Dyspnea and Risk in Suspected Coronary Disease
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Stress testing for the detection of coronary artery disease is most useful in patients considered on clinical grounds to be at intermediate risk. The patient’s age and sex and the nature of chest pain can be used to provide a simple estimate of the probability of coronary artery disease. Because the absence of chest pain has traditionally been interpreted to indicate a low likelihood of coronary disease—and, indeed, a low long-term risk—functional testing has been thought to contribute little to the evaluation of patients without angina.

Basing a selection strategy for stress testing on the evaluation of chest pain has several drawbacks. First, such strategies have usually been developed to guide the diagnostic evaluation of patients with clinically significant coronary artery disease, but many patients undergo stress testing for other reasons. Second, the absence of chest pain is not a good marker of the absence of coronary artery disease. Indeed, most patients who die suddenly without known symptoms of chest pain have underlying coronary disease. Some subgroups at particular risk for coronary artery disease (e.g., patients with diabetes mellitus) have silent ischemia, the outcome of which appears to be no different from that of painful ischemia. Third, symptoms other than typical angina may also be important. Although the presence of atypical chest pain indicates a low probability of coronary artery disease, possible angina is nonetheless associated with an increased risk of death from coronary disease. Moreover, even in the absence of chest pain, the presence of symptoms such as dyspnea may serve as an angina equivalent or a marker of underlying cardiac disease.

In this issue of the Journal, Abidov and coworkers provide evidence that dyspnea is a significant predictor of the risk of both death from cardiac causes and death from any cause. These authors examined the incremental value of presenting symptoms in nearly 18,000 patients who underwent myocardial perfusion imaging at rest and during stress. After a mean follow-up of 2.7 years, patients with dyspnea at presentation had four times the risk of death from cardiac causes as did patients with no symptoms and a significantly increased risk of death from any cause. The independent predictive role of dyspnea remained significant after propensity matching.

These findings supplement a reported link between dyspnea and coronary artery disease, as well as complement the results of two earlier studies that investigated a prognostic role for dyspnea in patients undergoing stress testing. In an evaluation of over 3000 patients undergoing stress echocardiography at the Mayo Clinic, Bergeron and colleagues found that patients with a history of dyspnea were older and had a lower exercise capacity, a lower ejection fraction, and more evidence of a previous myocardial infarction than those with a history of chest pain. Ischemia was present in 42 percent of those presenting with dyspnea, as compared with only 19 percent of those presenting with chest pain. During three years of follow-up, death from cardiac causes and nonfatal infarction were most common among patients with dyspnea (5.2 percent and 4.7 percent, respectively). These authors concluded that patients with unexplained dyspnea had a high likelihood of ischemia and an increased incidence of cardiac events.

In nearly 11,000 patients undergoing stress testing at the Cleveland Clinic, dyspnea was the presenting symptom in 8 percent, and the outcome among patients with dyspnea was similar to that among patients with typical angina. However, in a multivariate analysis after propensity matching, dyspnea was not a significant predictor of an ad-
verse outcome. As noted by Abidov et al., methodo-
logic differences between their study and that of
the Cleveland Clinic may explain the disparate find-
ings.7 Of particular importance may be the inclu-
sion of data from myocardial-perfusion scanning
in the present study but not in that by the Cleve-
land Clinic group.

Dyspnea, defined as difficult, labored, or un-
comfortable breathing, is a nonspecific symptom
provoked by the stimulation of lung and respira-
tory muscle mechanoreceptors, chemoreceptors,
or vascular receptors.11 Many underlying disorders,
including ischemia, deconditioning, heart failure,
obesity, and lung disease, can cause these path-
ways to be activated during exercise.

In the study by Abidov et al., ischemia did appear
to contribute to the adverse effect of dyspnea on
prognosis. Although the percentage of ischemic
myocardium in patients with dyspnea was similar
to that in asymptomatic patients and significantly
less than that in patients with typical angina, the
percentage of patients with dyspnea who had at
least some ischemia was significantly higher than
that among asymptomatic patients and, at least in
patients with known coronary artery disease, simi-
lar to that among patients with angina. Further-
more, although the difference between the annu-
alized event rates of positive and negative perfusion
scans has been shown to be greater among patients
without dyspnea than among those with dyspnea,

Figure 1. Rate of Death from Cardiac Causes among 1091
Patients with Dyspnea, According to the Severity of the
Defect on Myocardial-Perfusion Scanning.

P=0.01 for the comparison across the groups.

further analysis of the data of Abidov et al. indi-
cates that perfusion imaging can be used to predict
the outcome even in patients presenting with dys-
pnea alone (Fig. 1). Thus, it seems likely that ische-
mia was one of the factors contributing to the in-
fluence of dyspnea on the outcome.

However, because of the limited extent of is-
chemia in many of the patients with dyspnea, and
given the adverse effect of dyspnea even in the ab-
sence of ischemia, the association of dyspnea with
an adverse outcome is unlikely to be attributable
simply to ischemia. Other contributing factors in-
clude exercise capacity, which is recognized as a
major predictor of an adverse outcome12 and which
is often manifested as dyspnea. However, in the
present study, the effect of dyspnea was apparent
in patients subjected to either exercise-induced or
pharmacologically induced stress, implying that
the effect was present irrespective of the patients'
ability to exercise. Heart failure is a likely cause of
dyspnea, and the likelihood that this diagnosis
conttributed to an adverse outcome in the study by
Abidov et al.7 is supported by the greater freque-
cy of advanced age, atrial fibrillation, and left ven-
tricular hypertrophy and enlargement among pa-
tients with dyspnea. Although the effect of dyspnea
on the outcome was apparent in both subgroups
with and those without left ventricular hypertro-
phy and enlargement, diastolic dysfunction (which
was not directly assessed by Abidov et al.) is known
to decrease survival, even in the absence of heart
failure.13

Obesity is an increasingly common noncardiac
cause of exercise intolerance. Although Abidov et
al. did not provide data on obesity,7 patients with
dyspnea had a higher prevalence of factors asso-
ciated with obesity (such as diabetes and hyper-
tension). Despite this association, it should be ac-
knowledge that the same adverse effect of dyspnea
was seen in those with and those without factors
associated with obesity. Lung disease is the final
major noncardiac cause of dyspnea. Although not
quantified in the article, the role of lung disease is
evidenced by the predictive role of lung-function
variables.6

Dyspnea is a predictor of an adverse outcome in
patients with known or suspected coronary artery
disease who are undergoing stress testing.7,9 Al-
though questions remain about the mechanism,
ischemia, left ventricular dysfunction, and obesity
appear to be plausible contributors. At the very
least, these results should remind us that cardiac
Selective Adhesion-Molecule Therapy and Inflammatory Bowel Disease — A Tale of Janus?

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Although our understanding of the pathogenesis of the chief forms of inflammatory bowel disease, Crohn’s disease, and ulcerative colitis remains incomplete, progress is being made in identifying essential components. The presence of large numbers of varied leukocytes within affected tissue where they are normally sparse makes it axiomatic that active disease is dependent on the recruitment of these cell populations. Recruitment is now known to proceed through a stereotypical series of steps that depend on selective adhesion molecules (SAMs). These include cell-surface integrins, heterodimers formed by various combinations of α and β subunits. Integrins with an α4 chain appear to play an especially important role in the intestine. α4β1 integrin (a combination also known as very late antigen 4 [VLA-4]) is present on most leukocytes but not neutrophils and effects binding to vascular-cell adhesion molecule 1 on endothelium and dendritic cells. α4β7 integrin can also mediate binding to components of the extracellular matrix. In contrast, α4β7 integrin is expressed on subpopulations of lymphocytes, natural killer cells, and monocytes and selectively targets them to so-called gut-associated lymphoid tissue. Thus, in the latter guise, α4 integrin mediates tissue-specific transport of cells to the intestine.

Circumstantial and direct experimental evidence has suggested that α4 integrins are important in the recruitment and activation of cells in inflammatory bowel disease. Tissues affected by inflammatory bowel disease have increased levels of α4 integrins and their ligands. Moreover, a disease remarkably similar to ulcerative colitis spontaneously develops in cotton-top tamarins, and administration of a monoclonal antibody against α4 integrin led to the resolution of colitis in these animals. A subsequent study also showed that treatment with an antibody specific for α4β7 integrin was beneficial in the cotton-top tamarin model.

Over the past several years, insights into the mechanisms of recruitment have prompted efforts to develop agents to address unmet medical needs of patients with inflammatory bowel disease. A number of these agents are currently being evaluated, but the study that is farthest along is that of natalizumab, a humanized IgG4-class monoclonal antibody directed against α4 integrins that has already been approved for the treatment of patients with multiple sclerosis. Two early studies suggested

symptoms other than chest pain are of value in identifying patients with suspected coronary artery disease who should undergo functional testing.

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