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Exercise Testing
Part 2: The Value of Heart Rate Recovery

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In the last issue of *Cardiology Rounds*, the value of exercise electrocardiography as a diagnostic tool for coronary artery disease was questioned because the results of this commonly performed test may be inaccurate due to verification bias.[1,2] The issue also related how the currently accepted gold standard – coronary angiography – may also have severe inherent limitations because it is very often performed based on the outcome of exercise testing and may underestimate the burden of disease.[3] The true value of exercise electrocardiography is in its ability to assess prognosis with markers such as exercise capacity,[4,5] heart rate response during[6] and after exercise[7,8] and the Duke Treadmill Score.[9,10]

In terms of heart rate response, it has been observed in fit subjects that in the first few minutes after exercise, there is an initial steep fall in heart rate lasting about 30 seconds, followed by a shallower fall.[11] In patients with heart failure, however, there is never a steep fall. Instead, they have a shallow fall throughout recovery. It has been concluded therefore that heart rate recovery after exercise, particularly during the first 30 seconds, is closely related to vagal reactivation.[11] Because autonomic imbalances are associated with mortality,[12,13] and because of the associations between exercise heart rate responses and autonomic nervous system function, it was hypothesized that measures of heart rate response in the exercise lab would be an independent predictor of mortality.[14] With this hypothesis in mind, physicians at the Cleveland Clinic followed 2,428 patients referred for exercise nuclear testing to discern if an attenuated heart rate recovery, as a manifestation of vagal tone, would be independently predictive of increased risk of mortality.[14] The results of their findings are outlined in Part 2 of this review on exercise testing.

Heart rate recovery

In the early 1990s, 2,428 patients were referred for exercise nuclear testing at the Cleveland Clinic for evaluation of known or suspected coronary disease.[14] All of the subjects were potential first-time candidates for coronary angiography. Heart rate recovery was defined as the difference in heart rate at peak exercise and that measured one minute later. It should be noted that all subjects underwent a cool-down period during recovery; that is, after peak exercise had been achieved, they walked slowly at a shallow grade for two minutes before stopping exercise altogether. Based on maximization of a log rank chi square statistic, an abnormal heart rate recovery was defined as a value of ≤ 12 beats per minute (bpm). Thus, a person achieving a peak heart rate of 160 beats per minute (bpm) would have to get his/her heart rate below 148 bpm by one minute later in order to be considered to have a normal heart rate recovery.

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Figure 1: Association of an abnormal heart rate recovery (defined as ≤12 beats per minute during an upright cool-down period) in candidates for first-time coronary angiography who underwent exercise nuclear testing. (Reproduced from Reference 52 with permission.)

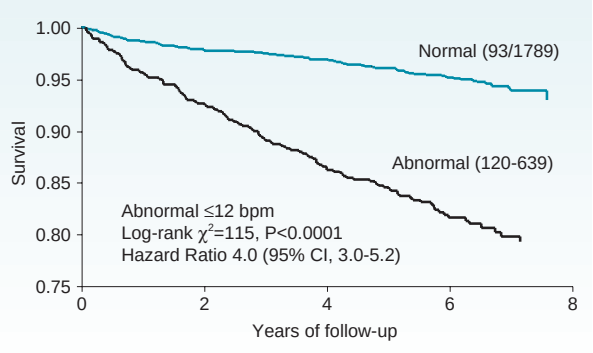
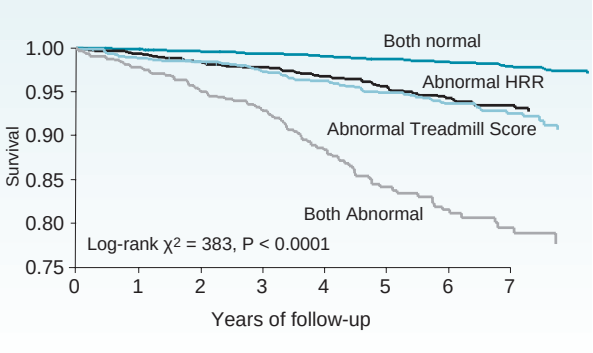


Figure 2: Association of an abnormal heart rate recovery and an abnormal Duke treadmill score (≤ 5) with mortality among 9,454 patients referred for exercise testing without imaging. (Reproduced from Reference 18 with permission).



As shown in Figure 1, patients with an abnormal heart rate recovery (≤12 bpm) were at markedly increased risk of death compared to those with a normal heart rate recovery. Abnormal heart rate recovery was consistently predictive of death in subsets of men, women, older and younger subjects, patients with and without known coronary disease, patients with and without a normal chronotropic response to exercise, and patients with and without perfusion abnormalities on nuclear scan. Of note, the presence of an abnormal heart rate recovery with a normal nuclear scan was associated with a death rate that was no different than the presence of nuclear abnormalities in patients with a normal heart rate recovery. Patients who had both perfusion abnormalities and an abnormal heart rate recovery had a very high mortality rate, over 25% at 6 years. Furthermore, heart rate recovery was predictive of death, *irrespective of use of beta-blockers* or vasodilators. In a multivariable analysis, heart rate recovery was predictive of death even after accounting for exercise capacity, age, gender, nuclear perfusion defects, chronotropic response to exercise, and multiple other potential confounders. Thus, in this first analysis, the hypothesis was confirmed in that heart rate recovery did emerge as an independent predictor of mortality.

Despite this initial observation, a number of important questions regarding the clinical usefulness of heart rate recovery remained to be answered.

Does heart rate recovery predict risk versus the Duke Treadmill Exercise Score?

It was not known whether heart rate recovery would predict risk independent of the Duke Treadmill Exercise Score,[9,10] which is the currently accepted standard for risk assessment on the treadmill test.[15-17] In a population involving 9,454 patients, who were referred specifically for electrocardiography without imaging,[7] we found that heart rate recovery did, indeed, predict risk over and above that estimated by the Duke Treadmill Score (Figure 2).

Is heart rate recovery predictive of risk once left ventricular function is taken into account?

Left ventricular systolic dysfunction is one of the most powerful predictors of risk in patients with known or suspected coronary disease.[18] We studied this issue in 5,438 patients who underwent exercise cardiography.[19] By the nature of the exercise echocardiography protocol, left ventricular systolic function was systematically measured in all subjects. In these patients, heart rate recovery again emerged as an independent predictor of risk, providing prognostic information over and above that provided by left ventricular systolic dysfunction. In fact, an abnormal heart rate recovery was associated with a risk of death that was just as high risk of death as a left ventricular ejection fraction of < 40%. The combination of an abnormal heart rate recovery with left ventricular systolic dysfunction was associated with a particularly high death rate.

Is the ability of heart rate recovery to predict death related to the type of recovery protocol used?

Patients undergoing stress echocardiography must cease all exercise immediately after peak exercise is reached, and furthermore, must assume a left lateral decubitus position. This would be expected to increase venous return, which might then lead to a reflex bradycardia mediated by volume receptors in the right and left atria. In fact, the distribution of heart rate recovery is different in patients undergoing stress echocardiography than in patients undergoing other types of exercise testing in which a stand-up cool-down period is used. Thus, we found that a cut-off point of ≤ 18 beats bpm was optimal for predicting death in patients undergoing stress echocardiography,[19] as compared to ≤ 12 bpm in patients under-

going stress testing with an upright cool-down period.[14] Nonetheless, heart rate recovery again emerged as an independent predictor of risk of death, even after taking into account exercise capacity, left ventricular systolic function, age, gender, and multiple other confounders.

Does heart rate recovery predict risk in asymptomatic individuals after taking into account other standard cardiovascular risk factors?

To answer this question, we examined 12-year outcomes of a cohort of over 5,000 subjects who participated in the Lipid Research Clinics' Prevalence Study.[20] These patients underwent near maximal exercise and had their heart rate recovery measured 2 minutes after completing exercise and assuming a sit-down position. Again, an abnormal heart rate recovery, here defined as ≤ 42 beats per minute over 2 minutes of recovery, was associated with a greater than twofold increased risk of death. Furthermore, this increased risk was independent of all standard cardiac risk factors, including blood pressure, smoking, LDL cholesterol, tryglyceride, HDL cholesterol, and blood glucose.

Would heart rate recovery be predictive of risk in a clinical population outside of the Cleveland Clinic?

Since the Clinic was where most of the initial studies were performed, this was a valid consideration. Shetler and colleagues followed the outcomes of over 2,000 patients undergoing exercise testing and coronary angiography.[21] They again found that, no matter which definition of an abnormal heart rate recovery was used, an attenuation of heart rate recovery was independently predictive of risk of death. This was true even after taking into account findings in coronary angiography. In a multivariable model, age, exercise capacity, and heart rate recovery were predictive of mortality, while ST-segment changes and angiographic severity of coronary disease were not.

Heart rate recovery and mortality – Summary

The association of heart rate recovery with mortality has been shown to be robustly associated with death in studies involving over 23,000 patients. The association was evaluated after development of an *a priori* biologically-based hypothesis. It has been shown to remain even after taking into account multiple different confounders, as well as different types of recovery protocols. Furthermore, it has been externally validated outside of the Cleveland Clinic.[20,21]

Recently, the value of heart rate recovery as a clinical tool has been questioned.[22] It has been pointed out that some of the studies involve patients who were referred for exercise testing for reasons outside of those listed in current ACC and AHA guidelines.[15,16] The cool-down period used at the Cleveland Clinic has been criticized as being unusual,[22] thereby decreasing the relevance of heart rate recovery in other populations. Only one comparison has been made with the Duke Treadmill Score.[7] Finally, evidence of ischemia as manifested by ST segment changes does not appear to predict risk once heart rate recovery and functional capacity are accounted for.[7,21] This has been greeted with skepticism.[22]

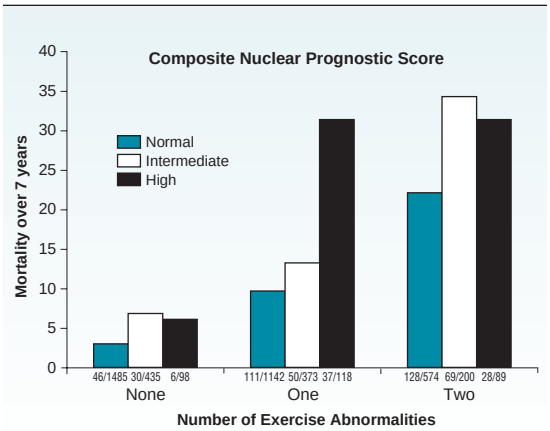
While heart rate recovery has been found to predict risk of death independently of the Duke Treadmill Score in one study, it must be appreciated that any comparison with the Duke Treadmill Score is inherently problematic. First and foremost, the Duke Treadmill Score requires interpretable ST segments. Thus, any patient taking digoxin or having any underlying abnormality of the resting ECG, cannot have the Duke Treadmill Score measured. It is different in the case of heart rate recovery, which can be measured in the vast majority of patients referred for exercising testing.[23] Second, it is often not appreciated that the Duke Treadmill Score was originally developed, albeit arguably, in a biased cohort of patients who underwent exercise testing and coronary angiography.[10,24] Although the Duke Treadmill Score has been validated in a number of cohorts, the only *component* of the Duke Treadmill Score that has been consistently validated has been exercise capacity.[7,21,25] The two other components of the Duke Treadmill Score, namely ST-segment changes and exercise-induced angina, have been consistently shown to *fail* to predict subsequent risk in a number of contemporary cohorts after exercise capacity has been accounted for.[7,21,24,25]

Use of functional capacity and heart rate dynamics in clinical care

As discussed above, ST segment changes have very limited value as a diagnostic tool because of problems of verification bias[5] and an inadequate gold standard.[1] Furthermore, when put alongside functional capacity and heart rate dynamics, the ST segment emerges as a weak predictor of risk.[7,21,24,25] Nonetheless, it may be easier to accept the ST segment as a clinically useful marker since exercise-induced ischemia might be a relatively easy disorder to treat. In contrast, the optimal management of impaired functional capacity or abnormal exercise heart rate dynamics is not known. Simply put, while we *do* know that impaired functional capacity and abnormal heart rate dynamics are very powerful predictors of risk, we *do not* know what to do when they are found to be abnormal.

The potential value of these measurements in current clinical practice is illustrated in Figure 3. Here, data on a cohort of over 5,000 patients undergoing exercise nuclear testing are presented.[23] None of these patients had undergone prior revascularization. Patients who had a normal functional capacity for age and gender and who had normal heart rate recovery, had a very low absolute risk of death, irrespective of abnormalities on the nuclear scan.

Figure 3: Association of exercise capacity, heart rate recovery, nuclear scintigraphy findings and 7-year mortality among patients who had not undergone prior revascularization. The blue bars refer to normal nuclear scans, the white bars intermediate risk scans, while the black bars refer to high risk scans. The numbers under the bars refer to the number of deaths and number of total patients in each subset.



Even those patients with very abnormal scans, had a death rate of < 1% per year and therefore, would not be considered to be appropriate candidates for revascularization. In contrast, patients with impaired functional capacity, abnormal heart rate recovery, or both, had substantially increased risks of death. Furthermore, in these patients, the nuclear scan was able to provide clinically meaningful differences in risk estimations. Thus, given today's state of knowledge, clinicians can confidently use functional capacity and heart rate recovery to easily and inexpensively identify patients who are at low risk of death. These patients can be managed conservatively without any need for further tests unless they suffer from refractory symptoms.

On the other hand, those patients who have abnormal exercise findings may well benefit from further testing and more aggressive testing[17] and management, although this remains to be determined. Future research will be necessary to determine how best to reduce risk in patients with impaired functional capacity, chronotropic incompetence, or an abnormal heart rate recovery.

Conclusion

Some physicians may consider the exercise test to be outdated and even obsolete now that sophisticated imaging procedures are readily available. However, I maintain that what is, in fact obsolete, is interpretation that is focused primarily on the diagnosis of coronary artery disease based on ST-segment changes. The relatively simple and inexpensive exercise test routinely yields a veritable treasure trove of information that has enormous prognostic strength for prediction of death, arguably the most important endpoint when considering the assessment and management of patients with known or suspected cardiac disease.[26]

Table 1 provides a summary of how best to utilize the exercise test to assess risk of death. Interpretation should focus on 3 main "axes" of findings:

• First, functional capacity in metabolic equivalents (METs) is estimated based on standard nomograms,[27] with age and gender taken into account to determine whether prognostically important impairment of physical fitness is present.[4] Among patients with interpretable ST segments, the Duke treadmill score can be used as an alternate risk measure that is largely related to functional capacity.[9,10,28]

• The second axis is chronotropic response,[6] which is measured only in patients who are not on beta-blockers and is based on proportion of heart rate reserve used.[29,30]

• The third axis is heart rate recovery.[7,14,19]

Among patients not taking beta-blockers, prognostic interpretation depends on how many of the 3 axes show abnormal findings.[31] Those who have no, or only 1 abnormality, likely have a death rate < 1% per year and probably need no further work-up. In contrast, patients with 2 or 3 abnormalities are at increased risk and therefore, are appropriate candidates for further evaluation. Among patients taking beta-blockers, interpretation should focus on functional capacity and heart rate recovery (Figure 3). An abnormality in either of these axes implies increased risk and might therefore warrant further assessment.

Despite its lack of novelty, the exercise stress test is arguably one of the most powerful prognostic tests that is available to clinicians today. Recent and ongoing research will hopefully increase interest in appropriate use of this test in routine clinical care.

Practical approach to stress testing

Step 1: Ask the right question

What is the risk of death for patients felt to be at intermediate to high risk of having coronary disease based on symptoms and/or risk factors?[15,16,32]

Step 2: Consider 3 main axes of interpretation

1) Functional capacity. Level of fitness based on age and gender[4] can be determined according to Table 1.

Values that are fair or poor imply increased mortality risk.[4] For patients who have interpretable ST segments, the Duke Treadmill Score[10] can be calculated as:

Minutes – (5 × maximum ST deviation) – (4 × angina score).

Minutes is based on a Bruce protocol standard; thus for patients not exercising by a Bruce protocol,

Table 1: Estimated functional capacity (METs)

Age	Poor	Fair	Average	Good	High
Women					
< 29	< 7.5	8-10	10-13	13-16	>16
30-39	< 7	7-9	9-11	11-15	>15
40-49	< 6	6-8	8-10	10-14	>14
50-59	< 5	5-7	7-9	9-13	>13
60-69	< 4.5	4.5-6	6-8	8-11.5	>11.5
70-79	< 3.5	3.5-4.5	4.5-6.5	6.5-8	> 8
>80	< 2.5	2.5-4	4-5.5	5.5-7	> 7
Men					
< 29	< 8	8-11	11-14	14-17	>17
30-39	< 7.5	7.5-10	10-12.5	12.5-16	>16
40-49	< 7	7-8.5	8.5-11.5	11.5-15	>15
50-59	< 6	6-8	8-11	11-14	>14
60-69	< 5.5	5.5-7	7-9.5	9.5-13	>13
70-79	< 4.5	4.5-5.5	5.5-8	8-9.5	> 9.5
> 80	< 3.5	3.5-4.5	4.5-6.5	6.5-7.5	> 7.5

standard nomograms are used to translate METs into minutes.[27] ST deviation is considered only if it is ≥ 1 mm and with a slope that is either horizontal or deviating away from baseline. Angina score is 0 if none, 1 if not test terminating, and 2 if test terminating. An overall score ≥ 5 implies low risk, 4 to -10 intermediate risk, and < -10 high risk.

2) For patients not on beta-blockers, calculate chronotropic response as the percentage of heart rate reserve used:

$$\%\mathrm{HRR}_{\mathrm{Used}} = \left(\frac{\mathrm{HR}_{\mathrm{peak}} - \mathrm{HR}_{\mathrm{rest}}}{220 - \mathrm{age} - \mathrm{HR}_{\mathrm{rest}}} \right) \times 100$$

If ≤ 80% chronotropic incompetence is present and risk is increased.[22]

3) Calculate heart rate recovery as:

$$\text{HR Recovery} = \mathrm{HR}_{\mathrm{peak}} - \mathrm{HR}_{\text{1 minute later}}$$

For patients undergoing an upright cool down period, a value of ≤ 12 bpm is abnormal.[14] For patients undergoing stress echocardiography or otherwise immediately assuming a supine position, a value of ≤ 18 bpm is abnormal.[19] If heart rate recovery is measured 2 minutes into recovery and in a supine position, a value of ≤ 22 bpm is abnormal.[21]

Step 3: Report a prognostic conclusion.

1) For patients not taking beta-blockers, consider all 3 axes (functional capacity and/or Duke score, chronotropic response, and heart rate recovery). Abnormalities of 2 or more of these axes implies a risk of death > 1% per year.[31] Further evaluation may therefore be appropriate.

2) For patients taking beta-blockers, consider 2 axes, namely functional capacity and/or Duke score and heart rate recovery. An abnormality in any 1 of these axes implies a risk of death >1% per year.[23] Further evaluation may therefore be appropriate.

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