Exercise is one of the most common noninvasive stressors used to risk stratify patients with suspected or established coronary disease. Functional capacity, time to onset of demand-induced ischemic ST-segment shifts or angina, complex ventricular arrhythmias, a progressive fall in systolic blood pressure during exercise, and abnormal heart rate (HR) responses either during or after exercise are all well-established independent predictors of long-term outcome and, when used in combination, have the potential to identify prognostic high-risk patients who may be candidates for coronary angiography and coronary revascularization. Among HR variables tested that are predictive of mortality, the most common include the ability to augment HR to age-predicted maximum (chronotropic response), the HR recovery response in the immediate postexercise phase, and the ST-segment response corrected for HR.

In 2005, Falcone et al published a report in Circulation indicating that a rapid HR increase at the onset of exercise ($\Delta HR_{1\text{ minute}} \geq 12$ bpm) predicts increased adverse cardiac events and cardiovascular mortality in patients with coronary artery disease even after adjustment for potential prognostic confounders. This finding is important because the observation would allow potential risk stratification of patients after only 1 minute of exercise, a useful parameter for patients who cannot perform more strenuous exertion. Notably, the authors comment that their findings require validation in a separate data set. In this issue of Circulation, Leeper et al examined initial HR responses using multiple different definitions, including $\Delta HR_{1\text{ seconds}}, \Delta HR_{2\text{ METS}},$ and $\Delta HR_{1\text{ minute}}$ and report that a rapid initial increase in HR predicts decreased total and cardiovascular mortality and that peak exercise HR is the most powerful predictor of cardiovascular prognosis after adjustment for prognostic confounders. How can both well-done studies reach the exact opposite conclusions? A careful analysis provides useful insight.

The exercise protocol that Falcone et al used was a symptom-limited semisupine bicycle ergometer with an initial workload of 25 W and fixed stepwise 25-W increments every 2 minutes. The 458 patients were selected for exercise testing after a cardiac catheterization had been performed and coronary disease confirmed. Presumably, patients with high-risk coronary disease were excluded from the study and referred for revascularization. $\beta$-Blockers and calcium antagonists were withdrawn before testing in 69% of subjects. Patients with signs or symptoms of heart failure, with impaired left ventricular ejection fraction, on digitalis, with evidence of valvular or congenital heart disease, and with a pacemaker or noninterpretable ECG were excluded from the study. Patients were followed up for a median of 6 years, and the cardiovascular end points tested were a composite of cardiac death (n=15) and nonfatal myocardial infarction (n=56). The overall mortality was very low (3.3% after a median of 6 years), indicating a low-risk population of patients with coronary artery disease.

In contrast, the exercise protocol used by Leeper et al was symptom-limited upright treadmill testing that started at 2 mph and 0% grade using a pretest questionnaire to estimate subsequent grade and speed to reach target aerobic capacity (ramp protocol) for individual patients. The US veterans were referred for stress testing as opposed to being selected for exercise testing after cardiac catheterization. Cardioactive medication was not stopped or decreased before testing. Of the 1959 patients studied, the mortality rate was 10% over a mean of 5.4 years, even though only 578 of the 1959 patients...
had a history consistent with coronary artery disease. Thus, the patient population was considerably sicker than the patients studied by Falcone et al. Leeper et al do not report data on incident nonfatal myocardial infarction rates. Exclusion criteria are not cited in the Leeper study; indeed, 10% of the patients with coronary disease had a prior history of heart failure, a condition associated with abnormal HR responses. Furthermore, 38% of the 578 patients in the subset with coronary artery disease were on β-adrenergic blocking therapy at the time of testing. Additional important differences between the report by Falcone et al and the Leeper et al subset of coronary artery disease patients that could affect HR response in early exercise are the incidence of diabetes, a condition associated with autonomic dysfunction (9.8% versus 19.3%); smoking history (75.3% versus 49.3%), a nicotine habit with the potential to rapidly increase catecholamine levels; β-adrenergic blocker use (38% in the Leeper et al study); and frequency of exercise-induced ischemia (37.5% in Falcone et al versus 57.4% in Leeper et al). In the report by Leeper et al, ΔHR1 minute in the 578 patients with coronary artery disease did not significantly correlate with cardiovascular mortality, although the difference was significant for the entire population of 1959 subjects. Both reports are silent on atrial fibrillation, a condition known to be associated with rapid increases in HR in the early stages of exercise.

Clearly, there are valid explanations as to why the 2 studies came to different conclusions. There are major imbalances between the 2 study designs. The test conditions were different. For example, the increase in HR with exercise in the supine position may be more rapid than in the upright position because stroke volume contributes only a small amount to the increase in cardiac output compared with the upright position, in which the increase is the result of augmented stroke volume and HR. There are important differences in the patient selection criteria, demographics, duration of follow-up, choice of end points, and overall mortality risk. Differences in β-adrenergic blocking drug use that would tend to blunt an early acceleration of HR, diabetes, smoking, and inclusion or exclusion of patients with impaired left ventricular function are all confounders that could explain in part the discrepant findings.

For the practicing clinician, the take-home message is clear. Rapid acceleration of HR in the early phases of exercise should not be used in the clinical setting to predict cardiovascular outcomes until a much better understanding of the autonomic mechanisms governing HR response in the early phases of exercise in patients with chronic ischemic heart disease are known for exercise in both the upright and nonupright positions and in patient populations on various cardioactive medications and with different comorbid conditions. In the interim, HR reserve used during exercise and HR recovery are the most useful HR variables that should be considered. Prognostic risk stratification using the exercise ECG test should incorporate the HR variables combined with other validated predictors of outcome that include functional capacity, time to onset of ECG ischemia or angina, exercise-induced complex ventricular arrhythmias, or abnormal blood pressure responses to optimize prognostic risk estimates.

Disclosures

None.

References


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