EDITORIALS

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.[1] 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.[2] 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.[3]

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.[1] 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.[4] 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.[5] 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.[6] 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.[7] 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,[8] 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[9] 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,[10] 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-

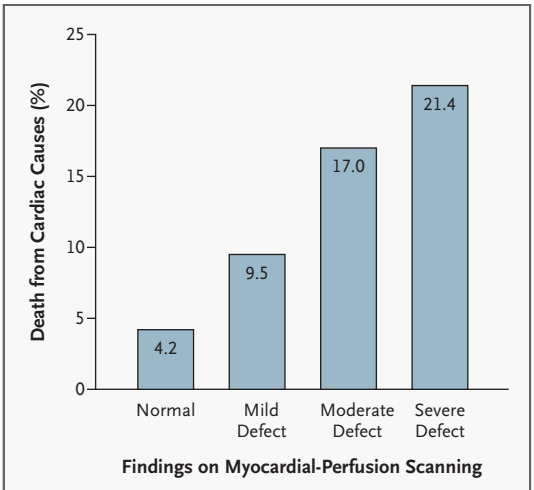

Figure 1. Rate of Death from Cardiac Causes among 1091 Patients with Dyspnea, According to the Severity of the Defect on Myocardial-Perfusion Scanning.

P=0.01 for the comparison across the groups.

verse outcome. As noted by Abidov et al., methodologic differences between their study and that of the Cleveland Clinic may explain the disparate findings.[7] Of particular importance may be the inclusion of data from myocardial-perfusion scanning in the present study but not in that by the Cleveland Clinic group.

Dyspnea, defined as difficult, labored, or uncomfortable breathing, is a nonspecific symptom provoked by the stimulation of lung and respiratory muscle mechanoreceptors, chemoreceptors, or vascular receptors.[11] Many underlying disorders, including ischemia, deconditioning, heart failure, obesity, and lung disease, can cause these pathways 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, similar to that among patients with angina. Furthermore, although the difference between the annualized event rates of positive and negative perfusion scans has been shown to be greater among patients without dyspnea than among those with dyspnea, further analysis of the data of Abidov et al. indicates that perfusion imaging can be used to predict the outcome even in patients presenting with dyspnea alone (Fig. 1). Thus, it seems likely that ischemia was one of the factors contributing to the influence of dyspnea on the outcome.

However, because of the limited extent of ischemia in many of the patients with dyspnea, and given the adverse effect of dyspnea even in the absence of ischemia, the association of dyspnea with an adverse outcome is unlikely to be attributable simply to ischemia. Other contributing factors include exercise capacity, which is recognized as a major predictor of an adverse outcome[12] 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 contributed to an adverse outcome in the study by Abidov et al.[7] is supported by the greater frequency of advanced age, atrial fibrillation, and left ventricular hypertrophy and enlargement among patients with dyspnea. Although the effect of dyspnea on the outcome was apparent in both subgroups with and those without left ventricular hypertrophy 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 associated with obesity (such as diabetes and hypertension). Despite this association, it should be acknowledged 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] Although 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

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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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.[1] 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 α_4 chain appear to play an especially important role in the intestine.[2] $\alpha_4\beta_1$ 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. $\alpha_4\beta_1$ Integrin can also mediate binding to components of the extracellular matrix. In contrast, $\alpha_4\beta_7$ 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, α_4 integrin mediates tissue-specific transport of cells to the intestine.

Circumstantial and direct experimental evidence has suggested that α_4 integrins are important in the recruitment and activation of cells in inflammatory bowel disease. Tissues affected by inflammatory bowel disease have increased levels of α_4 integrins and their ligands.[3] Moreover, a disease remarkably similar to ulcerative colitis spontaneously develops in cotton-top tamarins, and administration of a monoclonal antibody against α_4 integrin led to the resolution of colitis in these animals.[4] A subsequent study also showed that treatment with an antibody specific for $\alpha_4\beta_7$ integrin was beneficial in the cotton-top tamarin model.[5]

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 α_4 integrins that has already been approved for the treatment of patients with multiple sclerosis. Two early studies suggested