Rapid coronary artery disease progression and angiographic stenosis morphology

Juan Carlos Kaski

Coronary Artery Disease Research Unit, Department of Cardiological Sciences, St. George s Hospital Medical School, London, UK

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It is established that the progression of coronary artery disease is neither linear nor predictable. The unpredictable and often episodic nature of coronary disease progression can be explained by rapid increase of stenosis severity due to thrombosis, which occurs as a complication of the atherogenic process. Rapid coronary stenosis progression is most often responsible for the acute clinical manifestations of coronary artery disease, i.e. sudden cardiac death, acute myocardial infarction and unstable coronary syndromes. Recently, it has been shown that stenosis progression, whether clinically silent or associated with acute coronary events, is a strong predictor of cardiovascular risk.

Atheromatous plaques associated with rapid coronary artery disease progression have well defined anatomo-pathological characteristics and are usually termed vulnerable or unstable , terms which indicate both their propensity to acute disruption and increased thrombogenicity that may lead to the development of acute coronary events.

Plaques have been regarded, in the past, as being inert and staying almost unchanged for years. However, they are very active entities. The fibrous cap is in a balance between smooth muscle cells producing collagen and the macrophages degrading collagen. The thickness of the cap depends on the relative activity of those two components and there is, therefore, a danger of the fibrous cap rupturing.

Although only a relatively small proportion of all coronary artery lesions in patients with angina pectoris undergo complications that lead to fibrous cap disruption and acute coronary events, these stenoses are responsible for the majority of cases of serious coronary events. Thus the identification of vulnerable plaques that may lead to increased risk of coronary events will most certainly help in the rational management of patients with coronary artery disease.

Angiographic studies have indicated that complex lesion morphology is associated with increased risk of myocardial infarction and ulcerated plaques identify vulnerable lesions. We therefore reasoned that the identification of angiographically complex coronary stenoses could provide a valuable marker of cardiovascular risk in relation to rapid disease progression.

Our group sought to investigate the role of angiographically complex lesions as a marker of rapid disease progression in different clinical settings. We took advantage of the fact that patients with stable angina pectoris requiring routine myocardial revascularisation in our institution are put on waiting lists.

We observed that complex lesions progressed more than smooth stenoses of similar severity both in patients presenting with stable angina and in patients presenting with unstable angina.

Why complex plaques should be particularly vulnerable to rapid stenosis progression is speculative. In this paper we discuss the possible mechanisms that may explain an association between complex stenosis and acute coronary events.

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Address:

Prof. Juan Carlos Kaski, MD

Coronary Artery Disease Research Unit
Department of Cardiological Sciences
St. George s Hospital Medical School
Cranmer Terrace
London SW17 0RE, UK
E-mail:
jkaski@sghms.ac.uk

It is established that the progression of coronary artery disease is neither linear nor predictable[1]. The unpredictable and often episodic nature of coronary disease progression can be explained by rapid increase of stenosis severity due to thrombosis, which occurs as a complication of the atherogenic process. Rapid coronary stenosis progression is most often responsible for the acute clinical manifestations of coronary artery disease, i.e. sudden cardiac death, acute myocardial infarction and unstable coronary syndromes[2]. Recently, it has been shown that stenosis progression, whether clinically silent or associated with acute coronary events, is a strong predictor of cardiovascular risk[3,4]. Studies have demonstrated that atheromatous plaques of individuals who died suddenly or had suffered episodes of unstable angina or myocardial infarction, characteristically show a fissure of the fibrous cap that allows the contact between the atherosclerotic material contained in the core of the plaque and the circulating blood to take place[2]. This leads to the formation of an intracoronary thrombus whose magnitude and clinical impact will largely depend on local and systemic factors such as the

size of the tear of the fibrous cap and the thrombogenic-fibrinolytic activity of the individual patient at a given time. Plaque fissuring, however, is not the only mechanism responsible for acute intracoronary thrombosis as this may also result from the erosion of the endothelium in the absence of plaque rupture[5]. Atheromatous plaques associated with rapid coronary artery disease progression have well defined anatomo-pathological characteristics and are usually termed vulnerable or unstable , terms which indicate both their propensity to acute disruption and increased thrombogenicity that may lead to the development of acute coronary events[2]. These atheromatous lesions have a large lipid core and a thin fibrous cap which alter the biophysical and geometric properties of the plaque reducing both its strength and stability. More importantly perhaps is the fact that vulnerable plaques are the site of intense inflammatory activity[6]. Plaques have been regarded, in the past, as being inert and staying almost unchanged for years. However, they are very active entities[7]. The fibrous cap is in a balance between smooth muscle cells producing collagen and the macrophages degrading collagen. The thickness of the cap depends on the relative activity of those two components and there is, therefore, a danger of the fibrous cap rupturing[7]. Unstable plaques contain a large number of activated macrophages and T-lymphocytes and also show increased expression of a diversity of pro-inflammatory cytokines, tissue factor and endothelin-1. Activated macrophages synthesize proteases, i.e. the metalloproteinase family, that degrade the collagen matrix of plaques and may thus contribute to plaque disruption[8]. The lipid core occupies a space in the connective tissue of the plaque and is packed with free extracellular cholesterol. Macrophages contribute to the growth of the lipid core by digesting the connective tissue matrix. The synthesis of metalloproteinases by the macrophages is increased in the presence of pro-inflammatory cytokines and reduced by the administration of antioxidant agents and lipid lowering interventions[9]. Metalloproteinases digest the collagen matrix so that the core gets bigger. But, at the same time, the macrophages fill the core up with cholesterol as they contain ingested cholesterol. The core thus expands due to the activity of macrophages. Interestingly, however, plaques exist which contain no macrophages and the core is just an empty hole filled with cholesterol[7].

Although only a relatively small proportion of all coronary artery lesions in patients with angina pectoris undergo complications that lead to fibrous cap disruption and acute coronary events, these stenoses are responsible for the majority of cases of serious coronary events. Thus the identification of vulnerable plaques that may lead to increased risk of coronary events will most certainly help in the rational management of patients with coronary artery disease. On average, patients may have 20 or more plaques in a coronary artery, none of which will be identical to each other[7]. The patient may have one plaque that has the characteristics of vulnerability or, on the other hand, may have most of the plaques having those characteristics[7].

Stenosis severity and plaque vulnerability

There is no relation between the degree of stenosis and the characteristics of vulnerability. A vulnerable plaque may cause no stenosis or quite high-grade stenosis. Interestingly, most plaques that are vulnerable do not cause stenosis visible on angiography[7]. Indeed, stenoses that progress rapidly due to plaque disruption or endothelial erosion are not necessarily the most severe. Studies have shown that coronary lesions underlying myocardial infarction are often of moderate severity[10]. A recent report[11] from our group has shown that the severity of a preexistent coronary artery stenosis did not play a crucial role in determining rapid disease progression in patients with chronic stable angina and those with unstable angina. In our study a similar proportion of stenoses > 50% diameter reduction and lesions < 50% progressed rapidly[11]. We observed that total coronary occlusion in our study[11] developed more often at the site of mild lesions than in segments with severe diameter reductions. Thus, angiographic severity does not provide a useful marker of rapid coronary artery disease progression. This is despite the fact that angiography continues to be the gold standard regarding the anatomical characterisation of coronary artery disease, i.e. its presence, its extent and its severity.

Angiographic morphology and coronary events

Angiographic investigations by Ambrose et al.[12,13] showed that complex coronary artery stenoses are more commonly found in patients who develop myocardial infarction and unstable angina compared to patients with chronic stable angina. Complex plaques are likely to represent ulcerated lesions, disrupted plaques undergoing healing and stenosis with increased thrombogenic potential. In 1982, Levin and Fallon[14] suggested that coronary artery stenoses with complicated angiographic morphology are likely to represent the clinically more dangerous type . The so-called complicated or complex stenoses have irregular borders, overhanging edges and intracoronary thrombi. More recently, Davies et al.[15] found a strong correlation between stenosis morphology and hospital outcome in patients who underwent thrombolysis for myocardial infarction. Angiographic studies have indicated that complex lesion morphology is associated with increased risk of myocardial infarction[16] and ulcerated plaques identify vulnerable lesions. We therefore reasoned that the identification of angiographically complex coronary stenoses could provide a valuable marker of cardiovascular risk in relation to rapid disease progression[17].

Based on this background information our group sought to investigate the role of angiographically complex lesions as a marker of rapid disease progression in different clinical settings. We took advantage of the fact that patients with stable angina pectoris requiring routine myocardial revascularisation in our institution are put on waiting lists. Patients on the waiting list undergo routine angiography on at least two occasions: the first being the diagnostic angiogram and the second the angiography that is carried out either immediately preceding angioplasty or at the time of acute events, when these occur. All patients included in our studies were angina patients who underwent routine coronary arteriography and were considered to be candidates for routine, non-urgent coronary angioplasty. These patients were followed regularly whilst on the waiting list until revascularisation was carried out or the patient experienced an acute coronary event, defined as unstable angina requiring urgent hospital admission, non-fatal myocardial infarction and cardiac death. We used computerised coronary arteriography for the assessment of all coronary artery stenoses. Qualitative assessment was also carried out in every case and coronary lesions classified as complex and smooth . Our studies showed that compared to smooth lesions complex stenoses were more likely than to be associated with both rapid increase of severity and the development of acute coronary events. Briefly, in 1995 we studied the role of complex stenosis morphology in rapid disease progression in 94 consecutive patients awaiting routine coronary angioplasty[11]. Coronary arteriography was repeated at 8 – 3 month follow-up, immediately preceding angioplasty (68 patients) or after an acute coronary event (26 patients). Disease progression of 217 stenoses, of which 79 (36%) were complex and 138 (64%) were smooth , was assessed by computerised angiography. At presentation, 63 patients had stable angina pectoris and 31 had unstable angina that settled rapidly with medical therapy. At follow-up, 23 patients (24%) had progression of preexisting stenoses and 71 (76%) had no progression. Patients with progression did not differ from those without progression with regard to risk factors, previous myocardial infarction, or severity and extent of coronary disease. Twenty-three lesions (11%) progressed, 15 to total occlusion (11 complex and 4 smooth: 65%). Progression occurred in 17 of the 79 complex stenoses (22%) and in 6 of the 138 smooth lesions (4%) ($p = 0.002$). Mean stenosis diameter reduction was also significantly greater in complex than in smooth lesions (11.6% vs 3.9% change: $p < 0.001$). Acute coronary events occurred in 57% of patients with progression compared with 18% of those without progression ($p < 0.001$) and were more frequent in patients who presented with unstable angina ($p = 0.002$). Our study thus showed that rapid progression of preexisting stenoses was relatively common in patients with moderate or severe coronary artery disease who were on a waiting list for coronary angioplasty. Indeed, approximately 25% of our patients showed significant stenosis progression while on the waiting list. This study is important as it has a prospective design and included consecutive patients with coronary artery disease, representative of the population that undergoes routine coronary angioplasty in a general hospital.

We observed that complex lesions progressed more than smooth stenoses of similar severity both in patients presenting with stable angina and in patients presenting with unstable angina. This observation indicates that the morphological appearance of a stenosis is an independent factor in determining stenosis progression. This is consistent with recent observations by our group in patients with chronic stable angina and in patients who stabilised following an unstable episode[18]. Our data indicate that in angina patients (particularly, but not exclusively, unstable angina patients), active plaques may exist that progress rapidly, leading to total vessel occlusion and acute coronary events. The relatively short time in which significant stenosis progression took place in our study suggests that acute changes, rather than slow linear events, occurred at the stenosis site. This is in agreement with current pathophysiological knowledge whereby vascular injury and thrombus formation are key events in the origin and progression of coronary disease and in the pathogenesis of acute coronary syndromes.

To ascertain the role of stenosis severity, as opposed to angiographic morphology, in rapid disease progression we compared the evolution of stenoses that were considered target for angioplasty (usually the most severe lesions) and that of non-target (often mild) coronary artery stenoses, in patients with coronary artery disease who were on a waiting list for coronary angioplasty[19]. We prospectively studied 161 patients with stable angina and observed that despite significant differences in baseline stenosis severity, a similar proportion of target (9%) and non-target (8%) stenoses progressed rapidly (7 months). This observation is consistent with findings by other authors that acute coronary syndromes are often the result of rapid progression of mild coronary artery stenoses.

In a different investigation to assess the independent role of morphology in disease progression, we sought to compare the evolution of complex and smooth stenoses within the same coronary tree in patients with stable coronary artery disease[20]. Progression of coronary stenoses has prognostic significance and may be influenced by local and systemic factors, but no previous study had systematically assessed progression of complex and smooth stenoses within the same patient. We studied 50 men with stable angina who 1) had one complex coronary stenosis and one smooth stenosis in different non-infarct-related coronary vessels at initial coronary angiography, and 2) had a second angiogram after a median interval of 9 months. All patients remained in a stable condition during follow-up. Progression, defined as an increase in diameter stenosis by > 15% was seen in only eight complex stenoses (16%) but in no smooth le-

sions ($p < 0.01$). The severity of complex stenoses changed more than that of corresponding smooth stenoses (mean – 1 SD 5.8 – 13 vs -0.06 – 6%, $p < 0.01$). On average, the annual rate of growth was 11.4 – 28% and 1.5 – 14% for complex and smooth lesions, respectively ($p < 0.01$). Our study thus showed that complex and smooth coronary stenoses progress at different rates within the same coronary tree. Complex stenosis morphology itself is an important and independent determinant of progression of stenosis in patients with clinically stable coronary artery disease.

Stenosis morphology and coronary disease activity

Complex stenosis morphology is associated with the development of acute coronary events. Why complex plaques should be particularly vulnerable to rapid stenosis progression is speculative. Certainly the abnormal geometry may promote plaque disruption through shear stress and oscillatory stress. In addition, complex lesions are associated with increased platelet activation, inflammation and vasoconstriction. The pathogenetic basis for rapid stenosis progression after plaque disruption or endothelial erosion is likely to involve platelet aggregation, thrombosis and vasospasm in the acute phase and intimal proliferation in the subacute phase[21]. Several studies have investigated the association between angiographic stenosis morphology and markers of disease activity.

Benamer et al.[22] showed that in patients with unstable angina and angiographically proven coronary artery disease, increased cardiac troponin I, but not increased C-reactive protein, within 24 hours of admission is associated with an angiographic appearance of the culprit lesion carrying a high risk of complication, especially in the event of angioplasty. In patients with refractory angina Heeschen et al.[23] observed that complex lesion characteristics and visible thrombus formation at baseline were significantly linked to troponin T elevation. However, troponin T status was a more powerful predictor of increased cardiac risk and efficacy of treatment with abciximab than either. Relative to the angiogram, troponin T can thus be considered a more sensitive marker for the underlying pathology, identifying patients with unstable angina who will particularly benefit from antiplatelet treatment.

We have recently reported that the serum concentration of neopterin, a pterydine derivative synthesised by activated macrophages, is associated with the presence of complex coronary artery stenoses in patients with unstable angina[24]. Neopterin is a marker of activation of the immune system and has been shown to be elevated in patients with unstable angina and myocardial infarction, compared to patients with chronic stable angina and healthy controls[25-27]. Neopterin is secreted by monocyte-macrophages upon stimulation with interferon-γ. Activated T cells, which produce interferon-γ, have been found to be present in coronary artery stenoses responsible for acute coronary events and in patients with unstable angina[6]. In our study[24] in 50 patients with unstable angina, a significant correlation was found between serum neopterin and number of complex coronary artery stenoses. Multiple regression analysis revealed that neopterin was independently associated with active plaques. This finding suggests that neopterin may represent a useful marker of disease activity. This immune mediator is directly linked to rapid disease progression in patients with chronic stable angina, patients with unstable syndrome and post-myocardial infarction patients as shown in recent studies from our unit[25-27].

Future directions

Despite its usefulness for patient management in the clinical setting, angiography does not provide accurate information regarding plaque vulnerability. The information required about a patient s coronary arteries is not the degree of stenosis but the presence and number of vulnerable plaques that the patient has[7]. Unfortunately, there is not at present a diagnostic tool capable of providing this information. However, it is possible that magnetic resonance may be able to do this in the future. Magnetic resonance imaging is currently possible on static arteries. The use of intravascular ultrasound may be another possible strategy to identify active plaques in patients. Attempts have been made to assess inflammatory activity of plaques by measuring differences in temperature using intracoronary catheters during angiography[28].

At present, risk of acute coronary events appears to be best assessed by measuring total cholesterol and LDL-cholesterol, C-reactive protein (using ultrasensitive assays) and other serum markers of inflammation[29] (i.e. neopterin, serum amyloid A protein and fibrinogen) and myocardial damage such as the cardiac troponins. Although these markers do not identify specifically vulnerable lesions, they provide a global assessment of vulnerability. In selected cases qualitative analysis of the coronary angiogram may provide useful information regarding cardiovascular risk.

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