

Recent advances in ischaemic heart disease

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Ischaemic heart disease remains a prevalent condition and continues to be associated with a significant likelihood of future major cardiac events including myocardial infarction (MI) and death. Recent years have seen considerable advances in the understanding and management of coronary artery disease. This article will attempt to focus on some of the areas of greatest interest among these, though as this represents a broad field, it cannot hope to be exhaustive.

Role of inflammation in atherosclerosis and the acute coronary syndromes

Since the "incrustation" hypothesis of von Rokitsansky¹ in 1852 and "lipid" hypothesis of Virchow² in 1856 there has been great interest in the pathogenesis of atherosclerosis. Increasingly, the atherosclerotic process is seen as the response of the vessel wall to chronic, low grade injury.³⁻⁴ Initially there is dysfunction of the endothelium with accumulation of macrophages and lymphocytes subendothelially.⁵ The earliest discernible lesion of atherosclerosis is the "fatty streak" which histologically is an aggregation of lipid laden macrophages and T cells within the intima.⁵ The presence of fatty streaks are almost universal in adults and are found in the coronary arteries of 50% of children between 10 and 14 years of age.⁶⁻⁷ These fatty streaks precede the development of more complex lesions composed of a fibrous tissue cap containing smooth muscle cells overlying a core of lipid and necrotic material. As the volume of the plaque increases, there is initially remodelling of the arterial wall, increasing the external vessel diameter and reducing the degree of luminal narrowing.⁸ Plaques within the coronary circulation remain clinically "silent" until either:

(1) The process of vessel wall remodelling is overwhelmed and there is sufficient plaque encroachment into the vessel lumen to cause symptoms, or

(2) Rupture of the fibrous cap of the plaque occurs with subsequent thrombosis within the coronary artery sufficient to result in an acute coronary syndrome.

Within normal coronary arteries the circumferential wall stresses applied during the cardiac cycle are distributed evenly. In atherosclerotic segments of the vessel, due to the inelasticity of the fibrous cap of the plaque, considerable stress during systole is applied to relatively small focal areas of the cap.⁹ This increase in focal wall stress is increased where the cap is thin or uneven in thickness and in the absence of a high grade stenosis.

An in vitro study on human aortas has shown that fibrous caps which become infiltrated with macrophages lose mechanical strength and elasticity.¹⁰ Within the coronary vasculature,

the immediate site of plaque rupture or erosion has been found to be consistently marked by an inflammatory process at postmortem examination.¹¹⁻¹² Further postmortem data have demonstrated the presence of focal inflammatory cell infiltration within the fibrous caps of unruptured atherosclerotic plaques both within the coronary circulation and in peripheral vessels.¹³⁻¹⁵ This infiltration is most commonly seen at the edge of the plaque ("shoulder region") which computer modelling has shown to be the site of greatest systolic stress in eccentric plaques.¹⁵⁻¹⁶ In an elderly population with a mean age of 78 years, between 30% and 40% of the coronary plaques studied postmortem were found to have inflammatory cells within the fibrous cap and were considered to be at risk of rupture.¹⁴

Coronary atherectomy specimens taken from patients with acute coronary syndromes have shown evidence of recent immune activation with increases in the proportion of active T lymphocytes present.¹⁷ Among patients with acute coronary syndromes, inflammatory markers have been found to have prognostic importance. Evidence for this was initially found among 20 patients admitted to hospital with unstable angina. In those with an initial C reactive protein concentration greater than 3.0 mg/l (exceeding the 90th centile of the normal distribution) there were more ischaemic episodes and major adverse cardiac events on short term follow up than in those whose C reactive protein was below this level.¹⁸ The prognostic value of both C reactive protein and fibrinogen concentrations has since been confirmed in larger studies among patients with unstable angina and non-Q wave MI.¹⁹⁻²⁰

These results suggest the possibility of risk stratification of patients admitted to hospital with acute coronary syndromes based on their inflammatory markers. This has, however, not yet been tested in a large trial. A small study, which attempted to do this, followed up 72 patients who were admitted to hospital with chest pain refractory to medical treatment.²¹ Because of the small number of patients, the end points taken in this study were evidence of transient myocardial ischaemia and the presence of multivessel coronary disease or intracoronary thrombus on angiography. No correlation was found between C reactive protein and these end point criteria. The study was not powered to assess differences in clinical outcomes such as death or MI. Further work clearly is required to properly assess the role of inflammatory markers in prospectively determining the cardiovascular risk of patients admitted to hospital with cardiac symptoms. Were this found to be effective in identifying patients likely to experience future adverse events, it may be possible to direct these

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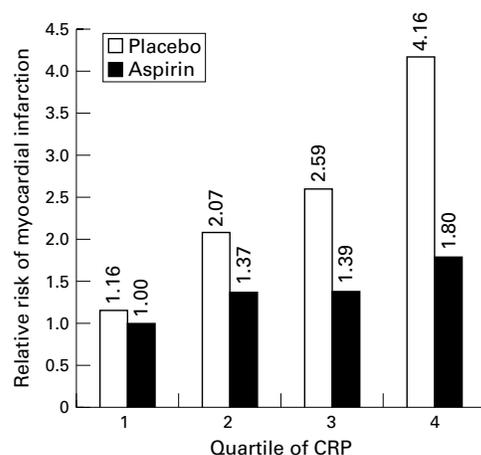


Figure 1 Relative risk of first myocardial infarction (MI) in healthy men separated by quartile of C reactive protein (CRP). It is a comparison of those taking aspirin with those on placebo (adapted from Ridker *et al*³⁰). Only the difference in risk of MI in the highest quartile of C reactive protein was statistically significant ($p < 0.02$).

patients quickly to appropriate investigation and treatment. Similarly, those patients at low risk could avoid unnecessary investigation.

There is evidence from large prospective population studies that the systemic level of inflammatory markers may also be predictive of the risk of future cardiovascular events in otherwise well individuals. The level of the acute phase protein fibrinogen was found to be directly related to the future risk of MI and stroke in men.²² Though this effect was subsequently demonstrated elsewhere,^{23, 24} it remained unclear whether it was due to an underlying inflammatory component or the result of alterations in coagulation.^{25, 26} Later, C reactive protein concentrations were found to parallel those of fibrinogen and are equally predictive of cardiovascular risk in both those with²⁷ and without^{28, 29} known coronary disease. Among apparently healthy men, it has been shown that those with a C reactive protein level within the highest quartile of the normal range have a risk of MI which is threefold greater than men who have a C reactive protein level in the lowest quartile.³⁰ Interestingly this study also demonstrated that the reduction in the risk of first MI associated with the use of aspirin appeared to be directly related to the initial level of C reactive protein (fig 1).³⁰

Role of intervention in the acute coronary syndromes

Despite greater understanding of these conditions, both unstable angina and non-Q wave MI remain prevalent and account for a significant proportion of hospital admissions. The event rate among these patients remains high with up to one third having an adverse outcome over a two month period.³¹ Those patients without ST elevation followed up in the GUSTO IIa study, were found to have a 30 day incidence of death or non-fatal MI in North American sites of 8.5%.³² As a result, patients with unstable angina are commonly referred for revascularisation in an attempt to reduce their morbidity and mortality. However, the

indications for, and the benefits of, these interventions have not been clearly delineated.^{33, 34}

An early invasive strategy with coronary angiography 18 to 48 hours after admission, and revascularisation if deemed appropriate in patients with unstable angina or non-Q wave MI was tested in the TIMI IIIB study.³⁵ Those in the conservative limb only underwent angiography if initial medical therapy was deemed to have failed. The primary end point (six week composite of death, MI, or "unsatisfactory" exercise test) occurred in 16.2% of those randomised to the early invasive strategy compared with 18.1% in the conservative group. This difference was not significant. As this was largely a North American study there was a high rate of "crossover" with 64% of the patients assigned to early conservative treatment undergoing cardiac catheterisation (90% of these before discharge). Overall, 49% in the conservative group underwent revascularisation, compared with 61% in the invasive group.³⁶ As a result, this study did not so much compare invasive with non-invasive treatment, but compared routine early angiography followed by revascularisation, with revascularisation where medical treatment had failed.

The second large trial comparing invasive and conservative management strategies in patients with non-Q wave MI was the VAN-QWISH study.^{37, 38} Those assigned to the early invasive limb followed the same management strategy as in the TIMI IIIB study.³⁵ Patients in the conservative limb underwent angiography if they had recurrent angina associated with electrocardiographic changes or ischaemia demonstrated on exercise testing or perfusion scanning. The primary end point (composite of all-cause mortality or non-fatal reinfarction) was higher in the invasive group before hospital discharge, at one month and at one year. By two years of follow up, an end point had occurred in 29.9% of those randomised to the invasive strategy and in 26.9% assigned to the conservative strategy ($p = 0.35$). In addition, the rate of death alone in the invasive group was higher at hospital discharge (4.5% *v* 1.3%, $p = 0.007$) and at one year (12.6% *v* 7.9%, $p = 0.025$).

Recently, the FRISC-2 trial has suggested that there may be benefit with an early invasive strategy.³⁹ These patients had unstable angina with electrocardiographic changes in addition to a raised CK-MB or cardiac Troponin-T concentration and underwent coronary angiography within seven days of admission. The in-hospital death rate was non-significantly higher in the invasive group (1.2% *v* 0.4%). However, by 30 days, the combined end point of death or MI was lower in the invasive group (9.5% *v* 12%, $p = 0.045$, risk ratio (RR) 0.79 (95% confidence interval (CI) 0.63 to 0.99)). This apparent benefit of revascularisation was most striking in males (30 day death/MI: 9.1% *v* 13.9%, $p = 0.002$).

Because of high rates of crossover between the invasive and conservative groups these studies have not directly compared revascularisation with intensive medical treatment alone. Due to differences in practice between the UK

and North America, invasive management here is better reflected by the conservative limbs of these studies. Studies comparing an ischaemia driven revascularisation strategy with medical treatment alone have not been conducted. On the basis of these studies there is little evidence to support routine intervention among unselected patients with unstable angina or non-Q wave MI. Although the FRISC-2 data appear promising, the 30 day composite end point here was only just significant in a large number of patients.

Glycoprotein IIb-IIIa inhibitors

As a result of the negative outcomes with intervention in the acute coronary syndromes, interest has focused on the platelet glycoprotein IIb-IIIa receptor which is essential to platelet activation. Agents that inhibit platelet cyclo-oxygenase such as aspirin or the newer agents ticlopidine and clopidogrel which inhibit ADP-induced platelet activation only result in partial platelet inhibition. Activation of the IIb-IIIa receptor allows it to bind to fibrinogen which is the final common pathway in platelet activation. Antagonists of this receptor can result in profound platelet inhibition. The role of these glycoprotein IIb-IIIa inhibitors in both unstable patients undergoing intervention and in those treated conservatively has been considered recently in a number of studies.

The EPIC trial was the first to assess this. Here the intravenous agent c7E3 (abciximab, ReoPro) was evaluated in patients undergoing high risk percutaneous transluminal coronary angioplasty (PTCA) (unstable angina, acute MI, or high risk lesions).⁴⁰⁻⁴⁴ The primary end point (composite of death, MI, need for a balloon pump, stent, coronary artery bypass graft (CABG), or repeat PTCA at 30 days) was reduced from 12.8% in the placebo group to 8.3% in the ReoPro infusion group ($p = 0.008$). Among patients with unstable angina, ReoPro appeared to have a more striking benefit with a 65% reduction in the 30 day composite end point (12.8% to 4.8%, $p = 0.012$). This benefit has since been shown to be maintained on three year follow up, with patients who had unstable angina or evolving MI having a 60% reduction in their mortality at three years.⁴³

This was further investigated in the CAPTURE trial, which examined the effect of ReoPro among patients with refractory unstable angina undergoing PTCA.⁴⁵ The composite end point of death, MI, need for a stent, balloon pump or urgent revascularisation at 30 days was reduced from 15.9% to 11.3% in the ReoPro group. A significant proportion of this reduction was due to a reduction in MI in the ReoPro group (8.2% *v* 4.1%, $p = 0.002$). However, the PTCA procedure was associated with a substantial increase in early MI (within 24 hours of the procedure), and it was this increase which was attenuated by pretreatment with ReoPro.

The role of another glycoprotein IIb-IIIa inhibitor tirofiban in unstable angina or non-Q wave MI was assessed by the PRISM study.⁴⁶

During the first 30 days 62% of patients underwent angiography, and 22% had PTCA. Among those undergoing PTCA, tirofiban was associated with a reduction in the composite end point (death, MI, or refractory ischaemia) at 30 days (21.6% *v* 27.3%, RR 0.72; 95% CI 0.53 to 0.98). However, this composite end point rate was significantly greater than in those treated with medical therapy alone (10% for tirofiban *v* 11.7% for heparin).

The PRISM-PLUS study further evaluated tirofiban among patients with acute coronary syndromes.⁴⁷ In contrast to PRISM,⁴⁶ between 48 and 96 hours, investigators were encouraged to perform angiography and PTCA if appropriate. Again, as had been previously shown in both the CAPTURE⁴⁵ and PRISM⁴⁶ studies there was an increase in death or MI associated with intervention. Though again this increase was attenuated by treatment with tirofiban. When the composite end point at 30 days was broadened to include, in addition to death or MI, readmission for unstable angina or refractory ischaemia, intervention compared more favourably. Among patients treated with PTCA, this composite end point occurred in 8.8% of the tirofiban group and 15.3% of the heparin only treated group, representing a 45% risk reduction. Among those treated medically, the corresponding composite end point rates were 14.8% and 16.8% respectively. Thus, at 30 days PTCA with adjunctive tirofiban resulted in a substantial reduction in readmission due to recurrent ischaemia compared with medical treatment.

These data from the trials of the glycoprotein IIb-IIIa inhibitors in acute coronary syndromes give cause for optimism though the event rate among those patients undergoing PTCA remains high. The assumption must be made however, that those requiring intervention in these studies represent a higher risk group than those treated conservatively. It is likely that the role of these agents will continue to increase among this group of patients and the evidence to date strongly supports their use in unstable patients who are to undergo PTCA.

Myocardial infarction

Treatment in acute MI is well established with the aim being to re-establish vessel patency as early as possible. The GUSTO-1 study demonstrated the importance of this, but in addition, the need not only for vessel patency but also for the resumption of normal flow within the infarct related artery.⁴⁸ However, thrombolytic therapies have been limited by their failure to establish vessel patency in a significant proportion of patients. Primary PTCA for acute MI results in a considerable improvement in this,⁴⁹ though is not widely available. To improve vessel patency with medical therapy, the glycoprotein IIb-IIIa inhibitor ReoPro has been used in combination with tissue plasminogen activator (rt-PA). At 90 minutes after the initiation of treatment, normal flow (TIMI grade 3) had been restored in 57% of patients treated with rt-PA alone and in 32% of those treated with ReoPro alone. When ReoPro was combined with a reduced dose of rt-PA, TIMI

grade 3 flow was restored in 76% of patients at 90 minutes.⁵⁰ Additionally, there was no excess of bleeding complications in the combination therapy group. If this treatment translates into improved outcomes in acute MI, it is likely to be increasingly used, though the increased cost with such a drug combination may be prohibitive.

Management of refractory angina

Though developments in conventional modes of revascularisation continue, there are a significant number of patients who remain symptomatic and are not treatable by either PTCA or CABG. Transmyocardial laser revascularisation (TMR) has recently been suggested as a new therapeutic modality for patients with otherwise untreatable coronary artery disease. The procedure involves creating a number (usually 15–30) of transmural laser channels through the left ventricular free wall, requiring the chest to be opened to gain access to the heart.

The Texas Heart Institute reported 12 month data on 21 patients undergoing TMR.^{51–52} All had Canadian Cardiac Society angina class 3 or 4 and 19 had undergone previous CABG. The mortality associated with this procedure was 24% at one year, with two deaths occurring within the first 30 days (9.5%). On follow up, the mean (SD) Canadian Cardiac Society angina class was 3.7 (0.4) before operation and 1.8 (0.6) after the procedure ($p < 0.01$). The Brigham and Women's Hospital reported upon 20 patients, all of whom had undergone previous revascularisation and had a Canadian Cardiac Society angina class 3 or 4.⁵³ The mortality of this procedure was again high. The 30 day mortality was 20%, including two deaths within the first 48 hours of the procedure. At follow up, the mean Canadian Cardiac Society angina class was reduced from 3.7 before the procedure to 1.0 after the procedure ($p < 0.01$).

It had been assumed that TMR improved myocardial perfusion via the laser channels that were created. However, the Texas Heart Institute group failed to show any improvement in perfusion with dobutamine stress echocardiography.^{51–52} Also long term patency of laser channels has not been consistently demonstrated.^{54–56} The largest experience analysed tissue from eight patients dying at various times after TMR.⁵⁶ Patency of laser channels was not demonstrated in any of these patients. However a developing network of capillaries was observed within granulation tissue at the treated sites. This led to the hypothesis that the induced inflammation stimulated angiogenesis, which improved myocardial perfusion. Myocardial denervation is another potential mechanism for the relief of symptoms that has been demonstrated.⁵⁷ However, to date the precise mechanism of action remains unclear.

Though TMR often results in a profound and almost immediate improvement in angina which appears to be sustained, it is limited by the need for surgery and the high rate of perioperative adverse events. The development of percutaneous myocardial revascularisation

(PMR) has allowed the procedure to be carried out less invasively reducing the early complications and augmenting clinical benefit.³⁸ The efficacy of PMR has been studied in the multicentre PACIFIC study (presented at American College of Cardiology, New Orleans, March 1999). A total of 221 patients, not amenable to conventional revascularisation, were randomised to PMR with medical treatment or medical treatment alone. In both groups, 60% of patients had Canadian Cardiac Society class 3 angina and 40% class 4 angina. At three months of follow up, there had been an average improvement of 1.3 angina classes in the PMR group compared with 0.13 classes in the medical group ($p < 0.000001$). By six months, the improvements in angina class were 1.4 and 0.25 respectively ($p < 0.000001$). There was a low rate of periprocedural adverse events with 1% developing pericardial tamponade and 1% having heart block requiring permanent pacing. No deaths, MIs, or strokes were reported.

These early data on the results of PMR are encouraging. However, again the mechanisms of action are poorly understood. Before these treatments become widely available it is likely that our knowledge base here will need to increase and this area remains the subject of intense research.

Summary

There continue to be important developments in the understanding of the pathogenesis of coronary artery disease. Advances have also been made in both the medical and interventional management of patients with ischaemic heart disease. This review has, however, not focused on the wider developments that have occurred in the area of percutaneous intervention. The vast array of new stent designs and other interventional devices have had a considerable impact on the treatment of obstructive coronary disease. In addition it is likely that further developments will be seen in areas such as intracoronary radiotherapy to reduce restenosis after PTCA and in gene therapy to promote angiogenesis in ischaemic myocardium. Both of which will be discussed in a future review of this area.

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