Ischaemia and outcome with normal coronary arteries

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This editorial refers to ‘Long-term survival of patients with chest pain syndrome and angiographically normal or near-normal coronary arteries: the additional prognostic value of dipyridamole echocardiography test’ by R. Sicari et al., on page 2136

Despite attempts to optimize patient selection for coronary angiography based on the clinical history and results of stress testing, the rate of normal coronary angiography in most laboratories ranges from 10 to 20%, more in women than in men.1 These patients generally have a good outcome, although many continue to complain of chest pain and some suffer cardiac events.2 Although traditionally considered a failing of clinical evaluation or stress test interpretation, these ‘false positive’ stress results may be due to one or more pathophysiological entities that do not encroach on the vessel lumen at coronary angiography.

Stress echocardiography may be particularly advantageous in understanding the pathophysiology of ischaemic syndromes with normal coronary arteries. Because it is a specific marker for ischaemia, few diseases other than ischaemia produce stress induced regional dysfunction. In contrast, although indirect assessment of small vessel disease is possible with perfusion imaging, coronary flow reserve may be influenced by non-vascular conditions such as hypertrophy, and in any case, standard perfusion imaging techniques examine relative rather than absolute flow.

Stress echocardiography is a useful prognostic tool in patients with known or suspected coronary artery disease. The presence, extent, location, and threshold of ischaemia have all been shown to be predictive of subsequent outcome,3 and further anatomic data provided by angiography are not incremental to the functional data from the test.4 In contrast, the results of stress echocardiography have been found to be incremental to angiography in situations where no significant coronary artery disease has been identified. First, in patients with dilated cardiomyopathy and no evidence of coronary artery disease, failure to augment ventricular function at stress testing identifies a higher risk group.5 The second situation of incremental benefit is described by Sicari et al.6 These investigators identified 457 patients who underwent high-dose dipyridamole echocardiography and a coronary angiogram showing non-significant coronary disease. A positive stress echo test was identified in 9.4% of these patients, which is consistent with the high specificity of dipyridamole echocardiography and also reflects the high likelihood of disease in this population (which exceeded 50% in over three-quarters of the patients). Patients with a positive stress echo accounted for 21% of follow-up mortality over the ensuing 7 years, as well as 21% of the cardiac mortality. Indeed, test positivity was an independent predictor of subsequent mortality, incremental to age, smoking history, coronary irregularities, and diabetes. The findings of this paper are consistent with the report from the Women’s Ischaemia Syndrome Evaluation (WISE) study, showing that women with chest pain in the absence of coronary stenoses demonstrate evidence of ischaemia with magnetic resonance spectroscopy, and that this finding was predictive of subsequent admissions and cost.7

The clinical application of these findings is difficult to anticipate. In patients who have gone directly to angiography without the performance of a stress echocardiogram, it is difficult to mount an argument that this test should be performed after a negative coronary angiogram, given that 90% of these will be negative and even among those that are positive, over 80% will survive 7 years and only 7% can be expected to die from cardiac reasons. However, it is the pathophysiological insight provided by this study that should prompt further consideration of the cause of events in patients with normal coronary arteries. Although some of these patients will have a misleading angiography result, for example, failure to identify significant stenoses due to technical problems with angiography, or difficulties in appreciating the severity of eccentric stenoses (particularly when the reference segment is pathological),8 this is unlikely to explain the paper’s findings, as the presence of mild disease was not predictive of outcome in this study. Moreover, although there are situations where subendocardial ischaemia occurs because of an imbalance between oxygen supply and demand, increased left ventricular cavity pressure, ventricular hypertrophy, or both do not appear pertinent to this study.

The most plausible explanation for the findings of Sicari et al.6 is that these presentations are due to abnormal vascular function, underlying small vessel pathology, or both. Abnormal arterial function may be due to coronary spasm, but this would be unlikely to provoke an abnormal stress echocardiogram, unless ergonovine stress echocardiography is used.9 Endothelial dysfunction is a possible
explanation, indeed, previous work with positron emission tomography has shown reduced dipyridamole responsiveness in subjects with Type II diabetes, who are thought to have endothelial dysfunction.10 Finally, various clinical syndromes linking ischaemia and normal coronary arteries have been attributed to small-vessel disease. Unfortunately, current imaging techniques have limited capacity to visualize these structures, but anatomic imaging seems unlikely to help the characterization of the problem, which very likely reflects problems with vascular control as much or more as it relates to vessel structure.

The results of this and similar studies should remind us to be thoughtful when we see a normal coronary angiogram after a positive stress echocardiogram. The finding may as much be due to a ‘false negative’ angiogram as a ‘false positive’ stress echocardiogram. The appropriate clinical management of patients with ischaemia and normal coronary arteries has been recommended,2 and ongoing efforts are needed to understand the mechanism of cardiac events in these patients.

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References