EDITORIAL COMMENT

The “Exercise” Part of Exercise Echocardiography

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One of the most important tasks clinical cardiologists perform is assessment of risk (1). Recent work has focused on the ability of a number of measures to predict the likelihood of death or major cardiac event for the purpose of optimally targeting treatment at patients who are most likely to benefit (1). A number of technologies, new and old, have been subjected to the test of long-term follow-up, including exercise testing (2,3), nuclear imaging (4,5), stress echocardiography (6), carotid intimal medial thickness (7) and ankle brachial index (8).

With such a plethora of tests available, what tests should clinicians obtain, in what order and in which patients? Recent guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) suggest that for patients thought to be at intermediate or high risk for coronary disease, as well as for patients with established disease, initial risk stratification test should involve some form of stress (9). If a patient can exercise, has an interpretable electrocardiogram and has not had prior revascularization, the test of choice is an exercise echocardiogram without concurrent imaging. Patients deemed to be high risk should then be referred to coronary angiography, whereas low risk patients can be treated conservatively. Those patients whose predicted risk is still uncertain are appropriate candidates for imaging.

See page 1345

In this issue of the Journal, McCully et al. (10) present an interesting analysis that questions the approach recommended by the ACC/AHA guidelines (9). Previously, this group showed that patients with normal exercise echocardiograms are at very low risk for subsequent cardiac events (11). Now, they present the outcomes of 1,874 patients who underwent stress echocardiography with abnormalities either at rest or during exercise and who had a “good exercise capacity” defined simply as ≥7 METs in men and ≥5 METs in women (10). Those patients whose left ventricular end-systolic size failed to decrease during exercise or whose end-exercise left ventricular systolic function was severely impaired were at increased risk for cardiac death and other major cardiac events. In a multivariable analysis, the only independent predictors of outcome were diabetes mellitus, history of prior myocardial infarction and failure of left ventricular end-systolic size to decrease. The authors conclude that among their patients with a good exercise capacity but abnormal exercise echocardiograms, sophisticated analyses of exercise echocardiographic variables provide incremental information for identification of higher and lower risk groups.

An obvious implication of this study is that stress testing without concurrent echocardiography is not enough, as even among patients with a “good exercise capacity” the echocardiogram was of additional prognostic value. Can clinicians trust the exercise test alone to satisfactorily identify low risk patients? Or must concurrent imaging be performed straight away, even in the large number of patients who can exercise, have interpretable electrocardiograms and have no history of revascularization?

To answer these questions, we must first examine the stress test itself and its ability to stratify risk. Probably the most powerful stress test predictor of risk is exercise capacity (9). Because exercise capacity is closely related to age and gender, some researchers have defined impaired capacity according to prespecified age and gender categories (3,12). This is important as, for example, an exercise capacity of 7 METs has a very different prognostic meaning in a 40-year-old man than in a 70-year-old man. In the 40-year-old man, an exercise capacity that low predicts a substantially increased risk of death (3,12), whereas in the 70-year-old risk would not be increased.

Two other exercise predictors of outcome that provide important prognostic information over and above functional capacity and clinical variables are chronotropic response (13) and heart rate recovery (7,14–16). Chronotropic incompetence is present when the heart rate rise during exercise is attenuated; its presence is at least as prognostically ominous as a nuclear perfusion abnormality (13). However, its value is unclear in the setting of beta-blockade. Heart rate recovery is the fall in heart rate during the first few minutes after exercise and is thought to reflect vagal tone (17). An impaired heart rate recovery is predictive of death independent of exercise capacity (2,14), left ventricular function (15,16), nuclear perfusion abnormalities (2) and extent of angiographic coronary disease (15). Furthermore, heart rate recovery is predictive of death even when measured in patients taking beta-blockers (2,15).

The prognostic value of the exercise test is maximized when multiple exercise findings are considered. More than a decade ago, the Duke treadmill score was derived (18) and validated (19), incorporating exercise capacity with ST-segment changes and exercise-induced angina. Recent studies have confirmed the overriding importance of exercise capacity as a predictor of all-cause death and cardiac events (4,12,15,20), while ST-segment changes have not emerged as an independent predictor (14,15,20). When exercise test
findings that truly have strong and independent prognostic value are considered together, the test is remarkably capable of identifying low and high risk patients (4,15,21,22).

Even if combining different exercise test findings does improve the ability of the test to stratify risk, we are still left with the question as to whether or not high risk patients might be missed if we were to rely on the exercise test alone. Two recent studies shed light on this issue. Shaw et al. (22) followed 3,620 medically treated patients who underwent exercise nuclear studies. A low risk Duke treadmill score was found in 921 patients (25%). Cardiac death rates among these patients with normal nuclear scans or with perfusion abnormalities in up to two vascular territories were only 0.3% and 0.4% per year. In the very few patients (n = 27) who had perfusion abnormalities in all three vascular territories, only one patient died. Diaz et al. (4) followed 7,163 patients for 6.7 years, during which time 855 died. Among the 4,514 patients who had not undergone prior revascularization, there were 2,018 (45%) who had at least average functional capacity for their age and gender and who had a normal 1-min heart rate recovery of >12 beats/min. All of these patients had all-cause death rates of <1% per year, even when the nuclear scan was substantially abnormal. There were 863 patients (19%) who had both impaired functional capacity and an abnormal heart rate recovery. In this group, the death rate exceeded 3% per year, even when the nuclear scan was completely normal. This left 1,633 patients (36%) who had either an impaired functional capacity or an abnormal heart rate recovery, but not both. It was among these patients that the nuclear scan was quite useful in separating the lower and higher risk subgroups.

Both of these large studies suggest that, irrespective of imaging data, the absolute risk of death is low when the exercise test, interpreted using some kind of composite measure, suggests low risk. A limitation of both reports (4,22), along with the current study of McCully et al. (10), is that they suffer from selection bias, in that the analyses were based on patients who for some reason were referred for stress testing combined with imaging. Patients in all three cohorts were higher risk with sizable subsets having established coronary disease or multiple risk factors. Thus, it is not all that surprising that the number of patients identified as low risk by the stress test alone was relatively low. In a recently reported cohort of 9,450 patients who were referred for stress testing alone without imaging, 86% of the patients could be identified as low risk with mortality rates of <1% per year when stress test prognostic interpretations incorporated the Duke treadmill score, chronotropic response and heart rate recovery (14,21).

Current ACC/AHA guidelines, backed up by the literature, support stress testing alone, especially when interpreted in an evidence-based sophisticated way, as a means to adequately identify low risk patients for whom further work-up is not needed. How then do we put the results of McCully et al. (10,11) into context?

The imaging technique they used was echocardiography, whereas most existing prognostic literature is based on nuclear imaging, which has been in common clinical use for a longer time. Comparative studies of the prognostic power of these two techniques are few, but suggest that they are probably similar (23).

The authors considered end points besides cardiac death, namely nonfatal myocardial infarction and late revascularization. These end points, which accounted for the vast majority of events, are clinically relevant, but likely suffer from ascertainment bias. Myocardial infarction was not adjudicated by a core laboratory, as is commonly done in clinical trials. Interpretations of electrocardiograms for diagnosis of myocardial infarction can be seriously biased when readers are aware of other clinical data (24). This is not just of academic interest, as it has been shown that electrocardiograms of patients with suspected acute coronary events are more predictive of subsequent events when evaluated by a core laboratory as opposed to local investigators (25). Similarly, it is quite plausible that performance of late revascularization is in some way influenced by clinicians’ knowledge of prior stress echocardiogram results. The most objective and probably least biased end point the investigators considered was cardiac death, which itself can suffer from significant ascertainment biases (26). Nevertheless, it is noteworthy that even in the cohort of patients of McCully et al. (10) with their definition of a good exercise capacity, failure of the left ventricular end-systolic size to decrease was associated with a cardiac death rate of only 1.1% per year.

The analyses by McCully et al. (10) provide evidence that careful, sophisticated interpretation of exercise echocardiograms can provide additional independent prognostic information over and above other clinical variables. Clinicians should realize, however, that sophisticated interpretation of the exercise stress test makes it an enormously powerful prognostic tool. Exercise capacity as a function of age and gender, chronotropic response and heart rate recovery should be routinely measured and considered. Among patients without a revascularization history, these measurements alone can identify a very large subset for whom conservative management and reassurance is appropriate. The real strength of imaging is found when it is performed in patients deemed to be at increased risk after clinical evaluation and after a carefully performed and interpreted exercise test.

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