Some thoughts on the continuing dilemma of angina pectoris

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This editorial refers to ‘Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events’1, by L. Jespersen et al., 33(6): 734-744

It is indeed surprising that, several hundred years after its elegant description and almost 100 years since its seemingly secure link with severe obstructive coronary artery disease (CAD), we are still uncertain about critically important aspects of a condition as common as angina pectoris. To this end, Jespersen and colleagues1 provide new data, confirming data from the Women’s Ischemic Syndrome Evaluation (WISE) study,2,3 that stable angina without obstructive CAD is associated with increased risk for adverse outcomes among women. Their findings also extend this conclusion to men for the first time.

Why the uncertainty?

The classical study on the relationship of angina to pathological findings concluded that ‘no patients with angina pectoris failed to show … occlusion in at least one of the major coronary arteries.’4 This concept was reinforced by early coronary angiography reports, and angina relief with occlusion relief by revascularization seemed to ‘close the loop’. Flow-limiting stenosis causing ischaemia was accepted as the aetiological explanation for angina. This association was not absolute, since in the occasional patient without severe stenosis, angina could be explained by other diseases that either markedly increased myocardial oxygen demand (e.g. severe aortic stenosis, hypertrophic cardiomyopathy, severe hypertension, etc.) or limited myocardial oxygen delivery (e.g. coronary spasm, profound anaemia, etc.). However, in the absence of these conditions or coronary obstruction, the clinician was at a loss to explain angina. The usual defaults were that (i) the patient really did not have angina; and/or (ii) the non-invasive findings suggesting ischaemia were ‘false positive’; and/or (iii) the patient had an undetected non-cardiac explanation for their symptoms.

This clinical ‘paradox of normal selective coronary arteriograms in patients considered to have unmistakable CAD’ was first placed into focus in 1967 by the report of 15 such women with ischaemic electrocardiographic abnormalities.5 Many reports followed documenting ischaemia by different methods in such patients but, in contrast to ischaemia associated with obstructive CAD, left ventricular wall motion appeared to be preserved. This finding led to speculation about long-term outcomes of such patients. Indeed multiple early reports suggested that outcomes were similar to those of selected subjects without angina and obstructive CAD. Unfortunately, this conclusion was widely embraced and led to dismissal of such patients from subspeciality care and also from general medical care.

During our attempts to identify reasons for higher ischaemic heart disease (IHD) event rates among women vs. men, it became clear that there was a strong bias against evaluation of women with chest pain and other findings suggesting IHD. The public message about this gender inequity then prompted referral of more women with these findings to coronary angiography. We began to see increasing numbers of such women who were not only disabled by persistent angina, but had serious adverse outcomes. These concerns led to the WISE study in 1996, and about two-thirds of the initial consecutive cohort of women with chest pain and other findings suggesting IHD were found to have no obstructive CAD: their adverse outcomes confirmed that this was not a benign syndrome, as initially believed.2

Also important was the application of coronary artery reactivity testing for endothelial and microvascular function (Figure 1). Among women with normal coronary arteries and non-obstructive CAD, WISE study data showed that most had endothelial and/or microvascular dysfunction. The latter was defined by low coronary flow reserve and independently predicted adverse cardiovascular events (e.g. first occurrence of death, myocardial infarction, stroke, or hospitalization for heart failure) after 5.4 years follow-up.7 These serious events are consistent with the cardiovascular disease continuum expected for a disorder involving the microvasculature. Furthermore, they consume a large amount of healthcare resources. Cardiac magnetic resonance imaging provided superior resolution to...
evaluate perfusion, and these patients were found to have a relative failure of subendocardial perfusion to increase with adenosine, which could explain the absence of major changes in left ventricular wall motion.6

What could cause angina in patients without obstructive coronary artery disease?

Although Jespersen and colleagues1 did not explore mechanisms, the evidence is strong for several inter-related mechanisms contributing to angina and findings for ischaemia among patients without flow-limiting stenosis. They include (i) endothelial dysfunction (ED); (ii) microvascular dysfunction (MVD); and (iii) coronary artery spasm (CAS) (Figures 1 and 2). Several, or all of these, may contribute in the same patient.

Endothelial dysfunction is a systemic disorder resulting from injury related to essentially all known atherosclerosis risk conditions. Thus it is present at the earliest stages of CAD before angiographic evidence of ‘raised lesions’ obstructing the lumen. Endothelial dysfunction has been linked with adverse outcomes in many conditions including women with and without coronary artery obstruction in the WISE study7 and men and women with non-obstructive CAD.8

Endothelial dysfunction is also seen among angina patients with CAS and those with MVD.

The term ‘microvascular angina’ was proposed9 to explain inappropriate vasodilation of the coronary microcirculation. This concept of MVD has received increasing attention10 and is defined as ‘a dysregulation of coronary blood flow, not attributable to obstructive CAD that results from either structural or functional mechanisms in the coronary microvasculature.’ A clinical classification of pathogenetic mechanisms has been proposed, and MVD has been linked with adverse outcomes in an increasing number of conditions.10 Recent data from the WISE study found that half of the women with angina and no obstructive CAD tested with adenosine had MVD, and this was an independent predictor of adverse events as noted above.3

Coronary artery spasm is an established mechanism for angina and ischaemia resulting from increased vascular smooth muscle sensitivity to agonists usually at sites of non-obstructive atherosclerosis, and may even occur in the microvessels. In the WISE study, only ~3–4% of unselected, consecutive women receiving acetylcholine (10−4 M into the left coronary) testing had CAS (unpublished data). This frequency is similar to that observed with unselected methylergonovine testing in stable angina patients.11

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**Figure 1** Coronal reactivity testing (top panels). With the use of different techniques (e.g. quantitative coronary angiography, intracoronary Doppler ultrasound, magnetic resonance imaging, etc.), large vessel reactivity and coronary blood flow (microvessel reactivity) can be assessed with infusion of endothelium-dependent [e.g. acetylcholine (ACh)] and endothelium-independent [e.g. nitroglycerin (NTG) and adenosine (Ado)] vasodilators. Endothelial dysfunction (bottom left) is indicated by an attenuated increase or decrease in the size of the macro- and microvessels in response to ACh. These patients also may have an exaggerated increase in coronary size in response to NTG. Microvascular dysfunction (bottom right) is indicated by an attenuated increase in coronary blood flow due to impaired dilation of pre-arteriolar vessels after Ado infusion. Spasm (bottom middle) is indicated by a decrease in coronary size and flow due to segmental or diffuse epicardial and/or microvascular constriction after ACh or methylergonovine. These patients also have exaggerated dilation with NTG.
Among patients with angina and findings of IHD without obstructive CAD, spasm testing is strongly recommended since a positive result provides direction for specific treatment. Also, recent data show that when patients without obstructive CAD evolve with acute coronary syndromes, CAS may be detected in half or more.12

How large is this problem?

An estimated 10 million Americans (~4 million males and ~5 million females) have angina,13 and ~3 million coronary angiograms were done in 2010. Although exact frequencies for referral of angina patients to angiography are unknown, at least half of the women and about a third of the men referred for angiography have non-obstructive CAD.14 These frequency estimates are supported by data from Jespersen et al.1 Thus millions of women and men with angina without obstructive CAD will probably be identified each year.

Do patients classed as having ‘normal coronary arteries’ truly have normal arteries?

A WISE substudy addressed this question by targeting a consecutive sample of 100 women with angina and ‘normal coronary angiograms’ as read onsite to estimate the frequency of coronary plaque by intravascular ultrasound (IVUS).15 About 80% of the women had atherosclerotic plaques. Considering the sampling limitations of IVUS, this probably underestimates plaque frequency among women with angina and findings of IHD. Evidence of positive remodelling, as the explanation for plaque concealment on angiography, was present in about a third. Accordingly, we have stopped using the term ‘normal coronary arteries’ in angiography reporting and believe that it is more appropriate simply to say that there is ‘no evidence for obstructive CAD’. If we extrapolate these finding to the Jespersen et al.1 data, and considering their risk factors, most of the 48% women with ‘normal coronary arteries’ would probably have coronary plaque.

What is the aetiology of adverse events among these patients?

Non-obstructive CAD is complex, and encompasses different pathophysiological substrates but, based on findings reported by Jespersen et al.1 and by others,2,3 it is associated with impaired prognosis. While ED, MVD, and/or CAS may explain angina and ischaemia, most acute coronary events are believed to result from thrombi associated with disruption (rupture or erosion) of ‘vulnerable’ plaques that are otherwise not detected by angiography. Among sudden coronary deaths, the underlying cause in the majority was plaque rupture; in a third, erosion; and in a few percent, the thrombi were attributed to calcified nodules.16 Plaque erosion was the cause of death in about one-third of women and less than one-sixth of men. However, in women <50 years old, erosion was the predominant cause of the acute coronary thrombi, while plaque rupture was the mechanism in women >50 years old.

Figure 2  Proposed mechanisms for angina and their possible inter-relationships among patients without obstructive coronary artery disease (CAD). Endothelial dysfunction (ED) probably underlies most cases, with microvascular dysfunction (MVD) and/or coronary artery spasm (CAS) and other mechanisms (not shown) contributing in some cases. While these mechanisms contribute to ischaemia, other processes [plaque disruption (rupture or erosion), heightened coagulation, inflammation, etc.] are responsible for the acute thrombotic clinical events. However, ED, MVD, and/or CAS have the potential to limit collateral perfusion and/or reperfusion during and following non-fatal thrombotic events to worsen ischaemia-related injury and increase adverse outcomes.
years old and in men regardless of age. Also ischaemic injury, caused by the acute plaque disruption, may be exacerbated in the presence of ED, MVD, and/or CAS, leading to worsened clinical outcomes.

The report by Jespersen et al. clearly contributes to advance our understanding of angina. In women, as well as men, angina with non-obstructive CAD requires further investigation. Dismissing this as a benign condition cannot be justified. While emerging evidence has linked MVD with adverse outcomes, the specific mechanisms and therapeutic targets remain to be clarified.

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References