 illustrates the processes that occur in the development of an acute coronary event.

The coronary arteries become stenosed with age by the deposition of lipid-rich atheroma in the sub-endothelial layer. There are a number of factors that have been shown to encourage the development of premature coronary disease. These include smoking, hypertension, hypercholesterolaemia, diabetes mellitus, obesity and a family history. Atherosclerotic plaque formation commences when macrophages are attracted to the site of vessel injury. A meshwork of extracellular matrix proteins (fibrous cap) surrounds a lipid core, the latter resulting from the incorporation of blood-stream lipids by activated macrophages. Deposits tend to accumulate around bifurcations of the arteries and result in reduced blood flow when there is >50% diameter reduction.

The medial muscle coat of the coronary arteries is under tonic contraction, mediated by the autonomic nervous system, which can affect changes in diameter by constriction or dilatation. The imbalance between coronary...

Fig. 1 Processes involved in reduction of blood flow during an acute coronary event.
blood flow and myocardial demand produces ischaemia, which is manifest as angina. Thus, although in most cases angina occurs in association with increased heart work during physical exercise, it can also occur as a result of autonomic changes. For example, angina is classically worse in cold weather because changing autonomic tone causes coronary artery constriction.

When angina only occurs with exercise and it is reproduced by the same degree of exercise, this is called chronic stable angina.

The pattern of angina may change with time over years, but can occur more abruptly over days. This is usually attributable to the development of a thrombus on the surface of an atheromatous plaque within the artery after plaque rupture or fissuring. Plaque rupture exposes a mixture of lipid and collagen, both of which promote the development of thrombus by platelet adherence and activation, as well as activation of the coagulation cascade. There are many factors involved in the adherence and activation of platelets (including ADP, 5-HT, and thromboxane A2) but the final common pathway of ‘white thrombus’ is the activation of glycoprotein (GP) IIb/IIIa receptors, the platelet surface membrane receptor for fibrinogen. Fibrinogen cross-links develop between activated GP IIb/IIIa receptors, leading to the formation of a platelet thrombus. Thrombus development is rapid and so symptom deterioration is sudden.

When the pattern changes so that it occurs more easily than previously, but still only on exercise, it is called crescendo angina. When angina occurs at rest this means that the myocardium is ischaemic even in the absence of an increase in workload and implies critical myocardial perfusion. This constitutes the diagnosis of unstable angina (UA). It is not necessary to have a severe artery stenosis in order to develop a thrombus. In the majority of cases it is the result of endothelial fissuring on the site of a non-significant stenosis.

Clinical scenarios

Unstable angina

The patient develops typical angina chest pain at rest. Usually the pain lasts for <30 min and then is relieved because the artery has re-opened. This occurs because of spontaneous lysis or relaxation of spasm that occurs as part of platelet activation by the release of thromboxane. If the pain persists for longer than 30–45 min then this usually means that the artery has remained blocked or microemboli have showered off down the coronary tributaries causing micro-infarction.

Myocardial infarction

The clinical presentation of an infarction is characteristic. Patients suddenly develop typical cardiac pain but this is unremitting, lasting several hours. Although the pain may be eased by sublingual nitrates (GTN), it is not abolished. The event is often associated with sweating and nausea; sometimes with vomiting and breathlessness. The duration of chest pain is the most useful way of distinguishing angina from infarction. In 90% of cases of infarctions a thrombus forms at the site of an atheromatous plaque. In about 70% of cases, the atheromatous plaque upon which the thrombus develops is not large and, were it not for the thrombus, would not be large enough to significantly impair blood flow down the artery.

MI has been redefined according to the changes seen on the electrocardiograph. Complete occlusion of a coronary artery causing full thickness myocardial ischaemia causes ST-segment elevation. Partial occlusion or small vessel occlusion by micro-emboli from a ruptured plaque causes ST-segment depression or T-wave inversion. Both may or may not be associated with subsequent myocardial cell death. Full thickness infarction causes the development of Q-waves on the ECG whereas partial thickness or subendocardial infarction does not.

It is important to recognize that ST-segment elevation can also be caused by spasm (Prinzmetal angina) or a combination of thrombus and spasm. Hence, not all patients presenting with chest pain and ST-segment elevation on the simultaneously recorded ECG will subsequently develop Q-waves. Similarly, there are many causes of ST-segment depression (e.g. digoxin, left ventricular hypertrophy and strain) and T-wave inversion (e.g. myocarditis, drugs, metabolic disturbance), which resolve and are not associated with permanent damage.

Thus, the clinical presentation of UA, non ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI) result from variations of the same pathological process (i.e. plaque rupture and coronary thrombosis). This has led to the logical development of differing treatment strategies.

Diagnosis of myocardial infarction

Historically, patients with suspected ischaemic chest pain were categorized as having MI or non-MI. This was based on World Health Organization (WHO) recommendations in which the diagnosis of MI required fulfilment of at least two of three criteria: (i) typical history of ischaemic chest pain, (ii) ECG changes of ST-segment elevation and development of Q-waves, and (iii) elevation of serum cardiac enzymes. Today, the diagnosis of an ACS still relies on the history, ECG changes and blood tests.

Electrocardiograph

Serial ECG changes reflect acute total coronary artery occlusion in STEMI (Fig. 2). The usual progression of ECG changes in STEMI is as follows:

(i) hyperacute (minutes)—tall-waves and progressive ST-elevation;
(ii) acute (minutes to hours)—obvious ST-elevation and gradual loss of R-wave;
(iii) early (hours to days)—development of Q-waves, return of ST-segments to baseline, T-wave inversion;
context of the presentation and ECG. The blood troponin result must therefore be interpreted in the clinical context of the presentation and ECG. The diagnosis of MI should be qualified by size, causation and time from occurrence. The fact that areas of myocardial necrosis weighing <1.0 g can now be identified will undoubtedly lead to an increase in the diagnosis of MI but should also lessen the number of false negative diagnoses. However, the diagnosis of MI has a significant impact on the patient with psychological, social, and occupational consequences. Over-diagnosis of MI is unhelpful.

### Management of ST-elevation myocardial infarction

#### Reperfusion

The presence of ST-segment elevation on the ECG suggests total occlusion of an epicardial coronary artery. Early reperfusion has been shown to reduce in-patient mortality and may be effected by either immediate percutaneous coronary intervention (PCI) using balloon angioplasty with or without a stent, or pharmacologically by thrombolysis. In both strategies, the key factor in determining the efficacy of treatment is the time to reperfusion, with a loss of benefit of 1.6 deaths per 1000 patients treated per hour delay up to 24 h.

I.V. thrombolysis is indicated in patients with a history compatible with acute MI and an admission ECG showing: (i) ST-segment elevation in 2 contiguous leads (at least 2 mm elevation in anterior leads and 1 mm elevation in inferior leads); or (ii) LBBB (new unless proven otherwise); or (iii) ST-segment depression in leads V1–V3 with a dominant R-wave in lead V1–V2 (true posterior infarction).

Currently, the main treatment modality for acute STEMI is thrombolysis. In most UK hospitals, primary PCI is not offered routinely. However, primary PCI should be arranged in patients with contraindications for immediate thrombolysis (Table 1). The choice of thrombolytic agent available has increased recently to include streptokinase, second-generation agents, such as recombinant tissue plasminogen activator (rt-PA), and third-generation agents with longer half-lives (e.g. reteplase, tenecteplase). Although the second-generation agents are more fibrin-specific, less antigenic and produce better early vessel patency rates, there is little evidence of significant mortality benefit in large trials. In young patients with anterior MI, rt-PA has been shown to have a slight advantage, saving an additional 10 patients per 1000 patients treated. However, streptokinase is cheaper, associated with a lower risk of bleeding and cerebral haemorrhage and is the preferred treatment in those at higher risk of stroke (i.e. the elderly, women, low BMI, hypertension on arrival and recent
stroke). Early re-infarction remains the most common complication of thrombolytic therapy and aggressive anti-thrombin strategies reduce this so that unfractionated or low molecular weight heparins (LMWHs) are indicated as adjunctive therapy with thrombolitics because the latter will have no effect on thrombin exposed after fibrinolysis and could thus, in theory, have a pro-thrombotic effect. Newer anti-thrombin agents like hirudin have also been shown to reduce re-infarction compared with heparin.

Primary PCI physically disrupts occlusive thrombus and restores blood flow in many but not all patients. A recent meta-analysis showed a small absolute mortality benefit for primary PCI over thrombolysis but the clinical trials comparing the two treatment strategies have been small and involved much patient selection. Primary PCI has other advantages over thrombolysis in that there is a lower non-fatal re-infarction rate and lower incidence of haemorrhagic stroke. The best results for primary PCI are in those with cardiogenic shock.

**Aspirin**

One of the most unexpected findings from the early ground breaking thrombolytic trials was that aspirin 300 mg, given as early as possible after onset of chest pain in acute STEMI, reduced hospital mortality by about the same extent as thrombolysis. Its mechanism of action is unknown.

**Secondary prevention**

A number of large clinical trials have shown that warfarin, β-adrenoeceptor blockers, ACE inhibitors, and statins reduce re-infarction and mortality after acute STEMI.

**Antithrombotic therapies**

**Aspirin**

Aspirin inhibits the formation of thromboxane A₂ and has been shown to reduce death or non-fatal MI in UA by 50%. It does not completely block platelet activation and has no effect on platelet adhesion. It remains the mainstay of therapy.

**Antithrombin therapies**

Both unfractionated heparin and LMWHs have been shown to be beneficial when given with aspirin to patients with UA. LMWHs are advantageous in that they have a more predictable pharmacokinetic profile, long half-life and do not require continuous infusion. In addition, it is not necessary to monitor activated partial thromboplastin time (APTT). The efficacy of LMWHs in UA is probably related to the anti-factor Xa:anti-factor IIa ratio. Enoxaparin (which has a relatively high anti-factor Xa:anti-Factor IIa ratio) has been shown to be superior to unfractionated heparin in reducing the rate of MI but without a significant effect on mortality or increase in major bleeding. However, their long half life and lack of suitable antidote makes them potentially

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**Table 1 Contraindications to thrombolysis**

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
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</thead>
<tbody>
<tr>
<td>Previous haemorrhagic stroke</td>
<td>Stroke &gt;2 months &lt;12 months</td>
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<tr>
<td>Any stroke within previous 2 months</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Intracranial neoplasm</td>
<td>Active peptic ulcer disease</td>
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<tr>
<td>Active bleeding within previous month (except menstrual)</td>
<td>Severe hypertension on presentation (&gt;180/110 mm Hg)</td>
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<tr>
<td>Aortic dissection</td>
<td>Surgery/trauma within previous month</td>
</tr>
<tr>
<td>Major surgery in last 3 weeks</td>
<td>Bleeding diathesis</td>
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<tr>
<td></td>
<td>CPR &gt;10 min</td>
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<tr>
<td></td>
<td>Non-compressible vascular puncture</td>
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<tr>
<td></td>
<td>Allergy</td>
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**Management of non-ST-segment myocardial infarction and unstable angina**

NSTEMI and UA occur as a result of the development of thrombus on an atheromatous plaque. Unlike in STEMI, the thrombus is non-occluding but distal vasospasm or embolisation may lead to subsequent myocardial necrosis. The aims of treatment include reduction of ischaemia and plaque stabilization. Thus, treatments are aimed at interrupting platelet aggregation (with aspirin, GpIIb/IIIa inhibitors and clopidogrel) and preventing propagating thrombus with unfractionated or LMWHs.

In UA, the risk of developing a MI in the presence of a normal ECG is <1% within 7 days. Even in the presence of an abnormal ECG, the risk of developing an infarction is only about 4%. About 6% of patients admitted to hospital with UA with a normal resting ECG on admission, will die or have an infarction within 6 months (10% with T-wave inversion and 25% with ST-segment depression).

Patients admitted with UA remain at relatively low risk with hospital mortality from all categories of patient of only 1.5%. Younger patients have a better outlook. Approximately 80% of patients who present with UA will be stabilized initially with anti-ischaemic medication and are mobilized quickly and discharged after 2–3 days.

Recent research suggests that intervention by angioplasty or coronary surgery soon after presentation with UA, especially in those patients with markers of muscle damage (troponin positive), reduces recurrent chest pain and MI. However, there is no evidence that mortality is reduced. Indeed, in the only British study, mortality after early intervention was higher than conservative therapy. Thus, although PCI for patients with NSTEMI/UA is helpful, it should not be considered in all patients; only in those considered to be high risk. This has led to the development of risk scores (e.g. TIMI risk score) and treatment algorithms, an example of which is shown in Figure 3.
more hazardous, especially in lower weight individuals where overdosage causes significant and serious haemorrhage.

**Glycoprotein IIb/IIIa inhibitors**
Glycoprotein IIb/IIIa inhibitors (tirofiban/abciximab/ eptifibatide) are now recommended in combination with aspirin and heparin as part of the initial treatment of high-risk NSTEMI/UUA patients. These drugs have also been shown to reduce the risk of non-fatal MI in NSTEMI patients undergoing PCI.

**Ticlopidine and clopidogrel**
Ticlopidine and clopidogrel inhibit ADP-mediated platelet aggregation and thus could potentially act in synergy with aspirin. Ticlopidine was withdrawn in March 2003 because its use was associated with thrombocytopenia and granulocytopenia. Clopidogrel has been shown to produce a 20% reduction in mortality when administered with aspirin in UA, compared with aspirin alone.

**Direct antithrombins**
Direct antithrombins inhibit thrombin activity (as opposed to heparin, which inhibits thrombin production). Examples include hirudin, hirulog and inogatran. Clinical trials have produced conflicting results to date and more work is needed to explore their efficacy and safety in UA.

**Thrombolytic therapies**
Thrombolytic therapies have no benefit in NSTEMI/UA. Indeed, it has been demonstrated that thrombolysis is associated with increased morbidity and mortality in these patients.
**Statins**
Statins, given in high dosage at the time of presentation with NSTEMI/UA, have been shown to reduce recurrent ischaemic events.

**Other drug treatments**
The most effective anti-ischaemic agents remain β-adrenoceptor blockers. Newer agents are particularly cardioselective (e.g. bisoprolol, celiprolol). Nitrates provide good symptomatic relief and can be given orally as isosorbide mononitrate or by the buccal or topical route.

**Acute coronary syndrome and anaesthesia**
Not surprisingly, a diagnosis of ACS is a major predictor of cardiac risk in a patient requiring anaesthesia. The major risk factors include: MI, coronary angioplasty or CABG within previous 6 weeks; UA; and persistent ischaemia post-MI. Patients with major risk factors have a five times greater perioperative risk. This is a consequence of perioperative sympathetic stimulation and hypercoagulability. In addition, the type of procedure may add to the risk. For example, patients having vascular surgery have a threefold increased risk of perioperative MI compared with nonvascular patients. Only emergency surgical procedures should be performed on these patients and the involvement of a cardiologist in perioperative care and decision-making is important.

**Troponins and critical illness**
Cardiac troponins reflect myocardial damage but do not reflect its mechanism. In the absence of other evidence of ischaemia, another cause should be sought. These include: sepsis, hypotension, chronic renal failure, hypotension, vasopressor administration, pulmonary embolism, postoperative non-cardiac surgery, and hypothyroidism. In sepsis, immunomodulatory changes, as opposed to ischaemia, could be the cause of elevated serum troponins. As in ACS, elevated troponin T is associated with a worse prognosis in sepsis but the strength of the correlation is not entirely clear, not least because of the varying mechanisms involved in the production of myocardial damage.

**Key references**

See multiple choice questions 128–132.