REVIEW

Advances in the early diagnosis and management of acute myocardial infarction

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Lessons from pathophysiology

Most cases of acute myocardial infarction follow the disruption of a weakened capsule of an atheromatous coronary plaque^{1 2} (fig 1). Plaque rupture first triggers platelet adhesion and then fibrin precipitation, leading to the formation of a progressive intraluminal clot. Initially the clot is soft and friable, but with time, as crosslinks form between fibrin strands, it becomes firmer. Clot formation and propagation may follow a stuttering pattern – mirrored in the clinical presentation – and it may occlude branch vessels as it progresses. Coronary flow may be impeded further by swelling of the vessel wall due to intraplaque haemorrhage. Vessel occlusion is also intensified by platelet derived vasoconstrictor hormones and by a diminished sensitivity of its wall to factors that usually cause relaxation.

In the myocardium, an abrupt cessation of blood flow rapidly affects normal diastolic function. In the wake of advancing ischaemia reduced contractility soon follows³; the myocardial segment in jeopardy becomes stiff. Compensation by the normally perfused muscle is common; its exaggerated contraction helps to maintain cardiac output and ejection fraction and to prevent a rise in the filling pressure of the ventricles (the end diastolic pressure).

Continuing ischaemia causes cellular swelling, the accumulation of intracellular calcium, the release of local catecholamines, and a change in the extracellular concentra-

tions of potassium and hydrogen ions. Cellular swelling further impedes perfusion; and the “vicious circle” of these changes both threatens the survival of myocardial cells and promotes malignant arrhythmias.

The evolving infarct often stimulates an inflammatory response which may be marked if reperfusion can be established through a reopened coronary vessel. This cellular response by neutrophils and macrophages generates oxygen free radicals,^{4 5} a highly damaging if short lived group of agents that can be deleterious to the recovery of the infarcting myocardium.⁶

In the face of profound painful myocardial ischaemia, an autonomic response is inevitable.⁷ Vagal tone is commonly increased, but so is sympathetic outflow; the “brake” and the “accelerator” are both made to work hard, a strong trigger for life threatening arrhythmias and a brittle haemodynamic state.

The pathophysiological changes of an evolving infarct are dynamic and unstable, and they pose an early threat to the survival of both myocardial cells and – even without extensive myocardial damage – to the patient. But they also provide an opportunity for early therapeutic intervention that can favourably influence the patient's outcome.

Early diagnosis

The diagnosis of acute myocardial infarction after several hours' observation is relatively straightforward. Accumulated information from the initial presentation, subsequent clinical course, serial electrocardiograms, and enzyme profiles in the peripheral blood usually confirm (or refute) myocardial necrosis – though localisation of the infarct may be difficult particularly in small, recurrent, or subendocardial episodes.

A greater challenge is to identify patients within the first few hours of their attack. The clinical history remains of central importance, though numerous factors influence the presentation of an infarct (table 1). Pain is common, but not invariable; its location characteristically involves the midline, but it may be more localised in the lateral chest, arm or jaw. Onset is rapid but not sudden. Associated symptoms of autonomic overactivity are common irrespective of infarct location.

Physical findings are subtle, but in context may point to a cardiac rather than non-cardiac cause for the presenting symptoms. In first

Figure 1 Factors responsible for acute coronary occlusion underlying most cases of acute myocardial infarction

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Table 1 Factors affecting the presentation of acute myocardial infarction

Age
Gender
Psychology
Diabetes
Other coexisting disease
Previous: angina
infarction
hypertension
coronary grafting
other coronary interventions
Current medication
Site of fresh coronary occlusion
Rate of thrombus formation
Degree of associated coronary spasm
Rate of spontaneous thrombolysis
Existence of collateral vessels
Site of jeopardised myocardium

infarcts, they may indicate the location of the affected myocardial wall: a palpable left parasternal heave (“anterior dyskinesia”) accompanies many anterior infarcts (resulting from the occlusion of the left anterior descending coronary artery); a relative bradycardia with raised venous pressure points to an inferior infarct (from right coronary occlusion) with the common association of right ventricular dysfunction.

The electrocardiogram

The 12-lead electrocardiogram retains its pivotal role in the diagnosis of acute myocardial infarction but its contribution needs careful understanding. The “classic” appearance of pathological Q waves, raised convex-upward ST segments, and T wave inversion (fig 2) was first described when recordings were only available several hours after the onset of symptoms. The recent emphasis on early care has brought to our routine experience ECGs recorded in the so called “hyperacute” phase of the attack. In the earliest phase, the T waves of the affected area become tall and broad (fig 3A) while the beginning of the ST segment remains isoelectric. Progression to more distinct ST segment elevation (fig 3B) is common, usually occurring within minutes. Characteristically, Q waves develop later – within hours – and are likely to reflect a full thickness (transmural) infarct. On many occasions, however, Q waves develop early. How commonly this represents stunning rather than necrosis has yet to be

Figure 2 Characteristic ECG pattern of acute myocardial infarction showing pathological Q waves and convex-upward ST segments

Figure 3 The ECG in the “hyperacute phase” of a myocardial infarct. (A) Tall peaked T waves with no distinct ST segment. (B) Progression to show early ST elevation

Table 2 ECG patterns recorded at home and later in hospital in 93 patients proven to have acute myocardial infarction. (Data from the GREAT study.⁹)

	Hospital ECG			
	Raised ST or BBB	Non-specific abnormality	Normal	Both
Home ECG				
Raised ST or BBB	45	10	0	55
Non-specific abnormality	11	21	4	36
Normal	0	2	0	2
Both	56	33	4	93

BBB, bundle branch block.

explored.⁸ (Stunning indicates a loss of myocardial electrical and/or mechanical activity that later recovers.)

Recent observations have shed further light on the behaviour of the ECG in acute myocardial infarction. Firstly, ST segment elevation can fluctuate, particularly in the “stuttering” case. In the Grampian Region early anistreplase trial of prehospital thrombolysis (GREAT),⁹ Rawles and colleagues showed a discordance between the ECG patterns recorded at 110 compared with 240 minutes after the onset of major symptoms (table 2).¹⁰ This discordance was sufficient to change the diagnostic classification of the trace in 29% of cases. Two practical implications result: that an electrocardiogram should be recorded at the earliest opportunity in any patient presenting with possible infarction; and that frequently repeated ECGs can be valuable where the diagnosis is in doubt or where symptoms are unstable.

Secondly, ST segment elevation appears to have a good (though not perfect) specificity for infarction (about 90%) while its sensitivity is less robust (about 50%).¹¹ Though this may seem discouraging, it is pertinent to note that patients who gain the most benefit from thrombolysis are those whose ST segments are clearly raised or who have bundle branch block (fig 4).¹²

The diagnostic value of ECG changes in acute myocardial infarction has been assessed by Rawles and his colleagues,¹⁰ using plots based on the “receiver operator characteristic”. Receiver operating characteristic (ROC) curves¹³ show the performance of a diagnostic test by plotting for each occasion the test is used its sensitivity (on the vertical axis) against 1 minus its specificity (on the horizontal axis)

Figure 4 The effects of the presenting ECG on mortality from acute myocardial infarction in patients receiving thrombolytic treatment (data taken from reference 12)

Figure 5 (A) Hypothetical receiver operator characteristic curves for an ideal and a completely non-discriminatory test. (B) Receiver operator characteristic for the ECG in patients admitted to hospital with suspected acute myocardial infarction. (Reproduced with permission from reference 10.)

(fig 5A). This is equivalent to plotting the cumulative percentage of true positives against the cumulative percent of the false positives as the test is applied to cases sampled from a known population. The area under the curve indicates the diagnostic accuracy of the test, which for an ideal case would be 100%.

The ROC curves constructed by Rawles for the diagnostic value of the hospital electrocardiogram in acute myocardial infarction are shown in fig 5B. The area under the curve is 86%.

ST segment depression associated with acute myocardial infarction shows two profiles depending on the presence or absence of simultaneous ST segment elevation. Occurring in leads electrically opposite those with a raised ST segment, this change can simply reflect a reciprocal electrical phenomenon.¹⁴ Even so, some investigators believe that this reflects a greater area of myocardium at risk and therefore a worsened prognosis than when such "reciprocal" changes are absent.¹⁵ Certainly, ST segment depression in the anteroseptal leads (V1–V3) with accompanying ST segment elevation in the inferior or inferolateral leads (II, III, AVF, V5, and V6) often reflects contiguous injury in the true posterior left ventricular wall (fig 6).

ST segment depression with no ST elevation is an unfavourable sign.¹⁶ Prognosis is poor, particularly if left ventricular failure or shock are also present. Moreover, patients in this group seem surprisingly unaffected, or even worsened, by the administration of thrombolytics.¹²

Figure 6 ST segment elevation in leads II, III, and AVF, reflecting an inferior infarct. The associated ST depression in the right chest leads, V1–V3, can indicate additional involvement of the true posterior LV wall

To extend the diagnostic reward of the conventional electrocardiogram, several novel approaches have been explored. These have comprised alternative lead configurations, multiple electrode precordial maps,¹⁷ and automatic interpretative systems based primarily on a computerised assessment of ST segment changes. No new technique has found widespread appeal, however, though standard electrocardiographs with automated interpretation are increasingly common and are 85–90% accurate in their diagnosis of an infarct associated with clear ST segment elevation. Unfortunately, like the human observer, interpretive electrocardiographs also find the hyperacute changes of fig 3A more challenging.

Biochemical markers

Necrosing myocardial cells release a variety of compounds into the perfusing blood, though it is important to realise that washout into the peripheral circulation represents a only a small fraction (<10%) of the locally released activity. The rate of rise of a circulating biochemical marker, the peak plasma level reached, and the profile of the subsequent fall are determined by several factors: the nature of the compound itself, the volume of the necrosing muscle, and the pattern of the blood flow through the infarct area. The latter will be determined by the detailed coronary anatomy – including collaterals – and by the degree of both spontaneous and therapeutic reperfusion.

The ideal biochemical marker would rise rapidly (within one hour), remain elevated for several days, be entirely specific for myocardial tissue, and show a good correlation between its concentration in the peripheral blood and the extent of myocardial necrosis. No current marker lives up to these ideals.

The best known marker is creatine kinase and its more specific myocardial fraction CK-MB. In as many as 25% of patients, creatine kinase activity rises within one hour of the onset of major symptoms, but a positive diagnostic yield is little over 50% by four hours rising only to 80% at six hours.¹⁸ The peak activity is at about 20–24 hours. A protein marker of more recent interest is myoglobin, though it shares with creatine kinase a lack of specificity for myocardial tissue. Myoglobin rises more quickly than creatine kinase – 89% positive at four hours – but its peak at 8–12 hours is short lived.

The diagnostic value of myoglobin, creatine kinase, and CK-MB estimated on admission by a near patient analyser for cases of suspected myocardial infarction was investigated recently by Lee and colleagues.¹⁹ Table 3, which summarises the results, indicates both the low sensitivity of these markers and the powerful influence of the ECG on the diagnosis at this early stage.

New markers for myocardial damage are under study. Components of the contractile protein, particularly troponin T, I, and C, invite interest because of their very high specificity for heart muscle.²⁰ These markers also remain in the blood for five to seven days,

Table 3 Sensitivity, specificity, and predictive accuracy of biochemical markers for acute myocardial infarction with and without additional evidence from the ECG. (Data from Lee et al.¹⁹)

Test	Sensitivity (%)	Specificity (%)	Predictive accuracy (%)
Creatine kinase	34	98	68
Creatine kinase-MB	43	100	73
Myoglobin	57	100	80
ECG alone	68	100	85
ECG with:			
creatine kinase	80	98	89
creatine kinase-MB	80	100	90
myoglobin	91	100	96

making accurate retrospective diagnosis a practical possibility. Unfortunately, recent studies²¹ confirm that the time course of appearance of troponin is similar to that of CK-MB, limiting its use for the confirmation of an infarct within the first few hours.

It is clear that urgent enzyme estimations – even with on-site analysis – play a limited role in the early diagnosis of acute myocardial infarction. A negative result even up to six hours is no guarantee against the occurrence of an infarct. Moreover, the value of the thrombolytic treatment for patients with an early creatine kinase rise where the ECG or history is equivocal has not yet been demonstrated.

Other diagnostic aids

The cases of acute myocardial infarction most likely to benefit from the treatment described below can often be identified on the basis of a straightforward history and unequivocal ECG. Diagnosis can be achieved by modest clinical and electrocardiographic skills, well within the grasp of suitably trained medical, nursing, or paramedical staff. In contrast, presentations that are less clear cut – because symptoms or the ECG are atypical – may require greater diagnostic acumen. Even in these cases, however, early management can often follow the pattern suggested of a typical infarct patient, while repeated ECGs, enzyme estimations, and expert help can be recruited to clarify the diagnosis, particularly to determine the need for thrombolysis.

Advanced computer systems have been designed to support decision making in the diagnosis of acute myocardial infarction.²⁴ They can provide a helpful aide memoire to those collecting the required clinical data, and can accurately determine the probability that an infarct has occurred. But their place in routine clinical practice has yet to be evaluated, particularly in the busy environment of an accident and emergency department. They may improve diagnostic accuracy, but their conclusions, like those of their human counterparts, will be profoundly influenced by the quality of the original clinical and ECG information obtained from the patient.

Management

Numerous strategies have evolved for the management of acute myocardial infarction. The agents listed below are presently the focus of attention and in general should form the

core of routine care. But an interest in pharmacotherapy should not detract from the urgent provision of emergency life support, particularly defibrillation. The majority of deaths from ischaemic heart disease, including acute myocardial infarction, still occur in the community, often within an hour or two of the onset of symptoms. Surprisingly, in spite of over 20 years' development of acute coronary care, this pattern has remained unchanged since the early 1970s. Bystander emergency life support, a rapid response by paramedics, and close liaison with the hospital base in the initial management of the infarct patient are areas that still require important consideration.

A detailed account of the management of acute myocardial infarction appears in several recent texts.^{25–27} The following is a summary of the pharmacological agents currently recommended for immediate treatment.

OXYGEN

Oxygen counters the hypoxaemia that occurs through ventilation-perfusion mismatch, even in patients with an uncomplicated attack. Its use becomes mandatory where left ventricular failure is suspected.

NITRATES

Nitrates dilate coronary arteries, particularly at the sites of thrombosis or spasm, improving myocardial blood flow. Nitrates also dilate peripheral arterioles and venous capacitance vessels, reducing myocardial workload. Though regular oral nitrate following infarction seems to produce no overall benefit,²⁸ the early use of sublingual or buccal nitrate seems worthwhile for pain relief, provided that the blood pressure is not unduly low. The cautious use of intravenous nitrates may still be valuable in patients with continuing pain or radiographic evidence of heart failure.

ANALGESIA

Pain relief brings comfort and also reduces the adverse effects of increased autonomic tone. This lessens both myocardial workload and the proarrhythmic effect of catecholamines, particularly when associated with a bradycardia. Opioids given by slow intravenous injection remain the recommended treatment. Diamorphine 5 mg at 1 mg/min or morphine 10 mg at 2 mg/min are preferred, using half this dose in elderly people or in patients with important chronic respiratory disease. Naloxone should always be available where opioid therapy is given. Nitrous oxide or nalbuphine are alternative analgesic agents.

ANTIEMETICS

The combination of high vagal tone and the emetic effect of opioid treatment can give unwelcome and often dangerous nausea or vomiting. Combining cyclizine 25–50 mg with the opioid is convenient but should be avoided in patients with severe left ventricular failure or cardiogenic shock.²⁹ Metaclopramide 10–20 mg intravenously is an alternative and can also be used to dissolve the opioid powder.

ASPIRIN

Following the results of the ISIS-2 trial, aspirin now forms an important part of the early management of patients with myocardial infarction. Though administration within the first 24 hours may not be critical, intuition suggests that it is preferable to give it earlier rather than later. A dose of 150–300 mg can be given whenever the patient is free from nausea or vomiting and after ensuring that no aspirin allergy exists. A chewable formulation of aspirin may speed absorption.

ANTIARRHYTHMIC AGENTS

The prophylactic use of antiarrhythmic agents after myocardial infarction is no longer felt necessary, but atropine, lignocaine, and adrenaline should be readily available for the treatment of important arrhythmias as they occur.

Atropine is helpful to counter either a profound bradycardia (less than 40 beats/min) or a less marked relative bradycardia that may complicate continuing chest pain or heart failure. Treating a slow sinus rate is also a useful strategy for extinguishing frequent premature ventricular beats and may be of greater help in this than introducing the myocardial suppressant effect of lignocaine or other antiarrhythmics.

Lignocaine is no longer recommended for routine prophylaxis, but it is appropriate in divided doses of 100–200 mg intravenously for the first line treatment of ventricular tachycardia with a palpable pulse, as well as late in the treatment algorithm for ventricular fibrillation. It may also be helpful as a continuous infusion to prevent the recurrence of either of these arrhythmias.

Adrenaline plays a prominent role in advanced life support following circulatory arrest from ventricular fibrillation, asystole, or electromechanical dissociation. An important component of its beneficial action is in constricting the peripheral vascular tree to enhance the effect on coronary perfusion of basic life support.

THROMBOLYSIS

Thrombolytic treatment, after a chequered early history, has become a mainstay of treatment for the infarct patient, but its benefit varies with age, presenting ECG, illness severity, and the delay to treatment.³⁰

The value of giving thrombolysis as soon as possible after the onset of major symptoms is undoubted; the goal is to provide treatment as rapidly as possible for cases for undoubted infarction. “Fast track” systems have been reviewed elsewhere³¹ and remain a challenge for practical implementation in many hospitals.

Many regard streptokinase as the most practical drug for use on a day to day basis, though there are theoretical grounds for recommending alteplase in a young patient with an antero-septal infarction and low blood pressure. Alteplase (or urokinase) will also be appropriate for those who are likely to have antibodies to streptokinase through previous

treatment.³² Other regimens and new thrombolytic agents are currently under evaluation.

MAGNESIUM

The use of intravenous magnesium on a routine basis in patients with myocardial infarction was encouraged by earlier studies,³³ but it has gained little support from the subsequent extensive multicentre trial, ISIS-4.²⁸ However, these recent results should not preclude from consideration the use of magnesium in patients with hypokalaemia or those whose infarct is complicated by malignant ventricular arrhythmias.

β BLOCKERS

Intravenous atenolol has been shown to reduce early mortality in acute myocardial infarction seemingly through its effect in preventing myocardial rupture.³⁴ Concerns that β blockers may cause cardiac failure may have been exaggerated, and in general these agents appear underused in the early hours of an attack. Patients with continuing pain, hypertension, tachycardia (in the absence of overt failure), and persistent ST elevation are particularly good candidates for β blockade. If doubt exists that a β blocker can be tolerated, the use of esmolol can be helpful. (Esmolol is a β blocker for intravenous use that has an extremely short half life.³⁵)

ACE INHIBITORS

ACE inhibitors improve the outcome of acute myocardial infarction in patients with impaired left ventricular function, but the initiation of treatment very early in the attack is associated with an increased incidence of hypotension and a trend in some studies to a higher mortality. Treatment starting on day 2 probably leads to the greatest benefit on left ventricular function³⁶ but in practice many eligible patients receive their first dose within 48–72 hours.

Conclusion

Early treatment of a patient with acute myocardial infarction will give him the greatest chance of survival, of myocardial salvage, and of a residual open coronary vessel. Management of this phase should exemplify close collaboration between the general practitioner, ambulance, and base hospital; improved communication would facilitate this collaboration in practice.

Thrombolysis brings undoubted benefit and strategies to minimise delay to treatment for the most deserving cases should be encouraged. But emphasis on drug treatment should not obscure the urgent need to provide early defibrillation. Myocardial infarction remains a condition for which the very early attrition rate is still unacceptably high.

Finally, diagnosis and management can only begin after medical help has been sought by the patient or relative. Public awareness of the symptoms of myocardial infarction and a well drilled response by healthcare personnel are fundamental to successful care.

Summary

The effective early diagnosis of acute myocardial infarction still rests primarily on the clinical history and the electrocardiogram. ST segment elevation is specific though sometimes short lived and less than ideally sensitive; but with bundle branch block it defines a population that benefits importantly from thrombolysis. Novel electrode configurations can further enhance diagnosis but have not become popular. Biochemical markers are rarely of help in the first four hours and cardiac scanning is impractical for routine care. Computerised diagnostic systems show promise in prototype but are not widely available. Early management involves re-establishing coronary flow by thrombolytic and antithrombotic agents and reducing myocardial oxygen requirement by analgesics and β blockers. Nitrates and magnesium have limited roles. Immediate access to defibrillation and advanced life support is mandatory. Diagnosis and management can only begin after help has been sought. Public alertness to the symptoms of myocardial infarction and a coordinated response by health care personnel are fundamental to successful care.

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