Acute Coronary Syndromes I: Recent Advances in Pathogenesis

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Summary

New knowledge on the pathogenesis of the acute coronary syndromes provides the clinician with a better understanding of these important, often life-threatening, events and opens up new ways of managing them. The identification of the vulnerable plaque whilst important and possible pathologically still requires elaborate and often invasive methods. The central role of inflammation and the platelets in these syndromes has already been translated into practical therapeutics. Identifying and predicting which plaque would rupture and thereby facilitating the formation of an acute obstructive thrombus continue as major challenges to the clinician, but, in the meantime, regressing and stabilising these plaques are achievable goals.

Key Words: Acute coronary syndrome, Vulnerable plaque, Platelets, Thrombosis, Pathogenesis

Acute coronary syndromes are clinical entities whose basic pathogenetic mechanism is the onset of an abrupt, marked reduction in coronary blood flow leading to myocardial ischaemia or even necrosis. These entities consist of unstable angina, non-Q acute myocardial infarction (AMI), acute myocardial infarction and a newly recognised entity, minor (or perhaps more accurately termed, acute) myocardial injury. Acute thrombosis after coronary angioplasty or stenting may also be considered an acute coronary syndrome, although this is not 'natural' and very much iatrogenic. The consequences of these syndromes are considerable and the substantial impairment to the prognosis of patients suffering from these entities is well known. For instance, AMI is associated with a 27 - 44% 1-year mortality[1] while unstable angina is associated with a 12 - 17% risk of AMI[2-3]. Minor myocardial injury, rather surprisingly, has a prognosis almost similar to that of AMI[4-5]. Be it the case, the tremendous improvements achieved by recent treatment modalities for these entities are truly impressive. With the use of thrombolytic therapy, for example, mortality from AMI has been reduced by an overall rate of 27%[6]. Further, the long-term prognosis of AMI has also been improved by other measures such as the use of beta-blockers, aspirin, angiotensin converting enzyme inhibitors, and HMG-CoA enzyme inhibitors.

Pathogenesis of Acute Coronary Syndromes

The pathologic basis for coronary artery disease is most commonly due to atherosclerosis. A number of pathologic processes are involved, including:

i. inflammation involving permeability and activation of the endothelium[7-8], and recruitment of the monocytes[9-10]
ii. growth through proliferation and migration of the smooth muscle cells[11-12] as well as matrix synthesis[13]
iii. degeneration which includes principally accumulation of lipids[14-15]
iv. necrosis through the cytotoxic effects of lipid oxidation[16-19]
v. active calcification[20]
vi. thrombosis with platelet activation and fibrin formation[21-23]

With the growth of the atherosclerotic plaque, the lumen of the coronary artery gets progressively narrower with time. When the plaque causes a critical narrowing in the lumen (usually at least a 75% diameter narrowing, giving a 90% reduction in coronary flow), myocardial ischaemia occurs giving rise to perhaps, angina pectoris. It is tempting to follow the concept to its logical conclusion, ie. with complete narrowing of the coronary lumen by this atherosclerotic plaque, total cessation of blood flow occurs giving rise to AMI. Angioscopic studies on patients with AMI over the last decade showed that this was not the case. These studies showed that total occlussion of the coronary artery was due to the formation of a thrombus overlying the atherosclerotic plaque[24-29]. Falk[30-31] and Davies[32] took these observations further by demonstrating that there were tears, fissuring, rupture of the fibrous cap and haemorrhage into the plaque over which the occluding thrombus then formed. With the disruption of the fibrous cap of the plaque, the plaque contents which, composed of cholesterol, smooth muscle cells, fibrous tisssue, etc, are highly thrombogenic induce the formation of the thrombus. On the other hand, it is also observed that in a minority of plaques there is superficial intimal erosion or denudation of the fibrous cap. This tends to be associated with pre-existing severe atherosclerotic stenosis[33-35].

These observations lead to a number of questions regarding plaque rupture and some answers are already available albeit preliminary in some. Some of these questions are:

a. Why do plaques rupture?
b. Which plaques tend to rupture?
c. When do plaques rupture?
d. Can the vulnerable plaque be identified?
e. Can plaque rupture be avoided?

Why do plaques rupture?

A combination of physical, mechanical, biochemical and biological factors seems to predispose, initiate and perhaps trigger plaque rupture. A number of intrinsic properties and extrinsic forces on the plaques have been identified to underlie this mechanism. Inflammation of the fibrous cap seems to be an important pathogenetic factor, causing the thinning of the cap thereby predisposing it to instability and propensity to rupture. Foam cell or macrophage infiltration of the disrupted fibrous cap has long been observed[30, 36-39]. It has also been noted that these cells are activated and involved in a process of inflammation[40]. Shoulder regions of eccentric lesions are sites of macrophage infiltration[41-43], active inflammation[30,38-39] and disruption[34]. Mechanical testing shows that macrophage infiltration weakens the cap locally, thus reducing its tensile strength[44]. These macrophages weaken the cap by degrading extracellular matrix through phagocytosis and secreting proteolytic enzymes such as plasminogen activators and metalloproteinases[45]. These macrophages also promote thrombin generation and acute thrombus formation over the disrupted plaques[46-47]. Other inflammatory cells involved in this process include mast cells[48] and neutrophils[8,35,49].

Biomechanical stresses experienced by the atheromatous plaque also contribute to the process of plaque disruption. These stresses have been identified as tensile stress (as provided by chronic as well as acute elevation of the blood pressure[44]), compressive stress (as present during vasospasm[38,50]), circumferential bending stress (as is consequent to the propagating pulse wave [51]), longitudinal flexion stress (as provided by the beating heart on the tethered coronary artery[52]) and haemodynamic stress (as caused by high blood velocity in stenotic lesions[53]).

Which plaques tend to rupture?

While it seems plausible that the bigger plaques (thus associated with more reduction in coronary blood flow) are the culprit lesions, a number of investigators testify to the contrary. Lesions which rupture tend to be the smaller and perhaps newer and earlier lesions which are identifiable angiographically as those with mild to moderate degree of stenosis[22,54,56]. These lesions tend to have a thin fibrous cap, a large vulnerable atheromatous pool mainly in the form of cholesterol esters[57-58], a high content of monocytes and macrophages and less amounts of collagen-rich matrix. These lesions have been termed the vulnerable plaques. The more stenotic lesions do progress to more severe or even complete occlusion. However this is usually

not accompanied or punctuated by myocardial infarction, probably due to the presence of well-developed collateral supply [59-60].

Thus conceptionally, there are plaques which tend not to rupture but keep on growing causing progressive obstruction to the coronary blood flow which may give rise to angina and perhaps result in chronic myocardial damage such as myocardial hibernation (reversible) or ischaemic cardiomyopathy (irreversible). On the other hand, there are plaques which are vulnerable to rupture and fissure giving rise to acute thrombosis, thus causing acute obstruction to the coronary flow leading to unstable angina or AMI. Which of these entities that the patient ends up with seems to depend on the extent and duration of the acute occlusive thrombus formed. Unstable angina and non-Q AMI seem to be associated with transient and incompletely occluded thrombus while transmural myocardial infarction tends to be associated with a completely occluded stable thrombus[23]. Overall vascular tone and collateral flow also act to modify the effect of these processes on the resultant myocardial perfusion[61].

When do plaques rupture?

It has been observed that acute coronary events do not occur evenly through-out the twenty-four hours. There is a propensity for these events to occur in the morning hours[62-65], during cold weather[66-67], emotional stress[68] or vigorous exercise[69]. Although so far no direct reason is put forward to account for this phenomenon, a number of observations may provide corroborative evidence and a pathogenetic basis why this is so. It has been noted, for instance, that the blood pressure and heart rate tend to rise in the morning hours providing an increased stress on the endothelium, the fibrous cap and the atherosclerotic plaque[70]. This then results in increased oxygen demand leading to transient, acute myocardial ischaemia. Further, the blood is more thrombogenic in the early hours with an increase in platelet aggregability[71-72], increased blood viscosity[73], impaired fibrinolysis[74-75] and vasoconstriction[76-77]. These intriguing observations should provide the clinician with a window of opportunity for intervention both in terms of the choice of therapy and in the delivery of the therapy such as drug dosing. For instance, one has to ensure that in a hypertensive patient particularly with ischaemic heart disease, the blood pressure control is truly over the twenty-four hours and that there is no period (often pre-dose at the trough of the anti-hypertensive agent) during which the drug may be suboptimal (occurs especially with drugs with low trough-peak ratio).

Can the vulnerable *plaques* be identified?

The composition and the pathophysiological mechanisms within these lesions give an opportunity for these lesions to be identified before they rupture and cause thrombosis. Coronary angiography, for long a gold standard in identifying and quantifying luminal narrowing in the coronary arteries, has been shown to have considerable limitations in assessing the endothelium and the arterial wall especially in characterising the plaques. New diagnostic modalities such as coronary angioscopy[26-29] and intravascular ultrasound, IVUS[78-79] have made major contributions in elucidating the morphologic characteristics of these lesions. IVUS, for instance, can differentiate the thin cap from a thick cap. The lipid pool within the plaque could be identified and the size estimated by IVUS. A major drawback of these techniques though is their cost and invasive nature. Whether with time, new imaging modalities such as electron-beam computerised tomography or 3-D echocardiography or other non-invasive diagnostic methods may be able to identify these lesions is interesting to speculate.

Can plaque rupture be avoided?

All these understanding on pathogenesis and even efforts to identify these vulnerable plaque will have little clinical utility if its natural history cannot be intervened and changed. If upon intervention, the clinical outcome is improved through a reduction in the incidence of acute coronary syndromes, for instance, one can surmise that the plaque may have been stabilised and that plaque rupture can be avoided and not inevitable after all.

In this respect, primary and secondary preventive measures have consistently shown a marked benefit not only on mortality but also on morbidity. Lipid lowering agents[80-82], ACE inhibitors[83-84], beta-blockers[85-

[86], calcium channel blockers[87-88], and change in life style such as smoking cessation[89-90] have all, to varying extent, been shown to effect a beneficial effect on the prognosis of patients with coronary artery disease. This may come about either by prevention of atherosclerotic plaque progression, or promotion of regression, or stabilisation of these plaques or a combination of these effects.

Clinical Implications

These new observations and concepts, whilst important in themselves, provide the clinician with new opportunities for intervention. They provide an explanation why mechanical revascularisation such as coronary artery bypass surgery, coronary angioplasty and stenting, though effective in reducing angina episodes for instance, may not necessarily influence the incidence of myocardial infarction. These mechanical strategies tend to address the large, flow-limiting plaques and not the mild-to-moderate nonflow-limiting but none-the-less plaques which are vulnerable to fissure and rupture.

The role of acute thrombus formation on a fissured, disrupted plaque brings to the fore the pre-eminent importance of thrombolytic therapy in the management of AMI and the use of anti-platelets and perhaps other anti-thrombotic agents in AMI and unstable angina. However, which thrombolytic agent (streptokinase or tisssue plasminogen activator, tPA, for instance) and how to give these agents (front-loaded or conventional infusion of tPA, for example) as well as which adjuvant therapy to adopt are important yet unsettled issues. The use of mechanical revascularisation strategies for these acute coronary syndromes by angioplasty with or without stenting, thus directly dealing with the underlying atherosclerotic plaque, is hotly debated in the literature. These issues will be discussed in detail in Part II of this series.

Conclusion

New knowledge on atherosclerosis brings about a clearer understanding of this common pathologic process and its consequences. Disruption of the plaque and the formation of an acute occluding potentially life-threatening thrombus are two major events which need be considered when addressing the acute coronary syndromes. These concepts enable newer opportunities for intervention and management. The identification of the vulnerable plaque ante-mortem continues to defy the clinician. Such accomplishment may enable yet further inroads into controlling this menace.

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QUIZ ON ACUTE CORONARY SYNDROME

1. Clinical entities of acute coronary syndrome include:
   a. unstable angina
   b. refractory angina
   c. acute myocardial infarction
   d. non-Q acute myocardial infarction
   e. minor myocardial injury

2. The underlying mechanisms involved in acute coronary syndromes are:
   a. progressive narrowing of the coronary lumen by atherosclerotic plaque
   b. erosion of the fibrous cap
   c. fissuring of the fibrous cap
   d. platelet adhesion to the endothelium overlying the plaque
   e. acute thrombus formation

3. Plaques predisposed to fissuring are those with:
   a. a large lipid core
   b. thin fibrous cap
   c. massive infiltration by inflammatory cells
   d. lipid content consisting mainly of crystalline cholesterol
   e. small size

4. The following predispose to plaque rupture
   a. surges of increased blood pressures
   b. cold weather
   c. emotional upheavals
   d. vigorous exercise
   e. regular exercise

5. The following statements are true:
   a. vulnerable plaques can be identified
   b. platelet aggregability is an important component in the pathogenesis of acute coronary syndromes
   c. stabilisation of plaques is achievable
   d. coronary angiography identifies vulnerable plaques
   e. regression of plaques is possible