Angina with normal coronary arteries: diagnosis, pathophysiology and treatment

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Approximately 20% of patients undergoing diagnostic coronary arteriography for acute or chronic cardiac ischaemia have angiographically normal coronary arteries. The mechanism behind this phenomenon is likely to be the result of a combination of functional or anatomical abnormalities in the coronary microcirculation, a metabolic disorder which affects the handling of energy substrates by the heart, insulin resistance and a neurological component affecting pain perception. Indeed, it has been demonstrated that these patients often exhibit an increase in sympathetic outflow to the cardiovascular system, which might account for the reduction in coronary flow reserve, changes in metabolic utilization and development of insulin resistance that are seen in some of these patients. Therapeutically, β-blockers appear to be most effective in controlling the symptoms associated with this condition, although those calcium antagonists which do not affect the neurohormonal system may be of some utility in patients with primary microvascular angina, in which microvascular spasm is operating or in whom excessive constriction of the distal component of the coronary circulation limits the vasodilatory reserve.

Key Words: β-blockers, calcium antagonists, syndrome X, microvascular angina, sympathetic nervous system.

Introduction

Approximately 20% of all patients undergoing diagnostic coronary arteriography for chronic or acute cardiac ischaemic syndromes have angiographically normal epicardial coronary arteries. Even allowing for the possibility that, in some of these patients, symptoms may be non-cardiac in origin, it seems reasonable to assume that at least one in 10 patients with typical angina has no significant coronary atheroma.

Originally described by Kemp in 1973 and named ‘syndrome X’ [1], the syndrome of angina and normal coronary arteries comprises a probably heterogeneous group of patients presenting with typical chest pain, a positive exercise stress test, angiographically smooth epicardial coronary arteries and no clinical or angiographic evidence to suggest the presence of spasm. Other clinical features supporting the diagnosis are the absence of systemic hypertension with or without ventricular hypertrophy and a normal resting systolic function which can be either normal or slightly impaired during exercise [2-4]. The discrepancy of the results probably depends on the different techniques employed by the different investigators and the heterogeneity of the study populations. Although some rare patients with syndrome X gradually develop left bundle branch block and eventually progress towards congestive cardiomyopathy [5], the condition, in general, bears an excellent prognosis and rarely evolves towards an adverse outcome.

The mechanisms responsible for the syndrome of angina with normal coronary arteries are probably varied and remain largely speculative. Three main hypotheses have so far been put forward. The first argues that the disease is caused by myocardial ischaemia and suggests that the dominant abnormality resides in the coronary microcirculation which is either functionally or anatomically abnormal [6-8]. The second hypothesis supports the idea that a metabolic disorder which affects the handling of energy substrates by the heart muscle is primarily responsible for the condition [9]. The third denies the syndrome the dignity of being a cardiac disease and suggests that symptoms, albeit sometimes so severe as to impair patients’ quality of life, are in fact the result of increased sensitivity to algogenic stimuli arising from a variety of organs, including the heart [10].

There is probably some truth in each of these theories and their relative role is likely to be different in individual patients. Accordingly, their relative weight in reported series is likely to be variable, depending upon the selection criteria, the activity of the disease, the adequacy of the techniques employed to answer specific questions and, last but not least, the investigators’ cultural bias.
Furthermore, one should not forget when labeling a patient as having syndrome X, that our ability to define anatomical 'normality' on purely angiographic criteria is far from ideal. Coronary atheroma is primarily a disease of the vascular wall that encroaches on the lumen only at a late, advanced stage, when it becomes 'angiographically visible'. Therefore, whilst our anatomical definitions should be reviewed critically, the possibility that 'angiographically invisible' atheroma may produce gross alterations in the coronary responses to physiological and pharmacological stimuli should be kept in mind.

In the next few paragraphs the available evidence supporting the different pathogenetic hypotheses, which have been formulated in an attempt to explain the occurrence of anginal attacks in the absence of obstructive coronary artery disease, will be summarized. As part of the discussion of microvascular angina, a pathophysiological classification for this condition will be proposed, based on the data of the literature as well as on some personal observations. Finally, we will propose the hypothesis that a sustained increase of the sympathetic outflow to the cardiovascular system may well account for many of the abnormalities observed in the syndrome and, as a result, suggest that β-blocking agents are the first-line drugs for its treatment.

**Microvascular angina**

In 1981, Opherk and coworkers[11] reported their observations in 21 patients who, in spite of showing angiographically normal coronary arteries, had a positive response to exercise testing, characterized by ischaemic-like ST-segment changes often associated with angina. They all had a markedly reduced vasodilator capacity in response to dipyridamole and, as seen in earlier studies[12,13], exhibited abnormal lactate extraction during atrial pacing. Myocardial biopsies consistently showed abnormal pathological findings, consisting of moderate to severe endothelial swelling. The authors concluded that myocardial ischaemia was the likely cause of chest pain in patients with angina and normal coronary arteries. They hypothesized that the reduced dilator capacity observed in their patients was either the result of metabolic alterations in the formation of transmitter substances or in the function of coronary receptors responsible for vasodilatation.

Some years later, Cannon et al[14] came to similar conclusions after showing, again using atrial pacing, that patients with angina and normal coronary arteries could not decrease coronary vascular resistance to the same extent as normal controls. The same authors observed that the limitation in vasodilator capacity could be affected, in a dynamic fashion, by agents that are known to interfere with coronary vascular tone, such as ergonovine. They suggested that sustained or transient constriction of coronary microvessels could, at least in part, contribute to the pathophysiology of the syndrome.

These observations generated the notion that the pathophysiological denominator common to most patients with angina and angiographically smooth coronary arteries was a functional or anatomical abnormality of the small coronary vessels. Initially it was felt that this abnormality mainly resulted in reduced vasodilator capacity in response to metabolically active stimuli. Later on, isolated reports published in the mid 1980s[15,16] suggested the possibility that transient, severe, active constriction of the coronary microcirculation had the potential for critically impairing myocardial perfusion and causing ischaemia.

Based on these observations, and by analogy with the pathophysiological classification of 'macrovascular' angina[17], one can assume that the abnormalities of the microvascular circulation may cause ischaemia and angina by the following mechanisms: (1) 'primary' forms may be due to transient reduction in regional myocardial perfusion, either related to abnormal constriction of coronary microvessels or to reversible intravascular plugging by blood constituents; (2) 'secondary' forms may be caused by a limitation in coronary flow reserve, that can be either due to anatomical restriction of vascular cross-section or to reduced vasodilator capacity. Theoretically, the former can be caused by medial hypertrophy, recurrent distal embolization or thrombosis; the latter can be related to a reduced ability of either the myocardium or the microvasculature to produce vasoactive metabolites. Alternatively, the underlying abnormality can be represented by impaired capacity of the distal bed to correctly translate the biochemical messages that physiologically promote vasodilatation; (3) in mixed forms (probably the most common presentation) the two pathophysiological mechanisms may coexist, in variable combinations, and play different relative roles within the individual patient.

β-blockers are more likely to be effective in secondary forms and, indeed, this has been shown to be the case by controlled clinical trials[18,19]. Calcium channel blockers, especially those which do not activate the neurohormonal system, are also likely to be of benefit in some patients in whom excessive constriction of the distal, resistive component of the coronary circulation contributes to limitation of the vasodilatory reserve. Furthermore, the latter agents are likely to be effective in the rare, pure 'primary' forms in which microvascular spasm is operating.

The mechanisms responsible for the reduced vasodilator capacity that is observed in some patients with angina and normal coronary arteries are unclear. Impairment of endothelium-mediated vasodilatation has been suggested by several investigators[20-22] and increased stimulation of coronary α-adrenergic receptors by augmented sympathetic activity has also been documented[23]. The two mechanisms can certainly coexist as the vasoconstrictor effects of α-adrenergic stimulation are potentiated by endothelial dysfunction. Decreased sensitivity to adenosine, the natural vasodilator released by the myocardium in response to metabolically active...
stimuli, has also been hypothesized\textsuperscript{[24]}. However, the
evidence to support this theory has never been obtained.

The site of the microvascular abnormality is also
unclear. Although most investigators believe that the
reduced vasodilator capacity involves, predominantly,
resistive arterioles\textsuperscript{[14]}, others\textsuperscript{[24]} have suggested that
the dysfunction is pre-arteriolar and is caused by reduced
production of endothelium-derived relaxing factor.

Isolated reports\textsuperscript{[15,16,25]} have shown that some
patients with angina and angiographically smooth
epicardial coronary arteries exhibit an extremely slow
progression of angiographic dye, which is more often
observed in one coronary branch, but sometimes in-
volves all major epicardial arteries. The 'slow-flow
phenomenon' is sometimes associated with typical chest
pain and ST-segment abnormalities; it is invariably
associated with transient perfusion abnormalities on
myocardial scintigraphy and is not reversed by nitrates
but is consistently relieved by intracoronary admin-
istration of the arteriolar dilator papaverine\textsuperscript{[23]}. This
observation, and the fact that patients with 'slow
flow' exhibit medial hypertrophy of intramyocardial
vessels\textsuperscript{[16]}, supports the idea that excessive constriction
of resistive arterioles (or pre-arterioles) is the cause of
the finding.

That abnormal microvascular constriction can
cause slow flow and severe myocardial ischaemia
has been shown by studies employing pharmacological
intracoronary doses of the sympathetic cotransmitter
Neuropeptide Y\textsuperscript{[26]}. However, the pathophysiological
role of this substance in causing arteriolar spasm in
microvascular angina remains to be established.

**Cardiac metabolic abnormalities in
syndrome X**

Compared with normal subjects, some patients with
syndrome X exhibit a peculiar pattern of myocardial
substrate utilization, characterized by reduced carbo-
hydrate oxidation and a proportionally greater uptake
of lipid 'fuels'\textsuperscript{[19,27]}. This alteration, per se, might affect
myocardial function and reduce efficiency of active
relaxation. Indeed, in a group of 22 patients with typical
angina and angiographically smooth epicardial coronary
arteries, we recently found consistent impairment of
e left ventricular diastolic filling, as assessed by Doppler
measurement of transmural flow velocity\textsuperscript{[28]}. The causes
of this finding remain unclear and whether the abnor-
mality is the result of primary metabolic dysfunction or,
rather, is secondary to myocardial ischaemia, is not yet
established. Certainly, the observation that, in these
patients, the diastolic filling pattern is consistently
improved, along with anginal symptoms, by long-term
treatment with \( \beta \)-blockers\textsuperscript{[28]}, makes the second hypoth-
thesis a likely one. However, it must be pointed out that
\( \beta \)-blockers, by reducing the circulating levels of free fatty
acids, may shift tissue metabolism towards greater car-
bohydrate uptake, via substrate competition. Therefore,
it is possible that these agents improve diastolic function
in patients with syndrome X by re-establishing the
physiological balance of carbohydrate and lipid fuels for
myocardial energy production.

Prolonged fasting increases the levels of circulating
fatty acids and ketone bodies by activating lipolysis
and reduces blood sugar and insulin levels. In these
conditions, the heart preferentially uses lipid fuels and
ketone bodies for energy production and handles little
or no glucose. However, studies performed in our insti-
tution and based on metabolic imaging by positron
emission computed tomography have shown that, in
fasting conditions, patients with angina and normal
coronary arteries consistently show myocardial uptake
of fluorine 18-deoxyglucose, a positron emitter that
traces transmembrane glucose transport\textsuperscript{[29]}. Again, the
abnormality is abolished by prolonged treatment with
oral \( \beta \)-blockers which revert cardiac metabolism to a
normal pattern (i.e. no glucose uptake during prolonged
fasting). This observation, along with the finding that
areas of increased glucose uptake often coincide with
regions of relative underperfusion (as evidenced by
stress-rest myocardial perfusion tomography), strongly
suggests that the abnormal regional glucose uptake
observed with positron emission computed tomography
scanning reflects the presence of anaerobic glycolysis
which, in turn, results from myocardial ischaemia.

This contention is further supported by our
recent observation that patients with syndrome X often
accumulate the paramagnetic contrast agent gadolinium
DTPA in the same regions that avidly take up glucose
during fasting\textsuperscript{[30]}. Regional myocardial enhancement
by gadolinium is observed during magnetic resonance
imaging in a variety of ischaemic conditions, including
myocardial infarction. The agent is believed to trace
interstitial water accumulation as typically occurs during
ischaemia. As for other cardiac abnormalities, myocard-
ial accumulation of the paramagnetic contrast agent
that is observed in syndrome X is reduced or abolished
by prolonged treatment with \( \beta \)-blockers.

Taken together, the observations discussed so far
suggest that, at least in some patients with syndrome
X, the abnormalities involving different myocardial
functions are more likely to reflect a subtle imbalance
between supply and demand rather than being caused by
a primary metabolic derangement.

**Altered pain perception in syndrome X**

A group of 29 carefully characterized patients with
syndrome X was recently studied by the Hammersmith
group using positron emission computed tomography
scanning\textsuperscript{[31]}. Quantitative measurements of regional
myocardial perfusion were obtained, using \( ^{15} \)O-labelled
water, both at rest and during dipyridamole infusion.

Coronary flow reserve (calculated as the ratio
between hyperaemic and resting flow) was not signifi-
cantly different when patients with syndrome X were
compared with a matched population of healthy
controls with no symptoms or risk factors of cardiovascular disease and normal resting and exercise ECG. Although the hyperaemic response to dipyridamole was normal, the majority of patients with syndrome X experienced pain and nearly one-third had diagnostic ST-segment changes. The authors concluded that their study cast further doubt on ischaemia as the basis of the reported chest pain, at least in the majority of patients. They also stressed the potential importance of sympathetic activation in the syndrome, as the interactions of the central and sympathetic nervous system can certainly influence pain perception.

The hypothesis that altered nociceptive perception may play a major role in determining cardiac pain in these patients received further support from the observation that the anti-depressant drug, imipramine, markedly improves symptoms in patients with chest pain and normal coronary angiograms. As the effect of imipramine was unrelated to the results of extensive cardiac testing, the authors concluded that it was mediated by a visceral analgesic mechanism.

The rationale for this study was based on the observation that imipramine is used successfully in a wide range of chronic pain syndromes, such as diabetic neuropathy, post-herpetic neuralgia, migraine headache and oesophageal pain. However, it must also be remembered that imipramine also affects sympathetic nerve traffic by affecting norepinephrine re-uptake. Furthermore, only a minority (22%) of study patients really fulfilled the diagnostic criteria of syndrome X and the effects of the drug were not apparently related to the presence or absence of documented ischaemia. Curiously enough, the authors of the study, Cannon and coworkers, were among the first to propose microvascular disease as a cause of angina in patients with angiographically normal coronary arteries.

In summary, although altered pain perception may certainly play an important role in the syndrome of angina and normal coronary arteries, the evidence gathered so far is probably insufficient to justify the position that, in most of these patients, the heart is 'entirely normal' and anxiety or neurosis are the real problem.

**Sympathetic overactivity: a unifying pathogenic hypothesis for syndrome X**

Recent studies employing computerized techniques for the assessment of heart rate variability have shown that patients with angina and angiographically smooth epicardial coronary arteries often exhibit an increase of the sympathetically outflow to the cardiovascular system. Excessive stimulation of the sympathetic nervous system is well known to exert a variety of cardiovascular effects that include increased myocardial oxygen demand and constriction of both epicardial and intramyocardial coronary arteries which, in turn, reduce coronary flow reserve.

The combination of increased demand and reduced vasodilator capacity may certainly promote the development of a supply/demand imbalance, not severe enough to cause 'full-blown' myocardial ischaemia and yet sufficient to induce subtle alterations of various cardiac functions. This interpretation could explain, for instance, the presence of resting diastolic dysfunction, the increase in regional glucose uptake and the interstitial deposition of gadolinium DTPA. It is likely that the reversal of these abnormalities by long-term treatment with β-blockers is the result of reduced myocardial oxygen consumption enabling a better supply/demand ratio. Furthermore, prolonged administration of these agents may also cause sympathetic tone to decrease.

Increased sympathetic activity also induces other effects that may affect cardiovascular function. Among these, excessive stimulation of myocardial β-receptors may increase intracellular calcium concentrations and cause a negative lusitropic effect which, in turn, may impair diastolic function. As already discussed, some patients with syndrome X preferentially utilize lipid fuel for myocardial energy production and have a proportionally lower oxidation of carbohydrates. Increased sympathetic activity can, by itself, contribute to this phenomenon and β-blockers may, potentially, reverse it. Furthermore, these agents reduce the levels of circulating free fatty acids that are typically increased by adrenergic stimulation.

The mechanisms responsible for increased sympathetic tone in these patients remain unclear. Certainly anxiety and a tendency to overreact to emotions and stressful situations can be, at least in part, responsible for excessive adrenergic activity. This could explain the symptomatic relief obtained in some of these patients with low-dose tricyclic antidepressants such as imipramine.

Finally, insulin resistance has also been suggested to contribute to the pathophysiology of the syndrome and, once again, excessive sympathetic activity may play a major role. Indeed, there are several mechanisms by which excessive sympathetic activity may lead to insulin resistance. Skeletal muscle vasoconstriction may increase the diffusion distance between the nutritional blood vessel and the metabolizing cell. This will impair delivery of glucose to the muscle cell, thereby creating a state of relative insulin resistance. In addition to the effect of vasoconstriction, sympathetic stimulation can also induce acute insulin resistance through β-adrenergic receptors and blockade with propranolol can reinstate a normal glucose uptake. Whatever the mechanism, insulin resistant states, such as diabetes and hypertension, have been linked with reduced activity of endothelium-derived relaxing factor. Insulin has also been shown to prompt smooth muscle cell proliferation in man. Such mechanisms may contribute to an abnormal vasoconstrictive response in syndrome X, leading to ischaemia.

In summary, excessive activation of the sympathetic outflow to the cardiovascular system can induce a number of effects that may account for many of the abnormalities that are typically found in patients with...
angina and angiographically smooth epicardial coronary arteries. Although many of these effects may play some role in determining the disorder, it is likely that the most relevant ones are the reduction in vasodilator reserve caused by α-mediated coronary constriction, along with increased metabolic demand. β-blockers probably represent the mainstay of the medical treatment of this condition but calcium antagonists, especially those which do not activate the neurohormonal system, are also likely to be of benefit, particularly in patients in whom excessive arteriolar constriction has a prominent role.

The lack of a convincing response to anti-anginal drugs should caution against the possibility that symptoms are, indeed, cardiac in origin and should direct the diagnosis towards other causes.

References


