LETTERS TO THE EDITOR

Exercise Testing in Asymptomatic Patients After Coronary Artery Bypass Graft Surgery

The recent article by Miller et al. (1) regarding thallium perfusion imaging in patients having had coronary artery bypass graft (CABG) surgery 2 years prior was well written and very informative. I agree that the use of provocative testing after CABG surgery is commonplace but is done without consensus regarding timing and indication.

Of the 411 patients in Miller’s group, 34% were asymptomatic at the time of the study and their outcome was included in the whole group analysis. I would want to know what the results of testing and outcome were of these asymptomatic patients specifically as I would expect it to be quite benign so soon following surgery. I also question the indication for testing in these patients, as the most recent guidelines from the American Heart Association/American College of Cardiology task force (a panel that included one author of the present study) regarding clinical use of radionuclide imaging classifies testing in asymptomatic patients after CABG surgery as a class III indication (2).

I have been reluctant to pursue perfusion imaging on post-CABG surgery patients without the presence of symptoms of cardiac ischemia or a decline in functional status, especially within the first 5 years of surgery. If it can be shown that asymptomatic patients do have a significant prevalence of abnormal studies and poorer outcome, I would feel obligated to do more routine, surveillance testing.

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References

Reply

We appreciate Dr. Miller’s concern about the possibility of inappropriately using exercise testing in asymptomatic patients. The American College of Cardiology/American Heart Association Guidelines for Clinical Use of Cardiac Radionuclide Imaging (1) do allow some latitude for testing asymptomatic patients after revascularization procedures. Although the routine assessment of asymptomatic patients after percutaneous transluminal coronary angioplasty or coronary artery bypass graft (CABG) surgery is considered a class III indication, the use of exercise or pharmacologic perfusion imaging in selected asymptomatic patients is a class I indication. Because our study cohort (2) was retrospectively identified using a computer database and these patients were referred for testing at the discretion of their physicians, we cannot comment further on the indications for testing in the patients who were asymptomatic.

In our study the variable “clinical chest pain class” was associated with the “soft” end point that included late revascularization but was not significantly associated with the “hard” end points of total mortality or cardiac death/myocardial infarction (MI), indicating that symptom status was not a major determinant of outcome. Given the relatively small numbers of hard end points (60 deaths and 53 cardiac deaths/MIs), one must recognize the shortcomings of performing subgroup analyses post hoc in view of limited statistical power. Bearing this limitation in mind, we did separately analyze the subset of 138 asymptomatic patients to address Dr. Miller’s concern. There were 19 deaths, 13 cardiac deaths/MIs and 15 total cardiac events. At 5 years, overall survival was 88%, survival free of cardiac death/MI 93% and survival free of cardiac death/MI late revascularization 90%. The number of abnormal T1-201 segments on the postexercise image, which was the most important variable in the total study population, was not significantly associated with any end point (total mortality, p = 0.09; cardiac death/MI, p = 0.30; cardiac death/MI late revascularization, p = 0.37) in this small number of patients with a limited number of events.

A recent study (3) from the Cleveland Clinic involving 873 symptom-free patients who underwent exercise T1-201 imaging at a median of approximately 6 years after CABG surgery reported that exercise T1-201 variables were predictive of outcome. The authors concluded that their findings challenged guideline recommendations against routine testing in this setting. An important limitation of all studies (2–8) that have been published to date examining the prognostic value of exercise testing after CABG surgery is the use of selected patient populations. The only approach to accurately address the issues Dr. Miller raises is to perform a prospective study on a large series of unselected patients.

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References
Interactions Between Infections/Inflammation and Risk Factors in Coronary Artery Disease

I read with interest the report by Mehta et al. (1) that relates coronary artery disease, and thus ischemic heart disease (IHD), to interactions between traditional risk factors and infections and inflammation. Although Mehta et al. suggested it is unlikely that a common pathogenetic process can explain atherosclerosis, a hypothesis I recently proposed, the altered homeostatic (AH) theory (2) provides a unitary way to explain atherosclerosis and IHD.

The AH theory is based on the spasm of resistance vessel (S-RV) concept of ischemic diseases (which asserts that S-RV directly induces symptoms in ischemic diseases as IHD) (3,4), and on a literature review (5) designed to provide more evidence for the S-RV concept. The findings of the literature review (5) seemed extraordinary. Major and diverse risk factors for IHD express the combination of a tendency toward S-RV and thromboses (S-RV/clotting); risk factors were abnormal lipids, homocysteine, emotional stress, smoking, circadian rhythm, chemotherapy, cold exposure, cocaine, diabetes and obesity.

Also, multiple and diverse factors that ameliorate IHD express vasodilation of resistance vessels (V-RV) and an antithrombotic tendency (V-RV/anticlotting); ameliorating factors were vasodilators, fish oils, magnesium, the exercised state, estrogens, aspirin and vitamins. Further, the set of risk and ameliorating factors for IHD, with few exceptions, also operates in hypertension, stroke, migraine and Raynaud’s disease, and a separate literature review (2) showed that many of these risk and ameliorating factors are known to operate in atherosclerosis.

The expression of S-RV/clotting by multiple risk factors for multiple disorders suggested that risk factors might operate through common mechanisms to induce a variety of diseases, and altered homeostasis seemed a reasonable way to explain these findings. The AH theory was developed through a series of steps, and important to the theory’s development was the findings that multiple ameliorating factors express V-RV/anticlotting and thus act opposite of risk factors that express S-RV/clotting.

In brief, the AH theory asserts that risk factors favor atherosclerosis, IHD, and other disorders by “inappropriately” shifting homeostasis towards defensive action (fight/flight) and thus favoring S-RV/clotting and disease; factors that ameliorate IHD shift homeostasis toward rest (conservation/withdrawal) and foster V-RV/anticlotting and disease improvement. The S-RV/clotting can act either directly to induce disease or act as markers for other mechanisms of altered homeostasis. Inflammation is a major defense mechanism and, in keeping with Mehta et al. (1), probably plays a significant role in atherosclerosis.

Of interest, the scheme proposed by Mehta et al. (1) for atherosclerosis includes multiple factors that were implicated by the AH theory in altered homeostasis (2). Of special significance to the AH theory, Mehta et al. listed spasm and thromboses; they also included inflammation, infection, dyslipidemia, homocysteine excess, folate deficiency, nitric oxide inactivation and free radicals.

The AH theory, if valid, has major therapeutic implications for preventing IHD. Instead of the primary goal of cholesterol-lowering, the primary goal would be reducing the expression of S-RV/clotting by multiple risk factors; this would include cholesterol-lowering, as cholesterol expresses S-RV/clotting.

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References

Reply
I thank Dr. Hellstrom for his comments on our review. I strongly believe that it is unlikely that a single risk factor or a combination of four or five risk factors explains a disease process (coronary atherosclerosis) that affects a majority of the world population. The proposed scheme for a role of infection in atherosclerosis in our review was designed to explain atherogenesis in a select group of genetically susceptible individuals. Whereas traditional risk factors may explain the development of atherosclerosis in a significant minority of patients with coronary artery disease (CAD), in others different factors, such as homocysteineemia or primary altered homeostasis, may be the culprit. I believe that the evidence for vasospasm as a primary or major causative factor in CAD is lacking, although it is quite likely that vasospasm is a result of altered endothelial and smooth muscle function secondary to some metabolic or neurohormonal alteration. An important role for altered activity of autonomic nervous system is plausible in inducing vasoconstriction (spasm) and in the precipitation of plaque rupture as a basis of acute coronary syndromes, as suggested by Hellstrom (his reference 2).

In view of multiple etiologies of coronary atherosclerosis, I suggest that attempts be made to identify and treat causative factor(s) leading to atherosclerosis in the individual patient, rather than using a “shot-gun” approach of use of cholesterol lowering drugs, antiplatelet and antithrombotic agents, beta-blocking agents and angiotensin-converting enzyme inhibitors in all patients. Current therapeutic approaches, including surgical procedures, may represent a “band-aid” or “patch” approach to treat an underlying problem that may vary from individual to individual.

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