Editorial Comment

Coronary Flow Reserve in Patients With Normal Coronary Angiograms*

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It has been estimated that 20% of patients who undergo coronary angiography for the evaluation of chest pain have angiographically normal coronary vessels with no other cardiac cause for their discomfort. Although the natural history of this patient group is favorable (1–3), the mechanisms responsible for the pain frequently remain mysterious. In the 1960s the explanations commonly given for this syndrome were a noncardiac cause of the pain (for example, esophageal spasm) and an inadequate number of angiographic projections to exclude coronary obstructive lesions or coronary spasm. In addition, a psychogenic cause was suspected in many such patients. It is now generally agreed that these mechanisms are not responsible for causing chest pain in the majority of patients with angina and normal coronary vessels.

Measuring the coronary reserve. In the past 5 to 10 years it has become increasingly evident that there are many disease states associated with decreased coronary reserve and angiographically normal coronary vessels. Ideally, coronary reserve should be assessed by measuring the minimal coronary vascular resistance in each of the transmural layers of the left ventricular myocardium served by major coronary vessels (4). Because this cannot be accomplished in humans with available methods, a composite index of coronary reserve is usually obtained by measuring the difference between resting and maximal coronary flow over all layers. In normal humans, the ratio between resting and maximal coronary flow is between 4 and 6 (5).

Role of cardiac hypertrophy. Almost all causes of pathologic cardiac hypertrophy are associated with substantial decreases in coronary reserve (6). Furthermore, the decrement in coronary reserve is often of sufficient severity to produce ischemia in the face of only a moderate increase in cardiac metabolism. The best known syndrome in this group of disease entities is angina pectoris in patients with severe stenosis, normal vessels and marked left ventricular hypertrophy (7).

Because systemic hypertension is by far the most common cause of cardiac hypertrophy in the western world and this type of cardiac enlargement is also associated with decreased coronary reserve (8–10), an accurate assessment of left ventricular mass should be performed in patients with "unexplained" angina pectoris. Although it might be suspected that the decrement in coronary reserve would be proportional to the severity of the cardiac hypertrophy, this has not been convincingly demonstrated in clinical or animal studies (7–10). It is of interest that systemic hypertension was present in about two thirds of the patients reported by Legrand et al. (11) in this issue of the Journal. It is likely that some of these patients had left ventricular hypertrophy that may have been responsible for their decreased coronary reserve.

Other potential causes of decreased coronary reserve. In addition to cardiac hypertrophy, other potential mechanisms of impaired coronary reserve in the presence of angiographically normal coronary vessels include severe anemia (12,13), polycythemia (13,14), hypoxia (13), abnormalities that adversely affect oxyhemoglobin dissociation (13), "syndrome x" (15,16) and previous myocardial infarction. Also, many patients with angiographically undetected diffuse coronary atherosclerosis and superimposed "minor luminal irregularities" are mistakenly told that they have no significant anatomic involvement of the coronary vessels. Such abnormalities can only be defined precisely by quantitative coronary angiography which can provide absolute measurements of the luminal cross-sectional area (17,18). Unfortunately, this procedure was not performed in the study reported by Legrand et al. (11). Although their studies have some imperfections, the results do contribute meaningful new knowledge in this area and have two important implications.

Implications of studies of Legrand et al. First, whenever possible, cardiologists should actively determine potential mechanisms that may explain the pathogenesis of myocardial ischemia in patients with apparently normal coronary vessels and the syndrome of angina pectoris. In addition to excluding coronary spasm by ergonovine testing in appropriate patients, quantitative measurements of luminal diameter of the major coronary branches should be obtained to exclude diffuse coronary disease (17). Left ventricular mass should be measured precisely, metabolic evidence of ischemia should be sought and coronary reserve should be measured directly. Obviously, available methods

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will be needed at the community level to make such measurements possible on a routine basis. Efforts to accomplish this are ongoing. In the near future, automated quantitative coronary angiography and videodensitometry will be more readily available in association with digital subtraction angiographic systems. Also, accurate methods of assessing left ventricular mass will be feasible with sophisticated tomographic imaging techniques including single photon emission tomography (19), magnetic resonance imaging (20) and cine computed tomography (21). Myocardial metabolism can be crudely assessed by measuring substances such as lactate in coronary venous blood or more elegant studies of myocardial metabolism can be obtained with positron emission tomography or magnetic resonance imaging. The most promising methods of measuring coronary flow include positron emission tomography (22), cine computed tomography (23), argon clearance (8,15), an intracoronary Doppler catheter (24), xenon clearance (25) and improved digital subtraction angiography. Cine computed tomography is the only current approach that may permit measurements of perfusion in both the subendocardial and subepicardial layers of the left ventricle. With these approaches to measuring coronary flow it will be possible to obtain flow measurements under control conditions and during maximal coronary dilation achieved with either intravenous dipyridamole (24) or intracoronary papaverine (26). Intracoronary contrast, the vasodilator agent used in this study reported by Legrand et al. (11), is not an ideal coronary dilator because it produces submaximal and somewhat variable coronary dilation (24). Studies that employ this type of dilator provide at best only an index of coronary reserve.

A second important implication of the study reported by Legrand et al. (11) is that the widespread practice of using patients with "angiographically normal coronary vessels" to determine the specificity of noninvasive imaging techniques for diagnosing myocardial ischemia (thallium-201 scintigraphy and exercise radionuclide angiography, for example) should be seriously questioned. An unknown percentage of such patients have impaired coronary reserve. To minimize this problem in the future it will be necessary to restrict the normal group for such studies to normal young volunteers without coronary risk factors and presumed normal coronary anatomy or patients with angiographically normal coronary vessels who have been demonstrated to have normal coronary vasodilator reserve.

Conclusions. For almost two decades, the visual interpretation of the coronary angiogram has been the standard utilized to determine physiologically significant coronary obstructions and to identify a subgroup of patients with angina and normal coronary arteries. We hope that it will not be many more years before the fallacy of this approach is widely recognized and that diagnostic evaluation of patients suspected of myocardial ischemia will include quantitative coronary angiography, a direct assessment of coronary reserve and myocardial metabolism in the major coronary vascular territories. When this becomes standard practice, the number of patients with unexplained "angina pectoris" is likely to be a small fraction of what it is today.

References


