Role of the vascular endothelium in patients with angina pectoris or acute myocardial infarction with normal coronary arteries

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Summary

Chest pain with normal coronary angiograms is a relatively common syndrome. The mode of presentation of this syndrome includes patients with syndrome X and patients with an acute myocardial infarction and angiographically normal coronary arteries. Different mechanisms have been proposed to elucidate the exact cause and to explain the various clinical presentations in these patients. Abnormalities of pain perception and the presence of oesophageal dysmotility have all been reported in patients with syndrome X. In situ thrombosis or embolization with subsequent clot lysis and recanalization, coronary artery spasm, cocaine abuse, and viral myocarditis have been described as potential mechanisms responsible for an acute myocardial infarction in patients with angiographically normal coronary arteries. Recent data suggest that both microvascular and epicardial endothelial dysfunction may play an important role in the pathophysiological mechanism of the syndrome of stable angina or acute myocardial infarction with normal coronary arteries.

Keywords: chest pain; coronary arteries; vascular endothelium; myocardial infarction; angina pectoris; syndrome X

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Typical angina pectoris and acute myocardial infarction (AMI) in patients with normal coronary angiographic arteries have been recognised for several years.^{1–7} In approximately 10 to 30% of patients undergoing cardiac catheterization to evaluate angina-like chest pain, coronary angiograms are found to be normal.^{5, 6} A whole host of mechanisms have been reported to explain the clinical presentations in these patients.

In this article, we discuss the role of the vascular endothelium in the development of angina pectoris and AMI in patients with normal coronary arteries. Clinical case presentations are used to illustrate different situations of patients with angina pectoris or AMI with normal coronary arteries.

Syndrome X

The term syndrome X, first used almost 20 years ago by Kemp,⁷ is now frequently used as a diagnostic label for patients with exertional angina, a positive response to exercise testing, and angiographically normal coronary arteries.⁸ Figure 1A shows the electrocardiogram (ECG) at rest of a 62-year-old woman with a diagnosis of syndrome X. The patient had been suffering from recurrent episodes of chest pain for several months. During the stress test ST-segment depression was observed in leads II, III, aVF and V3 to V6 (figure 1B). Thallium 201-myocardial scintigraphy (figure 2) showed a transient perfusion defect, compatible with ischaemia, in the inferior left ventricular region (arrows). The patient's coronary angiogram was normal.

Syndrome X is a heterogenous syndrome that encompasses different pathophysiological entities; its exact cause remains unknown. Patients with syndrome X are often women presenting with severe, invalidating chest pain. Although these patients have ST-segment depression during exercise testing, metabolic and haemodynamic evidence for myocardial ischaemia is demonstrable in only a small subset of patients.⁸ This discrepancy between the severity of symptoms and the lack of myocardial ischaemia has suggested to some authors alternative causes for this syndrome. Thus, oesophageal dysmotility, acid reflux, musculoskeletal pain, panic attacks or altered cardiac sensation due to a

Figure 1 (A) Normal ECG at rest; (B) ST-segment downsloping in leads II, III, aVF and in V3 to V6

Figure 2 Thallium-201 scintigraphic images showing a transient perfusion defect (arrow), compatible with ischaemia in the inferior left ventricular region

General characteristics of syndrome X

- anginal chest pain, often affecting women
- ST-segment depression during exercise testing
- angiographically normal coronary arteries
- objective evidence of ischaemia demonstrable only in a small subset of patients (thallium 201-myocardial scintigraphy)
- benign long-term prognosis except in patients with left bundle branch block (risk of left ventricular dysfunction)
- treatment either with calcium channel blockers, beta-blockers or ACE inhibitors
- possible potential benefit of oestrogen replacement

Box 1

Possible mechanisms for myocardial ischaemia in syndrome X

- dysfunction of small intramural pre-arteriolar coronary arteries ('microvascular angina')
- abnormal smooth muscle cell function
- hyperinsulinaemia, insulin resistance
- dysregulation of the autonomic nervous control
- microvascular endothelial dysfunction

Box 2

decreased cardiac pain threshold, have been proposed as possible aetiologies for the symptomatology of syndrome X.⁸⁻¹¹ All indicate the heterogeneous character of syndrome X patients (box 1).

PATHOPHYSIOLOGY

In 1985, Cannon and Epstein¹² proposed the term 'microvascular angina' for this patient population, suggesting a possible dysfunction of small intramural pre-arteriolar coronary arteries. These same authors also demonstrated that some patients with microvascular angina may have a generalised disorder of vascular and nonvascular smooth muscle function.¹³ Finally, some authors suggested a possible link between hyperinsulinaemia and microvascular dysfunction.¹⁴

Several studies have demonstrated that a group of patients with syndrome X have an increased myocardial perfusion at rest, and a diminished coronary flow reserve, established by thallium-201 scintigraphy or positron emission tomography.^{9 15 16} The most interesting model was proposed by Maseri *et al* in 1991.¹⁷ Patients with syndrome X may have a patchily distributed abnormal constriction of coronary pre-arteriolar vessels. This abnormal pre-arteriolar constriction could be caused by an abnormal smooth muscle cell function of these vessels,¹⁷ a dysregulation in the autonomic nervous control of the cardiovascular system with an increased adrenergic tone,¹⁸ an organic abnormality of the vessels,¹⁹ or by lack of endothelium-derived relaxing factor flow-mediated vasodilatation.²⁰⁻²² A recent study²³ proposed coronary microvascular spasm with subsequent myocardial ischaemia as a cause of chest pain in these patients. Although direct evidence of microvascular spasm is difficult to obtain in humans, this study presents an interesting hypothesis for the mechanism underlying syndrome X. The different possible mechanisms for myocardial ischaemia in syndrome X are listed in box 2.

ENDOTHELIAL DYSFUNCTION IN SYNDROME X

The vascular endothelium has numerous important functions, including the regulation of permeability, vascular tone, and blood flow.²⁴⁻²⁶ The endothelium serves a dual role in the control of vascular tone, it secretes both vasorelaxing (eg, nitric oxide (NO) and prostacyclin) and vasoconstricting factors (eg, endothelin-1).

NO is the endothelium-derived relaxing factor (EDRF), which was first described by Furchgott and Zawadzki,²⁷ and which acts as a potent vasodilator of normal coronary arteries. Normal coronary arteries dilate in response to intracoronary acetylcholine, papaverine or nitrates. While acetylcholine stimulates the production of the EDRF, causing an endothelium-dependent vasodilatation, nitrates and papaverine act as endothelium-independent dilators. Recently, Egashira *et al*²¹ have proposed a selective, endothelium-dependent dysfunction of the coronary microvascular endothelium. They infused the endothelium-independent vasodilator acetylcholine and endothelium-dependent vasodilators papaverine and isosorbide dinitrate in nine patients with angina-like chest pain and normal coronary arteries and in 10 control subjects. They found that acetylcholine-induced increases in coronary blood flow were significantly less in the patients than in the control subjects. The changes in coronary blood flow in response to papaverine and nitrates did not differ significantly between the groups. Chauhan *et al*²² found a significant impairment of increase in coronary blood flow in response to papaverine and to graded doses of acetylcholine in syndrome X patients compared with controls. The response to intracoronary nitrate was also lower in the syndrome X group, but the difference did not reach statistical significance. Mohri *et al*²³ showed that impaired NO-dependent vasodilatation could increase coronary microvessel tone and produce spasm.

Taken together, these data demonstrate that both endothelium-dependent vasodilatation (acetylcholine) and endothelium-independent dilatation (papaverine and nitrate) of the coronary microvasculature is impaired in syndrome X. Thus, patients with syndrome X may have an impaired endothelial function, resulting in a dynamic abnormality of the coronary microcirculation.

TREATMENT

Patients with syndrome X often do not respond to medical treatment, which may consist of either calcium channel blockers, beta-blockers or angiotensin-converting enzyme (ACE) inhibitors (box 1). A potential benefit of oestrogen replacement has been shown to improve endothelial function and to reduce the frequency of chest pain in post-menopausal women with syndrome X.²⁸

PROGNOSIS

Long-term cardiovascular prognosis of these patients is generally benign, despite persistence of chest pain for many years.^{5 8 29} However, recent studies suggest that a subgroup of patients may experience deterioration in left ventricular function over time,⁵ particularly patients with left bundle branch block.³⁰ Higher concentrations of endothelin, a potent vasoconstrictor peptide secreted by the coronary vascular endothelium, have been reported in this subgroup of patients. Endothelin may induce coronary vasoconstriction predominantly at the microvascular level and contribute to inflammatory mechanisms leading to the evolution of atheroma in syndrome X patients.^{31 32} Thus, deterioration of left ventricular function could be a consequence of microvascular dysfunction and resulting ischaemia.

Because of the refractory nature of the chest pain, a significant functional disability may remain in many patients with syndrome X, often women, and represent a considerable burden on hospital resources, as these patients continue to use hospital facilities, including emergency and coronary care beds.

AMI and normal coronary arteries

Approximately 6% of patients with an AMI and 10% of patients under 35 years of age with an AMI are found to have normal coronary arteries.¹⁻⁶ Before the era of thrombolytic treatment, this represented 1–3% of coronary angiograms but, since thrombolysis, this percentage has increased to about 15%,^{1 33} possibly due to a higher number of angiographic procedures and to shorter delays of this procedure after the lysis of the occluded coronary arteries.

Figure 3A illustrates the ECG on hospital admission of a 28-year-old man, a heavy smoker, with no previous cardiac history and no drug abuse, who presented with an acute episode of chest pain radiating to both arms at rest. A diagnosis of unstable angina was initially made. However, during follow-up, R waves almost disappeared in leads DIII and aVF (figure 3B) and there was a significant rise of serial creatine kinase and MB isoenzyme, 935 and 82 U/l, respectively, compatible with an inferior AMI. Cardiac catheterisation was performed, showing wall motion abnormalities of the left ventricular posterolateral regions, and left ventricular ejection fraction was 62%. However, coronary arteries were completely normal. The patient's post-infarction course under beta-blocker and aspirin treatment was symptomless. A technetium-99m sestamibi (MIBI) scintigraphy performed on day 10 showed the presence of an inferior infarction (figure 4). Taking into account the clinical history, particularly the heavy smoking, the ECG and enzymatic modifications, the normal viral serological laboratory screening and the persistence of a regional left ventricular wall motion

Figure 3 (A) Rest ECG showing a flat T wave in DIII; (B) subsequent disappearance of R waves in leads DIII and aVF

Figure 4 Technetium-99m sestamibi (MIBI) scintigraphy demonstrating the presence of an inferior infarction (arrows)

Characteristics of patients with normal coronary arteries and AMI

- young, most under 40 years old
- mostly cigarette smokers
- in women, association with oral contraceptives, pregnancy or peripartal period
- cocaine abuse
- favourable long-term prognosis if smoking stopped
- possible progression to significant coronary lesions if persistence of smoking, or of other cardiovascular risk factors

Box 3

Possible mechanisms for AMI with normal coronary arteries

- in situ thrombosis or embolization with subsequent clot lysis and recanalization of the coronary artery
- coronary artery spasm
- acute myocarditis
- endothelial dysfunction of the epicardial coronary arteries

Box 4

abnormality with normal coronary arteries, a final diagnosis of AMI with normal coronary arteries was made.

PATIENT CHARACTERISTICS

All the recent studies of AMI and normal coronary findings show a pattern of patients who are relatively young (under 40 years old), without any previous history of chest pain, no haemostatic factor disturbances,³⁴ and no risk factors other than cigarette smoking.^{2,3} In women, an association with oral contraceptives, pregnancy, or the peripartal period has been reported.³ The general characteristics of patients with AMI and normal coronary arteries are seen in box 3.

MECHANISMS

While the most common mechanism of an AMI is attributed to an acute occlusion of a coronary vessel associated with platelet aggregation and thrombus formation at the level of a significant coronary stenosis, several different mechanisms have been postulated for an AMI in patients with normal coronary arteries. These mechanisms include in situ thrombosis or embolization with subsequent clot lysis and recanalization,^{2,3} coronary artery spasm,³⁵ cocaine abuse,³⁶ and myocarditis.³⁷ Recently, vascular endothelial dysfunction has been suggested to explain the mechanism of this syndrome, particularly in relation to tobacco or cocaine.³⁸⁻⁴⁰ Finally, acute myocarditis, particularly of infectious origin, may in some rare situations 'mimick' an AMI.^{37,41,42} The different possible mechanisms for developing an AMI in the presence of normal coronary arteries are summarised in box 4.

THE ROLE OF CORONARY ARTERY SPASM

Coronary artery spasm has been shown to play an important role in the pathogenesis of not only variant angina, but also AMI and sudden death.⁴³ Prolonged coronary spasm may induce endothelial damage, release of vasoactive substances, and platelet aggregation, resulting in local thrombus formation. Recently, a deficiency in endothelial NO activity in spasm arteries has been shown to play a role in the mechanism of coronary spasm.⁴⁴

THE ROLE OF SMOKING

Smoking is a major risk factor for atherosclerosis, and coronary events.³⁹ Continued growth of tobacco use will undoubtedly be the major cause of increased cardiovascular disease in the developing world. It has been estimated that 10% of the current world population, some 450 million persons, will die prematurely because of the effects of cigarette smoking and tobacco use.⁴⁵

Cigarette smoking may induce endothelial damage, which may be the initiating mechanism for the development of an atherosclerotic plaque. Thus, tobacco may have a direct toxic effect on human endothelium associated with an increase in the number of endothelial cells with nuclear damage in the circulating blood.^{38,39}

In asymptomatic young smokers tobacco induces a dose-dependent impairment of endothelial dysfunction.³⁸ Young heavy smokers with angiographically normal coronary arteries have an abnormal coronary vasoconstriction induced by acetylcholine,⁴⁶ which means that NO is probably decreased locally. Since NO inhibits aggregation and adhesion of platelets, and also has a synergic anti-aggregatory effect with prostacycline, a decrease of NO release may be involved in the initiation of augmented platelet aggregation resulting in coronary thrombosis in non-stenosed coronary arteries.⁴⁷ The abnormal vasoconstrictor response to acetylcholine may also be due to excessive release of an endothelium-dependent vasoconstriction substance, for instance, thromboxane.^{48,49}

THE ROLE OF COCAINE

Cocaine abusers also represent a group of young patients who may develop an AMI with normal coronary arteries. Cocaine use in the USA has become widespread, with an estimated 5–6 million individuals using the drug on regular basis.⁴⁰

Cocaine increases serum catecholamine levels inducing vasoconstriction, predominantly by α -adrenergic stimulation, and leading to increased systemic blood pressure, coronary vascular resistance and myocardial oxygen demand.⁵⁰ This results in reduced myocardial oxygen supply, which is potentiated by β -adrenergic blockade.⁵¹ Recent data suggest that cocaine increases endothelin-1 release, facilitating vasospasm.⁵² Cocaine also increases platelet aggregability and thromboxane production, potentially resulting in thrombus formation.⁵³

It has been suggested that AMI due to cocaine abuse may result from either coronary artery spasm or thrombosis that lyses spontaneously, or some

combination of both events.^{36 50} Thus, the chronic use of cocaine may cause repetitive episodes of spasm, with or without platelet deposition, which may induce local endothelial cell lesion and dysfunction, and subsequent acceleration of atherosclerosis, comparable with chronic cigarette smokers.

ACUTE MYOCARDITIS

Acute myocarditis, particularly of infectious origin (Coxsackie virus), may simulate an AMI in patients with normal coronary arteries.^{37 41 42} Figure 5A shows the initial ECG of a 27-year-old man with no cardiovascular risk factors, a non-smoker, presenting with acute chest pain on hospital admission. Because of the ECG modifications and significant rise of creatine kinase and MB isoenzyme, a diagnosis of AMI was initially established and systemic thrombolysis was performed. A subsequent coronary arteriogram, however, showed totally normal coronary arteries. The patient's hospital course was symptomless and his ECG completely normalised (figure 5B). Taking into account a recent history of upper respiratory tract infection and a positive viral serology for Coxsackie virus, a final diagnosis of acute viral myocarditis was made.

The exact pathogenesis linking infection with the onset of AMI still remains to be elucidated. Viraemia may induce platelet alteration, resulting in agglutination and lysis with release of vasospastic substances (eg, thromboxane A2) and final formation of coronary thrombosis.³⁷ Recently, an association of myocarditis with endothelial dysfunction of the epicardial coronary arteries was proposed.⁵⁴ The infection could produce inflammation of the endothelium, resulting in loss of the endothelium-mediated vasodilatation and causing myocardial ischaemia.

TREATMENT

Systemic thrombolysis or percutaneous transluminal coronary angioplasty (PTCA) may be the first treatment strategy in this group of patients. Verapamil or nitrates are recommended in patients with cocaine-associated chest pain.⁵⁰ β -Adrenergic blockade may worsen cocaine-related ischaemia. During follow-up, aspirin is recommended.⁵⁰ Calcium channel blockers are the most appropriate treatment in patients with coronary artery spasm.⁴³ Finally, removal of cardiovascular risk factors, particularly of smoking, is important and may be of great potential benefit.

PROGNOSIS OF PATIENTS WITH AMI AND NORMAL CORONARY ARTERIES

Long-term prognosis in this group of patients is favourable with a low rate of coronary morbidity and mortality.¹⁻⁵ However, because of a high prevalence of smoking in young patients, coronary artery disease may rapidly progress (box 4), even in patients in whom initially the absence of significant obstructive lesions was demonstrated by coronary arteriography.⁵⁵ Furthermore, coronary events tend to occur in patients with an increased number of risk factors.^{1 2}

Major potential differences between patients with syndrome X and patients with an AMI and normal coronary arteries

Although dysfunction of the vascular endothelium may play an important role in a subset of patients with syndrome X and in young smokers or cocaine consumers who present with an AMI and no angiographically significant coronary artery stenosis, these two groups have important different features. First, patients with syndrome X are most often women with fewer coronary risk factors, particularly smoking. In the group of patients with AMI and normal coronary arteries, smoking appears to be the most predisposing risk factor. Second, the site of the vascular endothelial dysfunction is not similar in these two groups. Endothelial dysfunction probably most often involves the coronary microvasculature in patients with syndrome X. In the second group of patients, the epicardial coronary arteries are principally affected. Given the inherent limitations of angiography, the true prevalence of plaques in these patients is probably also underestimated. While the exact cause of the endothelial dysfunction in syndrome X patients remains unknown, the second group of patients are, in a certain sense, at an early stage of the atherosclerotic process. This means that the continuous exposure to smoking may lead to significant coronary lesions. In the same sense, it cannot be excluded that the smokers among the syndrome X patients may enter the second group at a certain moment of their evolution and present with an AMI.

Conclusion

Endothelial dysfunction can lead to a variety of presentations. There is probably no unifying pathogenic mechanism for the syndrome of chest pain with normal

coronary arteries. Syndrome X patients may have an impaired endothelial function predominating at the microvascular level and resulting in a dynamic abnormality of the coronary microcirculation. Although long-term cardiovascular prognosis in these patients remains favourable, they often seek medical care because of recurring and disabling chest pain, which may imply repetitive and costly invasive and non-invasive investigations. Patients with an AMI with normal coronary arteries may have an endothelial dysfunction of the epicardial coronary arteries. Both tobacco smoking and cocaine abuse contribute to the abnormal endothelial response. Counselling and removal of cardiovascular risk factors, particularly smoking, may be of great potential benefit in this type of patients.

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