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Concepts in Acute Coronary Syndromes

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ABSTRACT

Landmark pathological studies have deepened our understanding of the mechanisms behind acute coronary syndromes over the last decade. Thrombosis plays a key role and is a unifying feature in the pathogenesis. Platelet-rich thrombus superimposed over the disrupted atherosclerotic plaque or eroded plaque endothelium, with or without fibrin-thrombus extension, is evident in post-mortem necropsy, angiographic and angioscopic studies. However features which contribute to the risk of acute events lie in the atherosclerotic plaque itself. Plaque content and not plaque size is the important factor. A vulnerable plaque may be invisible on clinical stress testing and even coronary angiography; but it is prone to rupture if it has only a thin cap and a proportionally larger lipid core. There is a cellular preponderance of activated macrophages and T-lymphocytes; and high activity of matrix metalloproteinases in vulnerable plaques. Smooth muscle cell proliferation and collagen synthesis are downregulated. These features may serve as possible targets for detecting plaques at risk or for reversing the risk of vulnerable plaques.

Keywords: thrombosis, angiographic, atherosclerotic plaque

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Acute coronary syndromes (ACS) consisting of unstable angina, non-Q wave and Q wave myocardial infarction have been the subject of extensive research in the last decade. An understanding of the pathophysiology underlying these syndromes will help to explain clinical observations and provide the basis for targeting treatment. The well-known culprit atherosclerotic plaque consists of a fibrous cap, lipid core, varying proportions of inflammatory infiltrates (mainly T-lymphocytes and macrophages) and smooth muscle cells. It is now clear that the unifying pathology in acute coronary syndromes is the occlusion of the coronary artery by a platelet-rich thrombus superimposed on disrupted plaque or eroded endothelium of the plaque[1]. Coronary artery spasm, embolism and coronary artery or aortic dissection are the other rarer causes. Well-described post-mortem studies have shown that there may be two separate precipitating processes before thrombosis occurs over a plaque[2]. 25% of post-mortem patients were found to have only endothelial erosion or denudation over the plaque surface. The remaining had the better known plaque disruption or tearing of the plaque cap. Endothelial erosion seems to be the predominant process in females compared to males[3].

Plaque content not plaque size

This is a key concept in ACS pathophysiology. In pathological studies it was shown that most infarct-related arteries had no flow-limiting stenoses[4]. In necropsy specimens of patients dying from acute cardiac events where thrombi were found over disrupted plaques, >60% of the lesions had <60% stenosis[2]. Angiographic studies performed after thrombolysis during acute myocardial infarction have shown that the atherosclerotic lesions giving rise to the occlusive thrombus indeed did not have high grade stenoses in many cases. Indeed vulnerable plaques occur across the full spectrum of stenosis severity[5]. The previous notion that with increasing stenosis, the relatively proportion of the plaque occupied by acellular fibrous tissue or the lipid core also increases has been disproved by various necropsy, angiographic and angioscopy studies[1-3,5,11]. The more likely concept is that the degree of plaque vulnerability lies not in the plaque size or stenosis severity but on the make-up of the plaque itself. This is in keeping with the familiar scenario where a negative angiogram or stress test can mislead us about the potential for an acute coronary event. Angioplasty and surgical revascularisation serve to restore the blood flow to sites beyond significant stenoses and ameliorate angina but the greater the stenosis does not necessary mean the higher the risk of an acute event. Indeed, there is a positive remodelling process seen in atherosclerosis where as plaque increases in the vessel wall, there is compensatory enlargement of the vessel area and

increase in external diameter of the vessel seen together with adventitial area increase, ultimately preserving lumen area[6]. For many years or even decades, the plaque passes through this phase of formation by bulging outwards adluminally rather than encroaching on the arterial lumen. Significant plaque protrusion into the lumen and visibility on angiography comes only after the plaque burden approaches half of the luminal area. Clinically those with highly stenotic plaques would have had time to develop good collateral circulation so that thrombosis compromise would have less impact on coronary perfusion. With increasing stenosis, it has also been observed that circumferential peak stress on the plaque cap gets gradually less. This is over and above recent findings that chronic clinical or subclinical ischaemia in the form of stable angina may produce the phenomenon of preconditioning where such patients actually become protected as a result of the anginal episodes so that infarct-size is significantly reduced[7]. Again, this bodes ill for the individual who may be completely unaware of an existing small nonstenotic but vulnerable atheromatous plaque. Collaborating evidence is also seen in cholesterol lowering trials where although therapy failed to decrease the degree of established coronary stenosis, there was consistent success in preventing acute coronary events[8].

Correlating the clinical syndrome with pathophysiology

Recognised factors which put a plaque at risk are a large lipid core, a thin friable cap, high macrophage density and reduced smooth muscle cell content. Macrophage derived tissue factor found in abundance in the lipid rich core of the plaque is largely responsible for its intense thrombogenicity. The integrity of the fibrous cap overlying this lipid rich core however determines the stability of the plaque[9]. Rupture-prone plaques have thin friable caps which when torn, exposes the thrombogenic substrate to circulating blood and, in the presence of other prothrombotic factors, lead to thrombus formation. Different degrees of thrombus formation over the fissured plaque manifest in a spectrum of conditions. In its mildest form, minor intralesional platelet thrombus may be associated only with the intimal layer and contribute to plaque growth by stimulating further thrombin-mediated smooth muscle cell proliferation. Subclinical thrombosis plays an important part in the development of chronic stenoses that gives rise to stable angina[9]. In an autopsy study of patients with coronary atheroma who died of sudden noncardiac causes, 17% had small recent plaque disruption with thrombus within the lipid core[10]. Subjects who died of major plaque disruption had on an average, 2.5 smaller plaques elsewhere with evidence of minor disruption and thrombosis[11].

Where there is intraluminal extension of the thrombus, it may remain mural and non-occlusive. The white thrombus seen in these cases is platelet - and fibrin-rich with an outer layer of activated platelets. Where there is occlusive thrombus extension, red thrombus (consisting of fibrin and red cells) forms over the white platelet thrombus in a process dependent on stasis. Very few platelets are found in the luminal extension[12]. Although not strictly accurate, unstable angina is the condition associated with mural white platelet thrombus whilst acute myocardial infarction is seen with luminal extension of the occlusive red fibrin thrombus. This in part explains why thrombolysis, which acts against well against fibrin thrombus, has been effectively used in acute myocardial infarction but not in unstable angina. Non-Q MI represents a technically confusing territory. In one study, 75% of patients with non-Q MI were shown to have a patent infarct-related artery (IRA) whilst 25% had occluded IRA with well-perfused collaterals[9]. This suggests that there could be a range of pathology giving rise to the clinical condition seen as non-Q MI. Individuals with luminally non-occlusive thrombus develop non-Q MI or unstable angina depending on the duration of occlusion. In individuals with luminally occlusive disease, the presence or absence of well-developed collaterals determines whether non-Q MI or Q MI develops.

Cellular interactions in the plaque (see Fig. 1)

Emerging evidence has linked a) atherosclerosis development from an initial fatty streak to an atheromatous plaque, and b) acute clinical or subclinical plaque events to inflammatory processes. At the lesion site circulating macrophages and leukocytes adhere to and migrate through the vessel wall via interactions with cell adhesion molecules[13]. Macrophages or monocytes imbibe lipid and

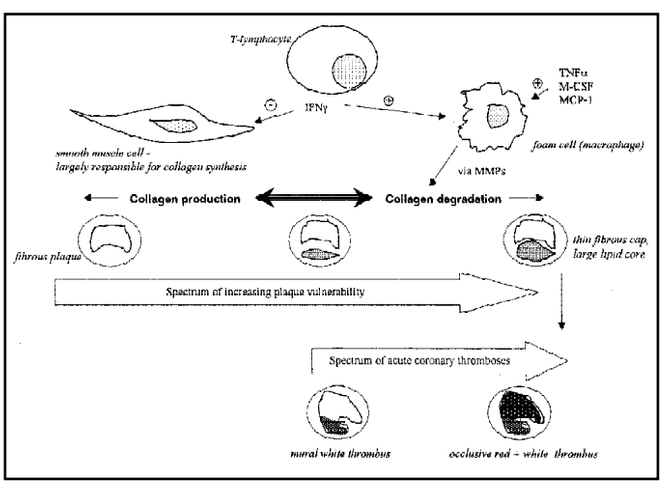

Fig. 1 Cellular interplay correlating to clinical pathology in acute coronary syndromes.

cholesterol and become incorporated into the lesion as lipid-laden foam cells. Foam cells are critical in a plaque because when activated they release special matrix metalloproteinases which are capable of degrading otherwise resistant fibrillar collagen and various matrix components[14]. This process contributes to the weakening of the fibrous cap and increases the risk of acute events. Regions in the fibrous cap relatively prone to disruption have been shown to contain an abundance of macrophages and T-cells[15]. T-lymphocytes have been shown to release the cytodine IFNy when activated by oxidised LDL and various other infectious agents including autoantigens like heat shock proteins[4]. IFN8 has specific actions on impairing smooth muscle cell synthesis of collagen, inhibiting smooth muscle cell proliferation in situ[16] and possibly also promoting foam cell activation. These functions effectively lead to further plaque cap weakening. Contrary to the preoccupation in post-angioplasty restenosis reduction where the aim has been to inhibit smooth muscle cell migration and proliferation, downregulation of the smooth muscle cell activity in atherosclerotic lesions seem to confer damage to plaque stability.

Oxidant factors like oxidised LDL and homocysteine, which is thought to promote peroxide production, may also contribute by switching on the apoptotic cell death apparatus[17]. Macrophage apoptosis allows the accumulation of extremely thrombogenic extracellular lipid in the plaque core. Apoptosis of smooth muscle cells results in reduced levels of collagen production. It is not clear yet how the balance of apoptosis within an atherosclerotic lesion contributes to plaque vulnerability. Indeed the challenge remains to discover what determines the vulnerability index in patients (ie the ratio of stable plaque to vulnerable plaque).

Possible applications

These concepts could provide a possible basis for developing investigative tools that can be used to detect unstable plaques.

Currently there is a myriad of diagnostic tests available for investigating a symptomatic patient with angina. Among these, coronary angiography, the gold-standard by most accounts, is used to demonstrate structural stenoses. In patients with unstable angina or acute myocardial infarction it is useful for risk stratification and is certainly required if the patient remains symptomatic despite therapy (ref). More recently, magnetic resonance (MR) angiography has come to provide a non-invasive means to do the same. By gating for respiration and ECG or by breath-holding, MR angiogram can be done during peak systole and mid-diastole (during which there is maximum coronary arterial blood flow) to give a fairly sensitive indication of the stenotic coronary lesions[18]. Electron beam computed tomography (EBCT) has been proposed as yet another non-invasive means for detecting early coronary artery disease[19]. ln a similar way to MR imaging, images in EBCT can be obtained at various times during the cardiac cycle by ECG gating. EBCT has an added edge in that it can provide transaxial cardiac images with excellent spatial and temporal resolution, capable of various forms of post-processing including multiplanar reconstruction and shaded surface display. It can be used to detect and quantify not just the degree of stenosis but was in fact designed to also detect the coronary calcification load in plaques. Resolution and sensitivity in MR angiography and EBCT can be further enhanced if the patient is given intravenous contrast.

However, all these diagnostic modalites primarily demonstrate degree of stenoses in coronary arteries. It is still debatable if coronary calcification load is reflective of plaques at risk[20]. Identifying culprit stenotic lesions that may be the cause for limiting angina is done readily with this host of tests but the definitive challenge remains to find a tool which can be used in an asymptomatic individual to detect the presence of vulnerable plaques. This tool could then also be used obviously in a patient with symptoms to localise the lesion at risk. Plaques at risk are often angiographically invisible and patients with stable angina are just as likely to have many or just few vulnerable plaques.

Perhaps the intravascular ultrasound (IVUS) device comes closer at the moment to providing images of plaque fibrous and 'gruel' components under optimum conditions[21] Unfortunately, IVUS images are easily distorted by calcification. Minor position changes in the probe have been shown to produce variable changes in measurements. IVUS cannot give information on macrophage content. Coronary angioscopy which has been discussed briefly above, can show plaque surfaces and hence give a hint as to which plaque is vulnerable. Even so limitations to the technique exist. Not least, these are expensive invasive procedures not entirely justifiable for an asymptomatic individual. Casscells et al have shown that heat detectors in the form of thermistors or an infrared camera can be used to identify heat generating activated macrophages[22]. This remains a technology to be tested clinically for intracoronary plaques[23]. With rapidly expanding technology in PET and SPECT, it may become possible to use markers to identify plaques at risk if a suitably specific target is

found in such lesions. Indeed these are possible candidates for the ideal non-invasive 'screening' test to detect vulnerable plaques.

In addition, biochemical markers have been identified which may be useful in the risk assessment of acute syndromes[24]. Mediators of the inflammatory response such as acute phase proteins, cytokines and cellular adhesion molecules are potential markers which go a step beyond markers of myocardial necrosis like CK-MB, cardiac troponins and myoglobin. A recently developed high-sensitivity assay for c-reactive protein (hs-CRP) is being investigated for such purposes[25]. Nonetheless it is still difficult at present to get a handle on how confounding factors of non-cardiac inflammatory processes may be accounted for in such tests.

In terms of therapeutics, studies suggest that antioxidant therapy may have effectively reduced cardiac mortality through mechanisms which stabilise the atheromatous plaque[26,27]. Cholesterol lowering appears to have a similar effect through the processes of reducing lipid core size, decreasing macrophage infiltrate, reducing matrix metalloproteinase activity and reducing apoptotic activity within the plaque[28]. Endothelium-mediated vasodilatation has been shown to improve with cholesterol-lowering and antioxidant therapy[29]. In recent randomised trials, vigorous cholesterol-lowering by low fat diet and cholesterol-lowering drugs (such as pravastatin in 4S and CARE) resulted in stopping progression or partial regression of coronary artery disease in up to 85% of treated subjects[8,30-32]. The anatomical regression in these trials was only modest – 3-10% diameter stenosis regression depending on stenoses severity at baseline. But the impressive reduction in clinical events (cardiac death, MI, need for revascularisation) was substantially larger – 30-85%. This again underscores the poor association between lesion size (degree of stenosis) and event rates (risk of an acute coronary event).

Based on a better understanding of the processes behind acute thromboses and platelet aggregation, new targets for antiplatelet therapy have been identified. Traditionally, aspirin has been used to irreversibly inhibit platelet cyclooxygenase, which is one of many enzymes leading to platelet activation. Ticlopidine is another platelet antagonist which acts by inhibiting the signal transduction pathway involving ADP. Clopidogrel acts in a similar way as ticlopidine but is without the associated risk of neutropenia. Glycoprotein IIb/IIIa receptor inhibition however appear to be the most potent form of platelet antagonism presently. Pathways which lead to platelet aggregation appear to converge to amplify the expression of GP IIb/IIIa receptors on the platelet surface which in turn bind its ligand, fibrinogen[33]. Fibrinogen in turn forms bridges between platelets and ultimately result in platelet aggregation and platelet thrombus. Of relevance to acute coronary syndromes, GP IIb/lIIa inhibition has been used in large-scale randomised trials (PRISM, PRISM-PLUS, PURSUIT, PARAGON and PARADIGM) but the efficacy is still being debated[34-36].

Treatment directed at the ensuing thrombotic process after a plaque ruptures is important in the context of a patient suffering from the acute event. But as the processes that lead to plaque rupture itself unfold through experimental and clinical investigations, the opportunity arises to direct therapy towards stabilising the vulnerable plaque at risk. As mentioned before, antioxidant and cholesterol-lowering therapy appear to be effective via this means. In addition, possible targets for halting the progress of an atherosclerotic lesion appear to be downregulation of T-lymphocyte and macrophage activity or promoting collagen deposition to strengthen the fibrous cap. Various tools such as genetic manipulation using antisense oligonucleotides are being studied[37]. This invariable implies the need to further dissect the molecular mechanisms behind the variety of plaque cellular components.

CONCLUSION

Negative angiographic or functional noninvasive echo or nuclear test results have been known to give patients and even physicians a false sense of security. The pathology behind acute coronary events shows that indeed it is the plaque content and not the size that confers vulnerability or instability. Vulnerable plaques are unfortunately often angiographically invisible. Tools that can be used to confidently detect vulnerable plaques before rupture remain to be discovered. Such a tool will take a place to become as ubiquitous as the coronary angiogram is today. When it one day becomes possible to identify vulnerable nonstenotic plaques, hopefully it would by then be possibly also to provide treatment to reverse the vulnerability.

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