How quickly the heart rate recovers after treadmill exercise testing has been the subject of much interest over the last several years. The observations of Imai et al1 first prompted the clinical evaluation of heart rate recovery. In healthy subjects, athletes, and patients with heart failure, they demonstrated that early (within 1 minute) heart rate recovery was principally the result of vagal reactivation. The phenomenon was abolished by atropine, unaffected by β-blockers, independent of workload or age, blunted with heart failure, and accelerated in athletes. The hypothesis joining heart rate recovery and mortality arose from work that developed to the point at which autonomic tone is considered a cardiovascular risk factor.3 Particular interest has focused on the ability of heart rate recovery to predict all-cause mortality.4–13

Michael Lauer’s group from The Cleveland Clinic has been the driving force behind this field of investigation. In this issue of Circulation, these investigators present a further, provocative analysis of data from their center that explores the question of whether heart rate recovery can predict who will survive after coronary revascularization. In their study, Chen et al14 address an issue that is typically dealt with via randomized controlled studies. In lieu of such a trial, they compiled observational data and applied a modified case-control study design. From a group of 8861 patients who underwent treadmill exercise tests with imaging, they found 552 patients who underwent early (ie, within 3 months of the exercise test) coronary revascularization. Using propensity matching, Chen and colleagues were able to match 508 patients from this group with 508 patients from the >8000 patients who did not undergo early revascularization. The final study group of 1016 patients comprised 2 groups matched for 48 clinically relevant factors except early revascularization status. Overall, no benefit from revascularization could be ascribed to patients without inducible ischemia, but the benefit was significant in those with ischemia. They found that in patients with inducible ischemia, abnormal heart rate recovery was associated with a nonsignificant trend toward a diminished survival benefit from revascularization. The sample size that Chen et al used in this particular analysis was small, and as pointed out by their power analysis, their study in retrospect was underpowered to address the question posed. Therefore, a nonsignificant trend does not disprove their original hypothesis, but it does provide clear support.

Another intriguing observation involves the patient subgroup with both inducible ischemia and abnormal functional capacity. Within this subgroup, patients with normal heart rate recovery benefited from revascularization and those with abnormal heart rate recovery did not. The group with the best survival rate was the one with normal heart rate recovery that underwent revascularization.

In their discussion, Chen et al admit the obvious: Irrespective of what their final conclusions were, this was a nonrandomized observational study. Their study design attempted to mimic the principal effect of randomization (ie, to equalize the baseline characteristics of the 2 study groups). As with all observational studies, their conclusions are at best hypothesis generating rather than hypothesis proving. Nevertheless, it is unlikely that a randomized trial to directly confirm their conclusions will be performed.

Taking into consideration the above reality and the results of their study, where should this field of investigation go from here? First, if larger databases with available and comparable exercise test and imaging data exist, then a reevaluation of the hypothesis of Chen et al should be attempted with the same study design. The emphasis should be on including large numbers of symptomatic patients who underwent revascularization that separate analyses might be performed on bypass and angioplasty populations. Whether this proposal is realistic is unclear, but it is nevertheless worthy of consideration.

Second, heart rate recovery as a prognostic variable deserves further investigation and refinement. In 2002, Gibbons15 provided commentary on the role of heart rate recovery in making clinical decisions. Although noting that the available studies at the time were large, with long follow-up and rigorous analyses, Gibbons pointed out 7 limitations of the available literature:

1. Limited evaluation in symptomatic populations
2. Variable recovery protocols
3. Variable criterion for abnormality
4. Limited assessment in centers outside The Cleveland Clinic
5. Limited assessment of incremental value over other exercise test criteria or scores
6. Risk end points limited to all-cause mortality
7. Unresolved issues relating to the effects of chronotropic incompetence and β-blocker use

He did not support the widespread application of heart rate recovery until the issues concerning limitations were addressed. Since Gibbons’s review, 4 additional studies have evaluated heart rate recovery and prognosis and did not involve patients from The Cleveland Clinic population. Using Gibbons’s 7-point outline, I will update the status of each point:

1. The assessment of patients with symptoms of suspected ischemia with or without known coronary disease remains limited. The majority of patients are asymptomatic and derived from healthy cohorts. One study did, however, evaluate patients after a recent myocardial infarction.

2. Recovery protocols still are not standardized. To simplify this situation, I would recommend 2 protocols: immediate cessation of exercise with assumption of the supine position and a cool-down protocol. The first of these protocols is necessitated by the nature of the exercise echocardiographic protocol but could be used without this imaging modality. This protocol is easy to standardize. A cool-down protocol is problematic in this regard and differences in heart rate recovery with protocols of varying intensity could continue to confound future studies. The recovery protocol used at The Cleveland Clinic, although somewhat arbitrary, is not unreasonable (first 2 min of 1.5 mph at 2.5%). The Clinic has used it throughout their studies.

3. The criterion for abnormality varies depending on the institution and the available data. Of the 4 additional studies, 2 used The Cleveland Clinic standard cutpoint of ≤12 bpm (a Cleveland Clinic criterion for use with exercise echocardiography of ≤18 bpm also exists). Although cutpoints provide for a normal or abnormal interpretation, it is difficult to accept that the risk of a patient with a recovery of 11 bpm differs substantially from the risk of a patient with a recovery of 13 bpm. Chen et al provide data that confirm this continuity of risk. The cutpoints are convenient, but they do not tell the whole story. A better way needs to be developed to incorporate a continuous rather than a discrete variable into the analysis.

4. Centers other than The Cleveland Clinic have submitted analyses, but centers that use the same protocols and criteria of abnormality also need to provide analyses.

5. Despite engendering no additional cost and being easy to measure, confirming the incremental value of heart rate recovery in the proper sequence of testing is needed. One study suggests that such confirmation adds to the Duke treadmill score, but the Duke score was developed to predict cardiovascular death, not all-cause mortality.

6. The Framingham study suggests that end points other than all-cause mortality are predicted by abnormal heart rate recovery. Although Chen et al failed to confirm the cutpoints developed at The Cleveland Clinic, the Framingham investigators used a different recovery protocol.

7. The issue of the effect of β-blockers and chronotropic incompetence on heart rate recovery has not been settled. Most prognostic studies adjust for β-blocker use and peak heart rate achieved; however, whether these factors influence the measurement of heart rate recovery is unresolved.

Third, and most important, once the methodological issues of heart rate recovery have been addressed, interventions designed to affect the abnormal autonomic milieu should be developed and tested in trials in which heart rate recovery is considered in the randomization process.

Having identified a patient with an abnormal heart rate recovery and assuming that this signifies increased cardiac risk related to an autonomic imbalance, what should be done? The obvious answer would be to improve the heart rate recovery response. This presumes that an abnormal heart rate recovery is modifiable and that modifying it changes risk. Is there evidence that heart recovery is modifiable? Yes, on 2 fronts: pharmacological therapy and exercise training. Given their beneficial effects on mortality in a variety of settings, β-blockers would be an obvious candidate, especially because of their effect on parasympathetic tone in the postmyocardial infarction setting. Pavia et al have demonstrated that in patients with coronary disease and normal left ventricular function, the slope of the heart rate recovery curves was steeper in those receiving metoprolol as compared with those not taking a β-blocker. Countering this are the original observations of Imai et al concerning a lack of effect by β-blockers on early heart rate recovery. In addition, Racine et al demonstrated no effect in 6 months of β-blocker therapy on the markedly abnormal heart rate recovery noted in patients with congestive heart failure. Thus, considerable equipoise on the effect of β-blockers on heart rate recovery remains.

On a different pharmacological horizon, Androne et al evaluated the effects of pyridostigmine, an acetylcholinesterase inhibitor, on heart rate recovery in patients with stable congestive heart failure. They found that although peak heart rate was not increased, pyridostigmine increased heart rate recovery at 1 minute but not at 3 minutes. This small single dose study provides no insight, however, into whether pyridostigmine would be tolerated long-term and, more important, whether this alteration in heart rate recovery would translate into a survival benefit.

Two studies on exercise training provide supportive evidence that heart rate recovery can be improved; however, neither study was large enough to assess for effects on mortality. Likewise, neither study focused on patients with a distinctly abnormal heart rate recovery. Thus, the void of knowledge is considerable concerning whether heart rate recovery can be modified by medications or exercise training so as to have a meaningful effect on survival. We have hardly begun to address this question seriously.

In summary, although the study of Chen et al is in essence a “negative” study, it does not settle the issue of whether heart rate recovery provides a means to stratify patients with ischemia undergoing revascularizationinto groups that will and will not experience a survival benefit. The investigators at The Cleveland Clinic have led the way in investigating the significance of heart rate recovery and have been consistent in their methodology. Subsequent studies from other institutions have been less consistent in their methodology, principally because of the lack of equivalent data. For this area of investigation to move forward, future investigations should embrace The Cleveland Clinic methodology and clearly and
concisely determine the role of heart rate recovery in assigning risk and assessing therapy.

References

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