Etiology of chest pain syndrome with normal coronary arteries. A significant minority of patients with a chest pain syndrome who undergo cardiac catheterization have normal or nearly normal appearing coronary arteries (1,2). Although in some patients the hemodynamic significance of a coronary stenosis might be underestimated (3) or coronary spasm might be demonstrable if appropriately provoked (4), in most the epicardial arteries are probably not a pathogenetic factor in the pain syndrome. Atypical characteristics of the patient’s symptoms for ischemic cardiac pain with regard to provocation, severity, duration and response to antianginal medications often support the cardiologist’s belief that normal coronary arteriograms indicate that the pain is of noncardiac origin. Such patients can be reassured and further cardiac evaluation and hospitalizations avoided, although most will continue to experience chest pain (5,6). However, there is no shortage of noncardiac explanations for the pain (7-15), further supporting the clinician’s belief and decision.

And yet studies periodically appear steering attention back to the heart. For almost 25 years evidence has accumulated indicating that at least a subset of patients have signs of myocardial ischemia during stress, most likely a consequence of abnormal coronary flow reserve (16-24). Our group (19,20) believes that these findings reflect dysfunction of small coronary arteries. Although of pathophysiologic interest with regard to the potential role of the coronary microcirculation in ischemic heart disease, after so many years in which attention was focused on the epicardial arteries, these studies have put cardiologists in an awkward situation, even those willing to consider a coronary microvascular etiology for symptoms.

How can patients with abnormal flow reserve be identified? Our group has reported that the majority of patients with what we call “microvascular angina” (24) have abnormal left ventricular ejection fraction responses to exercise by radionuclide angiography (25). However, the degree of abnormality is often subtle and in some cases might be influenced by the patient’s gender, age or work load achieved during exercise. Certainly invasive studies of coronary flow reserve, even using state of the art technology, are unlikely to be widely adopted for further evaluation of these patients during diagnostic catheterization. Moreover, cardiologists are reluctant to redirect attention to the heart when symptoms are atypical for classic angina pectoris and the prognosis with respect to mortality is good.

The present study. A noninvasive test that could demonstrate abnormal coronary flow reserve would be of significant benefit in separating patients with a true abnormality of the coronary circulation from those with no cardiac abnormality and with angiographically defined normal coronary anatomy. The report of Geltman et al. (26) in this issue of the Journal is thus of particular interest. They report that 8 of 17 patients with chest pain and angiographically normal or nearly normal coronary arteriograms had limited coronary flow reserve in response to dipyridamole infusion (<2.5-fold increase in coronary flow from baseline) as assessed by positron emission tomography with oxygen-15-labeled water (H_2O) as the flow tracer. This limited flow reserve was interpreted as a consequence not only of higher flow at rest, but also of reduced peak flow compared with that of normal control subjects. Characteristics of the patient’s symptoms, nitrate responsiveness and conventional noninvasive testing (exercise electrocardiography, thallium scintigraphy) were not helpful in identifying patients with what the investigators interpreted as abnormal flow reserve response to dipyridamole by positron emission tomography.

However, several limitations of this study should be considered. Three of the eight patients had “<50% stenoses”; this angiographic assessment might underestimate the true hemodynamic significance of the lesion (3). Although no regional differences in flow reserve were noted by the investigators, the ungated acquisition of data during positron emission tomography could have obscured minor variations in regional flow. Another concern is that the dose of dipyridamole used (0.56 mg/kg body weight) and the timing of positron emission tomography acquisition after drug administration might have resulted in an underestimation of coronary flow reserve, even though all patients (and control subjects) received the same dose of dipyridamole and the imaging was performed under the same conditions. Also, control subjects were significantly younger than the study patients, with no overlap in age between men and women, and flow reserve might decrease with age. The authors...
report, however, that studies in older control subjects (data not included) are similar to those in the younger control subjects. One third of patients were hypertensive and no data were provided for the presence or absence of left ventricular hypertrophy by echocardiography. If present, hypertrophy could account for limited coronary flow reserve (27). In our study of patients with hypertension without left ventricular hypertrophy, the abnormal microvascular responses to pacing stress and ergonovine were similar to the responses of normotensive persons (28). Finally, the separation of patients into two groups on the basis of a myocardial perfusion reserve of 2.5 seems arbitrary because two of their 16 control subjects had abnormal myocardial perfusion reserve as assessed by this criterion.

Other mechanisms for the chest pain. A more clinically relevant problem arises if the positron emission tomographic studies of Geltman et al. (26) do truly identify patients who have limited coronary flow reserve despite angiographically normal coronary arteries. Why should this relatively modest limitation in flow reserve result in the symptoms commonly described by such patients—chest pain that is often severe and protracted with variable threshold of onset including pain at rest or with emotional stress and variably responsive to standard antianginal medications? Indeed, the clinical characteristics of the groups with low and normal myocardial perfusion reserve were similar. The same question can be put to our studies in which the majority of patients did not have transmural myocardial ischemia during pacing stress even after ergonovine administration (20,24). (although subendocardial ischemia was possible).

Recent observations by Shapiro et al. (29) and our group (30) indicate that abnormal intracardiac nociception may be a fundamental problem in this syndrome. The manipulation of catheters within the right atrium and right ventricle, pacing from the right ventricular apex at heart rates slightly faster than basal and intracoronary injection of contrast dye commonly provoke the patient’s typical chest pain (30). Similar observations and conclusions have been drawn from esophageal studies with balloon distension (31,32). In a recent study (32) we found that almost 90% of our patients experienced their typical pain during cardiac and esophageal attacks could explain these abnormal visceral pain responses.

Conclusions. Noninvasive testing by positron emission tomography may identify patients with abnormal coronary microvascular function, and calcium channel blockers may provide coronary functional and symptom benefit in some patients (33,34). However, the symptoms may well be caused by several different mechanisms and the greater symptomatic benefit may await an understanding of all of the potential mechanisms responsible for decreased vasodilator reserve as well as of the activation of sensory pain receptors within visceral structures in these patients.

References


