Pathogenic mechanisms in unstable angina

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Many theories have been developed to explain the pathogenesis of unstable angina, but so far none has adequately explained all the known facts about this disease. Most patients with unstable angina have atheromatous deposits in their coronary arteries, and progressive stenosis caused by large atheromatous plaques was once thought to be responsible for the development of ischaemic symptoms. However, a study comparing the coronary arteries of patients who had a history of chronic stable angina for at least two years with those who had a history of unstable angina failed to support this hypothesis.¹ The study found that the severity of atheroma varies greatly between individuals and that patients with uncomplicated chronic stable angina tended to have more severe atheroma than patients who have unstable angina as the first clinical manifestation of ischaemic heart disease.

An alternative theory that has gained wide acceptance attributes unstable angina to the sudden fissure or rupture of an atherosclerotic plaque. This exposes the highly thrombogenic endothelium to the circulation, and a platelet rich thrombus rapidly develops over the site of plaque rupture. The thrombus obstructs but usually does not fully occlude the vessel. Blood flow may be occasionally reduced causing distal ischaemia but the myocardium remains viable. Although thrombosis undoubtedly has a central role in unstable angina, recent studies indicate that other mechanisms also play a part in some patients. It is therefore appropriate to reconsider the evidence concerning the aetiology of this condition.

Evidence against plaque fissure as the fundamental cause of instability

The first piece of evidence indicating that other mechanisms are present comes from clinical observations. One would expect that thrombosis over the site of plaque rupture would be an acute event, from which the patient would either recover or die. In either case the time course of the illness would be short, whereas unstable angina tends to wax and wane, sometimes over several days or weeks. Mortality from unstable angina is highest in the early stages and then declines gradually, not reaching a steady state for about two to three months (fig 1).² This pattern is inconsistent with an acute thrombotic event and demands further investigation.

More evidence comes from two postmortem studies of patients dying from acute coronary syndromes.^{3,4} In 40% and 46% of cases, respectively, there was no evidence of a fissured atherosclerotic plaque underlying the coronary artery thrombus. These results make it impossible to sustain the theory that plaque fissure is

a necessary prerequisite for thrombosis, and show that other triggers for thrombosis must also exist. In addition, 10–25% of people dying of non-cardiac causes have evidence of plaque fissure without thrombosis at postmortem examination,⁵ providing further evidence that fissure and thrombosis are not as closely linked as once thought.

Role of inflammation

The hypothesis that inflammation could be the trigger for the development of instability was developed to explain both clinical and post-mortem observations. Inflammation was proposed as a mechanism for activation of the coronary artery endothelium, leading in turn to thrombosis. Support for this theory has been provided by two separate studies showing that the prognosis in unstable angina can be improved by antibiotic treatment.^{6,7} It is not entirely clear whether the beneficial effect of antibiotics is caused by an antibacterial action or by the anti-inflammatory and anticytokine action of the macrolide antibiotics used in these studies, but these results do suggest that inflammation plays a part in the development of unstable angina. However, other workers have also found inflammatory infiltrates at postmortem examination in the arteries of chronic stable angina patients dying of non-cardiac causes.⁸ These findings suggest that although inflammation appears to play an important part in the transition from stable angina to unstable angina, it is unlikely to be the sole cause.

Culprit lesions

It has been customary to think of unstable angina as being caused by a single culprit lesion, but a paper presented at the 1996 American Heart Association meeting suggests that this may not be accurate.⁹ This study measured the myeloperoxidase content of granulocytes from two sites (aorta and great

Figure 1 Mortality of patients with unstable angina over time.

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Figure 2 Event free survival over 12 months according to CRP concentrations at hospital discharge.

cardiac vein) in patients who had stable angina with left anterior descending artery (LAD) disease, unstable angina and LAD disease, and unstable angina and right coronary disease (controls). There was no difference in the degree of granulocyte activation between the two sampling sites in patients with stable angina, but in patients with unstable angina and LAD disease there was evidence of granulocyte activation in the coronary circulation, with a lower myeloperoxidase content in the great cardiac vein than in the aorta. This finding is consistent with the theory of an inflammatory component in unstable angina. However, a similar pattern of granulocyte activation in the great cardiac vein was also found in patients with unstable angina and right coronary artery disease. This finding was unexpected because the right coronary circulation does not drain into the great cardiac vein. It therefore appears that inflammation in unstable angina is not localised to the site of the culprit lesion but is a more diffuse phenomenon occurring throughout the coronary circulation.

Indices of inflammation

If it could be shown that prognosis in unstable angina was linked to the severity of the inflammatory response, this would support the hypothesis that inflammation is an important pathogenic factor. Serum C reactive protein (CRP) concentrations provide a marker of the inflammatory response. CRP is a marker of interleukin 6 release (and hence interleukin 1 release) and offers a convenient method of measuring cytokine activation.^{10 11} CRP is easy to measure and has a half life of 19 hours, whereas interleukin 6 has a half life of six hours and the half life of interleukin 1 is very short. CRP concentrations are not increased in variant angina caused by spasm, even when the resulting ischaemia is severe, and any increase in concentrations in unstable angina are therefore not the result of necrosis. It is also important to stress the observation that while evidence of inflammation is detectable in most patients in whom infarction is preceded by unstable angina, it is detectable only in a

minority of those in whom infarction was totally unheralded.

PREDICTIVE VALUE OF CRP ON ADMISSION

A recent study of CRP in unstable angina enrolled 102 patients with Braunwald class 3B unstable angina.¹² Blood was taken for CRP estimation at the time of admission and compared with the eventual outcome. Out of 53 patients with an initial CRP > 3 mg/l, 13 (24.5%) went on to develop acute myocardial infarction (MI), whereas only two of 49 (4.1%) patients with an initial CRP < 3 mg/l developed MI. Other factors, such as chest pain or ECG changes, did not predict the development of MI, and the correlation between CRP and MI was independent of all other criteria studied. These findings, suggesting that admission CRP has a useful predictive role in unstable angina, provide additional support to earlier studies.¹¹

DISCHARGE CRP AND FUTURE COURSE

The concentration of CRP at the time of hospital discharge may also have predictive value. In one recent study, 49% of patients with Braunwald class 3B unstable angina had raised CRP concentrations (> 3 mg/l) at the time of discharge from hospital.¹³ At three months, CRP remained raised in almost all of them (47%), suggesting an ongoing process in these patients. A persistently raised CRP was related to a poor outcome. The patients with a normal CRP (< 3 mg/l) at discharge had a very low risk of further events during the next year, whereas the risk was approximately seven times greater among patients with raised CRP (fig 2).

Patients in this study were also investigated for evidence of an immune response to *Chlamydia pneumoniae*. Although there was evidence of chlamydial infection in some patients, it did not appear to have an independent predictive value. It is therefore not possible to draw firm conclusions about the role of chlamydia in unstable angina.

Discussion

Our understanding of the pathogenesis of unstable angina is still not complete. It is becoming increasingly clear that unstable angina is a multifactorial condition, with the balance of different factors varying from patient to patient. There is little doubt that thrombosis is central in this disease, but it may develop on a variety of different though interdependent backgrounds. For example, reduced coronary blood flow may be the result of thrombosis, a dynamic stenosis, or microvascular dysfunction (fig 3).¹⁴ We already know that the severity of atherosclerosis varies greatly among unstable angina patients.¹ Thrombosis itself may further contribute to reduced arterial flow through the production of vasoconstrictor agents. Depending on the reactivity of the local smooth muscle, the resulting vasoconstriction may then produce a dynamic stenosis that is superimposed over the original physical stenosis and may be sufficient to tip the patient into overt ischaemia.

Figure 3 Mechanisms for the development of myocardial ischaemia in unstable angina. Reproduced from Maseri¹⁴ with permission of Churchill Livingstone.

Conclusion

The precise mechanisms that precipitate coronary thrombosis and cause it to become a mechanism of disease rather than remaining a natural repair process of vascular injury are largely unknown. At present the focus of treatment is based on the development of more and more powerful antithrombotic agents. However, this approach necessarily implies that the alteration of the haemostatic equilibrium of the whole body occurs in order to prevent and treat a local thrombotic event.¹⁴ Additional, more specific forms of treatment could become available from a better understanding of the mechanisms that determine the immunological¹⁵ and inflammatory¹⁶ responses in unstable angina and the absence of any detectable

inflammatory response in most patients with unheralded infarction.¹¹

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