ACUTE CORONARY SYNDROMES (ACS)

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KEY POINTS

- Acute coronary syndromes covers ST segment elevation and Q wave MI, non-ST segment elevation and non-Q wave elevation MI and unstable angina.
- The new terminology is driven by improved understanding of pathophysiology and improvements in management.
- The ECG remains the most important diagnostic and prognostic procedure in infarction.
- Troponins are cardiospecific and in conjunction with the clinical picture, ECGs and early stress testing enable management of ACS to be streamlined.
- Third generation antiplatelet agents, IIb/IIIa inhibitors, are the most exciting recent drugs to be used in ACS.
- The obsession with an open artery policy should be replaced with the goal of obtaining normal myocardial tissue perfusion.

The popularity of the term 'acute coronary syndromes' to describe the presentation of patients with a variety of chest pains or other symptoms caused by myocardial ischaemia is reflected by a quarterly journal solely devoted to the subject[1], numerous articles and presentations at learned meetings and supplements to major journals[2]. The introduction of thrombolysis and improved understanding of patho-physiological processes led to the use of acute coronary syndromes to cover Q wave infarction, non-Q wave infarction and unstable angina which replaced the older classification into acute myocardial infarction, unstable angina and intermediate coronary syndromes. Now we are increasingly moving to a classification of ACS into ST segment elevation myocardial infarction (MI), non-ST segment elevation MI and unstable angina, which sounds ponderous but is likely to be justified by improvements in management.

The aim of management is to separate high-risk patients from those with lower risk so that rapid, effective treatment may be given to both groups. An improved management strategy should enable low-risk patients to be discharged from hospital more quickly than now, releasing bed space. Accepted standard practice is reviewed in this article but areas of interest and controversy will be emphasised. These include:

- the diagnostic use of troponins
- low molecular weight heparins
- statins in the acute phase
- GP IIb and IIIa inhibitors
- invasive versus non-invasive policies.

Alteration in nomenclature is justified only if it leads to improved care of patients and the primary care physician remains at the cutting edge of the management of acute chest pain and has the responsibility to initiate rapid effective treatment. The value of contemporary thinking will be evident if it enables primary care groups (trusts) to work with cardiologists to provide optimal effective care.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES[3,4]

Disruption or erosion of atheromatous plaques with superimposed thrombosis is regarded as the cause in the majority of patients with ACS. In unstable angina, the atheromatous plaque has a thin fibrous cap and a fissure commonly occurs at one corner leading to the release of lipid-rich material. If thrombus formation is temporary, it typically causes pain at rest with vascular occlusion of 10-20 minutes. Longer thrombotic occlusions of up to one hour may lead to non-Q wave infarction. Larger plaque fissures and persistent thrombotic occlusions result in raised ST/Q wave infarcts. It is clear now that small plaques of atheroma are more likely to be involved in sudden coronary events, coronary angiography is poor at demonstrating such lesions because remodelling of the arteries with preservation of the lumen prevents the narrowing which is necessary for angiography to be diagnostic. Imaging with intravascular ultrasound confirms remodelling with unstable plaques in unstable angina.

This simplified account is not the whole answer and logical management schemes must take other possible mechanisms into consideration. These include:

- Vasoconstriction affecting large coronary vessels in Printzmetal's angina or small arteries in microvascular angina. Effective treatment usually involves coronary vasodilators including nitrates and calcium channel blockers.
- Inflammation: Infection with *chlamydia pneumoniae, helicobacter pylori* and *cytomeglovirus* have been cited as possible causes of inflammation of the atherosclerotic plaques. Macrophages release proteinases which may break down plaques leading to fissuring. Inflammatory response has been measured by C-reactive protein and increased levels with poor prognosis have been found in patients with unstable angina. So far, treatment with

macrolide antibiotics has met with a varied and, on the whole, disappointing response.

- Hypercoagulable states: Hypercholesterolaemia, high catecholamine drive in cigarette smoking and perhaps infections may lead to hypercoagulable states and this has been implicated in thrombus formation in the one-third of patients with ACS who have superficial erosions of large, stenotic fibrous plaques.

- Increased myocardial oxygen demand. If there is major flow-limiting coronary atherosclerosis, increased oxygen demand may cause unstable angina in thyrotoxicosis, infections and arrhythmias.

THE MANAGEMENT OF ACUTE CORONARY SYNDROMES

When coronary care units (CCUs) were introduced in the 1960s, the emphasis was on the management of life-threatening arrhythmias. Subsequently beta blockers, nitrates and calcium channel inhibitors were used to reduce myocardial oxygen consumption in an attempt to prevent unstable angina and acute infarction.

In the last decade, antiplatelet therapy with aspirin plus thrombolytics such as streptokinase and tPA have been used for 'drug reperfusion' and the debate about the need for coronary angioplasty rather than drug reperfusion is ongoing. An 'open artery policy' aims to restore full patency, the so-called TIMI 3 result, and this has been the agreed goal in recent years.

All management options are aimed at delivering the optimal treatment in the minimum time.

THE INITIAL MANAGEMENT OF PATIENTS WITH CHEST PAIN

The aim is to fast-track patients with high probability of infarction to receive thrombolytic therapy. In Lancaster and Kendal, paramedics ring ahead to the CCU or general practitioners ring the bleep holder on call, which has reduced the door-to-needle time. Pre-hospital ECG and reperfusion therapy is even better if it can be introduced safely. Patients admitted to the A&E department are thrombolysed in the department before transfer and, if the CCU is full, care, including monitoring by telemetry, is provided on the Medical Assessment Unit. The first hour after the onset of pain, the 'golden hour', is when the best results can be obtained with thrombolysis.

All patients have blood taken for a full blood count, full biochemical profile, plasma glucose and lipids but the crucial early diagnostic tool is the electrocardiogram, which is the immediate procedure of choice for the diagnosis of infarction and is of high value in prognosis. From the Gusto IIb trial, the rate of death or reinfarction within six months in AC syndromes is 8.1% with T wave inversion; 12.3% with ST elevation; 15.4% with ST depression and 15.7% with a combination of ST elevation and depression. The extent and type of ST-T deviation also provides prognostic information in non-infarction ACS (TIMI III trial), eg anterior ST deviation has a worse prognosis than any other location and deep negative T waves in the chest leads suggest critical stenosis of the left anterior descending artery.

The use of biochemical markers is changing. The traditional serial AST and CK measurements over three days are wasteful of hospital bed space and patients' time. The early markers of infarction such as MB-CK mass and myoglobin have little to add to the history and ECGs but the troponins promise to alter the management of ACS dramatically and may well result in further reappraisal of the diagnostic categories.

THE TROPONINS

These are proteins in the contractile apparatus in muscle which regulate calcium dependent interaction of myosin and actin. Troponins T and I are cardiospecific and only in rare instances (such as renal disease with troponin T) can non-cardiac causes produce a rise. We are shortly to introduce guidelines for the use of troponin T in the Acute Trust in the bay area. Normally, no troponin is found in the peripheral blood but with myocardial damage, levels start to rise in two to three hours and remain raised for up to three weeks.

The clearest value of troponin testing is in deciding if patients with chest pain can safely be discharged within 24 hours of hospital referral. Probable non-cardiac pain with normal ECGs and normal troponin eight hours after pain allows early discharge in safety. Patients with ischaemic pain but normal troponin at eight hours and who stabilise clinically are regarded as safe to discharge regardless of ECG changes. Patients with unstable angina and positive troponin measurements are thought to have microemboli discharged from the plaques which cause myocytic damage and release of troponins.

A strategy for using the clinical picture, ECGs, troponins and early treadmill testing in selected patients is to be proposed locally. It should enable us quickly to identify patients at high risk of subsequent cardiac events and those with clear cardiac pain but low immediate risk, and to establish a non-cardiac cause for pain in other patients[5].

DRUG TREATMENT OF ACS

Control of chest pain with opiates supplemented by nitrates is essential and beta blockers and nitrates are usually enough to improve myocardial ischaemia. Calcium channel antagonists such as nifedipine and amlodipine are contraindicated because they may carry increased risk, particularly if used without beta blockade. They are often used despite this advice. Nicorandil, the potassium channel opener, may help in patients with pain uncontrolled by other agents.

The use of thrombolysis with streptokinase or tPA is well-tried and accepted and local guidelines provide details. The aim is to treat the acute raised ST segment MI but delays inevitably lead to some cases being treated when they have already established Q waves. In non-ST segment elevation/non-Q MI and unstable angina, thrombolytics have consistently failed to show benefit and there is a tendency to slight increase in mortality.

ANTICOAGULANTS[6]

Unfractionated heparin has usually been given to patient with unstable angina even though the extra benefit of heparin and aspirin over aspirin alone requires meta-analysis to demonstrate. Low molecular weight heparins (LMWH) are

replacing unfractionated heparin in most coronary units because they are given subcutaneously and do not require routine monitoring.

ANTIPLATELET AGENTS

1) *First generation:* aspirin remains the drug of choice and is effective at 75 mg daily: it inhibits cyclo-oxygenase activity in cells.

2) *Second generation:* The thienopyridines, clopidogrel and ticlopidine, inhibit the ADP receptor responsible for platelet aggregation. Clopidogrel has fewer side-effects than ticlopidine but is reserved for patients who are unable to tolerate aspirin. Clopidogrel is not licensed for unstable angina and may not be effective in the early stages of ACS because it has a delayed onset of action.

3) *Third generation:* The glycoprotein (GP) IIb/IIIa inhibitors are the most exciting recent drugs to be used in ACS. They may be classified into:

   a) Direct receptor blockade by monoclonal antibodies, eg abciximab (Reopro).

   b) Competitive inhibitors:
      intravenous (eg eptifibatide, tirofiban, lamifiban)
      oral (eg orbofiban, sibrafiban).

The extent of the interest in these agents is shown by a glossary of 22 trials of GP IIb/IIIa inhibitors in an article in 1998[7]. Oral agents have proved universally disappointing so far but intravenous use in over 30,000 patients in randomised studies has shown benefit in non-ST segment elevation ACS. In the 'Four P' trials (PRISM, PRISM-PLUS, PURSUIT, PARAGON), there is a 12% reduction in events at 30 days and current trials are investigating the possibility of even better results from low-dose thrombolytic plus a GP IIb/IIIa inhibitor. At the November 1999 American Heart Association meeting, Topol suggests that patients with positive troponin tests should be treated with intravenous IIb/IIIa inhibitors and it may prove a cost-effective policy in such patients.

STATINS

There is no doubt that lipid-lowering by statins is effective in the longterm management of patients with coronary artery disease but there is a surprising lack of randomised trial data on the possible early stabilisation of plaques by early lipid lowering. It seems reasonable to start statins immediately in most patients.

THE DEBATE ABOUT EARLY REVASCULARISATION AND PERCUTANEOUS INTERVENTION (PCI)

A completely patent artery, the TIMI 3 result, is the goal of successful reperfusion therapy of acute ST segment elevation MI and in skilled hands, primary angioplasty is superior to thrombolytic therapy in the short term and probably in the long term too. If patients are seen later, the initial hazard is to be balanced by a longterm benefit which may take years to be apparent.

Drug reperfusion in GISSI I improves from a patency at 90 minutes of 30% with SK to 54% with tPA with a 15% reduction in mortality. Although newer plasminogen activators such as reteplase (rPA), tenectoplase (TNK) and lanetoplase (nPA) have been shown to achieve more rapid and complete vessel patency than tPA there is no mortality benefit, implying that the 'open artery policy' is not directly and solely related to survival. Microvascular obstruction has been suggested as the reason for the discrepancy and at least one in four patients with TIMI 3 flow are estimated to have impaired tissue perfusion. In other words, the obsession with an open artery policy with a patent coronary vessel should be replaced by the goal of obtaining normal myocardial tissue perfusion.

Angioplasty may cause microemboli which result in microvascular obstruction distally, and it is realised now that our 'thrombolytics' have more downside than originally envisaged. In fact, our thrombolytic agents are fibrinolytics; the thrombin which is enmeshed in the fibrin of a clot is unaffected by the drugs and when exposed, has a prothrombotic effect with potent platelet aggregatory properties. The GP IIb/IIIa inhibitors are potent agents for dissolution of platelet thrombi when given intravenously and the use of these drugs with half dosage of plasminogen activators has improved microvascular perfusion in preliminary trials, spawning a series of major trials which should confirm whether or not this promising approach is a significant development for relief of microvascular obstruction and the improvement of myocardial perfusion. Therefore, the arguments between the merits of early angioplasty and drug reperfusion for infarction seem likely to be replaced by discussion on how to maintain tissue perfusion by the addition of potent anti-platelet agents such as the GP IIb/IIIa inhibitors to either thrombolytic (fibrinolytic) drugs or to percutaneous intervention.

Patients with non-ST segment elevation ACS may benefit from PCI in the long term but no trials have been large enough with sufficient length of follow-up to give a clear answer. It seems that a policy of 'watchful waiting' rather than early PCI is reasonable for this group. The waiting period is curtailed if intractable pains persist despite full drug treatment and if investigation such as treadmill testing indicates severe ischaemia. Such patients warrant coronary angiography so that PCI or bypass surgery may be considered.

THE FUTURE

The best catalyst for answering treatment questions would be to understand the vulnerability of the coronary atherosclerotic plaque. Magnetic resonance imaging and positron emission tomography show promise for the assessment of plaques and are predicted to be developed in the near future[8].

In the meantime, ongoing trials are investigating:

a) The plaque stabilising effects of statins.

b) The possibility of improving the open artery policy in ST elevation MI by using half-dose thrombolytics plus GP IIb/IIIa inhibition.

c) The management of high risk patients identified by measurement of troponin. There are intriguing suggestions that LMWH and GP IIb/IIIa antagonists benefit patients who are troponin positive.

d) Possibility of improving endothelial function by folic acid or angiotensin converting enzyme inhibitors.

Further trials should help to decide whether watchful waiting in patients with non-ST elevation ACS remains an acceptable alternative to early revascularisation.

SUMMARY

The exciting improvements in diagnostic methods and new drugs such as the GP IIb/IIIa inhibitors point the way to better management of acute coronary syndromes with the ultimate goal that no-one with evolving infarction will suffer permanent myocardial damage.

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