

## Heart Rate Response in Stress Testing: Clinical Implications

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### Introduction

Exercise testing is one of the most commonly performed noninvasive tests in clinical cardiology. In most laboratories, test interpretation is based primarily on ST-segment changes, exercise-induced angina and exercise capacity. The heart rate rise with exercise is considered as an adjunct measure of test adequacy; if a patient achieves 85% of his/her age-predicted maximum heart rate, the test is considered to be adequate for detection of myocardial ischemia. Failure to reach that heart rate target leads to a test being labeled as “nondiagnostic” or “submaximal” but not necessarily abnormal. Some laboratories use the heart rate target as the test stopping point, rather than waiting for the patient to become physically exhausted.

Recently, the changes in heart rate during and after exercise have emerged as powerful measures of risk in their own right. This discussion will focus on the prognostic implications of the heart rate rise during exercise, known as the chronotropic response, and the heart rate fall immediately after exercise, or heart rate recovery.

### Chronotropic Response

The increase in heart rate during exercise is the main mechanism by which cardiac output is increased to meet the demands of working skeletal muscle. During early exercise, heart rate rises because of a central withdrawal of parasympathetic tone (Figure 1). Once the heart rate exceeds about 100 beats per minute, further increases in heart rate are mediated by sympathetic stimulation as well as circulating catecholamines.

Although the autonomic nervous system's role in regulating heart rates during exercise is well known, the prognostic implications of this association have only recently been appreciated. There is an extensive literature relating imbalances of autonomic function with increased risk of mortality and myocardial infarction. Autonomic function has been traditionally measured by heart rate variability and baroreflex sensitivity. Neither of these measures has made it into routine clinical practice, perhaps because they require special equipment or do not have an intuitive appeal to practicing clinicians. In contrast, the chronotropic response

to exercise is already routinely measured during exercise testing and is relatively easy to understand.

### Measures of Chronotropic Response and Chronotropic Incompetence

The easiest measure of chronotropic response (Table 1) is the peak heart rate. Unfortunately, this measure is also highly confounded by exercise capacity and age. Therefore, most exercise laboratories use the percentage of age-predicted maximum heart rate achieved, where the maximum predicted heart rate is estimated to be 220 minus age. Although this measure does remove some of the age-confounding, it is also limited by its association with exercise capacity and resting heart rate, itself an important correlate of cardiovascular risk.

A third measure of chronotropic response is based on the concept of chronotropic reserve. If one thinks of a patient at rest with a certain resting heart rate, that person has a potential to increase their heart rate up to their age-predicted maximum. The difference between the maximum possible heart rate and the resting heart rate is the chronotropic reserve (Figure 1). The proportion of chronotropic response used has been termed the “chronotropic index.” Unlike the percent of age-predicted maximum heart rate achieved, this measure of chronotropy is almost entirely independent of age, exercise capacity and resting heart rate.

Failure of a patient to use up at least 80% of their chronotropic reserve represents chronotropic incompetence. Almost all patients who fail to reach 85% of their age-predicted maximum heart rate also fail to use 80% of their chronotropic response, but a fair number of patients who do achieve 85% of their age-predicted maximum do in fact have chronotropic incompetence when the chronotropic index is calculated.

### Chronotropic Incompetence and Risk

Among patients not taking beta-blockers, chronotropic incompetence, as defined by failure to use 80% of chronotropic reserve, is typically observed in 15–25%. Several studies have shown that patients with chronotropic incompetence are at increased risk for death, even after accounting for standard cardiovascular risk factors and noninvasive measures, including nuclear perfusion defects, echocardiographic wall-motion abnormalities induced by exercise and severe angiographic coronary disease (Table 2). Furthermore, the presence of chronotropic incompetence is just as prognostically ominous as the presence of perfusion defects. Patients who have both chronotropic incompetence and perfusion defects are at markedly increased risk.

There are two major clinical implications of these findings. First, the failure of a patient to achieve a normal chronotropic response does not merely mean that the test is “suboptimal” or “nondiagnostic.” These terms imply that there is something wrong with the test but not necessarily with the patient. On the contrary, chronotropic incompe-

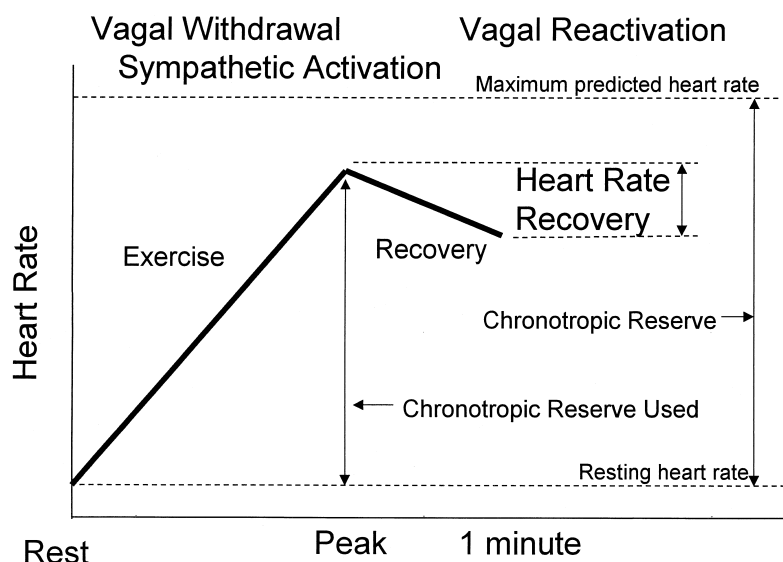


Figure 1. Heart rate changes during and after exercise.

tence indicates that there is something wrong with the patient. Just as physicians and patients are worried after an abnormal nuclear scan, they should be similarly worried with a finding of chronotropic incompetence. Patients who have normal nuclear scans and a normal chronotropic response are at very low risk and can be confidently reassured.

The second implication specifically applies to patients undergoing exercise nuclear testing. It has been argued that because the diagnostic sensitivity of nuclear scanning is decreased when patients fail to increase their heart rates to at least 85% of their age-predicted maximum, chronotropic incompetence is a reason why a nuclear isotope should not be injected. Instead, patients should then be referred to pharmacological testing. As patients with both chronotropic incompetence and nuclear perfusion defects repre-

sent a particularly high-risk group, these are precisely the patients where nuclear scanning may be most useful.

### Correlates of Chronotropic Incompetence

Chronotropic incompetence is common in patients with congestive heart failure, in which a decreased sensitivity of the sinus node to sympathetic stimulation has been demonstrated. Heart failure patients suffer from serious autonomic imbalances, with high levels of resting sympathetic tone that correlate well with mortality risk. Chronotropic incompetence in heart failure patients not taking beta-blockers is predictive of death, even after accounting for measured oxygen consumption and other risk factors.

Another important and common correlate of chronotropic incompetence is cigarette smoking. Nicotine, as a sympathomimetic agent, creates a state of chronic exogenous sympathetic overload and therefore might be expected to be associated with chronotropic incompetence, analogous to the sympathetic overload of heart failure. In fact, two studies found that chronotropic incompetence is substantially more common among smokers. Smokers who have chronotropic incompetence are at particularly increased risk for death. Former smokers have lower rates of chronotropic incompetence than current smokers. Therefore, while all smokers should be counseled to quit, those who have chronotropic incompetence should be targets for especially aggressive counseling.

### Heart Rate Recovery

The heart rate fall immediately after exercise, or heart rate recovery, is thought to be due to rapid central vagal reactivation (Figure 1). People with high levels of resting parasympathetic activity, such as athletes, have dramatic decreases in post-exercise heart rate whereas patients with heart failure show marked attenuations in heart rate recovery.

Table 1. Heart Rate Measures During and After Exercise

Type of Measure	Method of Measurement	Comments
Chronotropic Response	Peak Heart Rate	Confounded by age and functional capacity
	Percent of age-adjusted maximum heart rate	Peak heart rate/(220 - age) Less age confounding but still related to functional capacity and resting heart rate <85% abnormal
	Proportion of chronotropic reserve used	(Peak heart rate - resting rate)/(220 - age) Independent of age, functional capacity and resting heart rate ≤80% abnormal
Heart Rate Recovery	One-minute heart rate recovery	Following maximal, symptom-limited exercise Assumes upright, slow-walking cool-down period ≤12 beats minute abnormal

**Table 2.** Absolute and Relative Risks of Abnormal Heart Rate Responses and Standard Stress Testing Variables in Two Different, Non-Overlapping Cohorts From the Cleveland Clinical Foundation

Reference	Type of Test	Variables	Number of Patients	Follow-Up (years)	Mortality Rates (If Variable Present vs. Variable Absent)	Hazard Ratio (95% CI)	Adjusted Hazard Ratio* (95% CI)
Nishime et al. (8)	Exercise ECG, no imaging	Chronotropic incompetence	9454 patients	5.2 years	9% vs. 2%	4.7 (3.7 to 5.8)	2.0 (1.5 to 2.5)
		Abnormal heart rate recovery			8% vs. 2%	4.3 (3.4 to 5.4)	2.1 (1.6 to 2.8)
		Abnormal Duke score			8% vs. 2%	4.2 (3.3 to 5.2)	1.5 (1.2 to 1.9)
Diaz et al. (3)	Exercise Thallium SPECT	Abnormal heart rate recovery	7163 patients	6.7 years	18% vs. 9%	2.4 (2.1 to 2.8)	1.6 (1.4 to 1.9)
		Impaired exercise capacity			22% vs. 6%	4.0 (3.5 to 4.6)	2.3 (2.0 to 2.8)
		Moderate risk nuclear scan			14% vs. 9%	1.7 (1.4 to 2.0)	1.5 (1.3 to 1.8)
		High risk nuclear scan			24% vs. 9%	3.0 (2.5 to 3.6)	2.8 (2.1 to 2.6)

\* After adjustments for other stress variables listed, age, gender, standard cardiovascular risk factors, prior cardiac history and medications.

ery. When athletes or normal subjects are given atropine, a parasympathetic blocker, their immediate post-exercise heart rate recoveries are essentially abolished.

### Heart Rate Recovery and Risk

After treadmill exercise testing, many laboratories incorporate a “cool-down” period during which time patients remain upright and walk at a very slow pace for two minutes (Table 1). With this type of protocol, heart rate typically falls by 17–20 beats per minute during the first minute of recovery. Thus, a patient with a peak heart rate of 160 should have a heart rate of 140–143 or less 1 minute later. Analyses of low- and intermediate-risk cohorts of patients with known or suspected coronary disease have shown that patients with a heart rate recovery of  $\leq 12$  beats per minute have a fourfold increased risk of death. An abnormal heart rate recovery predicts death independently of, and in addition to, decreased exercise capacity, ST-segment changes, exercise-induced angina, standard cardiovascular risk factors and nuclear perfusion defects (Table 2).

The use of exercise testing as a screening modality for life-threatening cardiovascular disease has been a matter of debate. Recent studies have found that heart rate recovery can be used to assess risk for cardiac and all-cause death among seemingly healthy adults. Indeed, the prognostic implications of an abnormal heart rate recovery are similar in magnitude to those of an elevated LDL cholesterol.

### Correlates of Heart Rate Recovery

The most important correlate of an abnormal heart rate recovery is functional capacity. There is a steady gradient whereby the likelihood of an abnormal heart rate recovery increases as functional capacity declines. No other definite independent predictors of heart rate recovery have been identified. Unlike the case with chronotropic incompetence, for example, there is no clear-cut association between use of beta-blockers and an abnormal heart rate recovery.

### Clinical Implications and Unanswered Questions

Although current evidence supports use of chronotropic incompetence and heart-rate recovery for risk stratification, it is important to note that at this time it is not known

whether these findings are modifiable risk factors. Simply put, what’s a clinician to do with a patient who has an abnormal heart rate response during or after exercise?

The simple answer is that we do not know. We know that these are higher risk patients, and therefore it seems reasonable to treat all other modifiable risk factors aggressively. Use of other non-invasive tests to look for treatable ischemia may also be prudent. Still, future research will be needed to determine how best to manage these patients.

The important and immediately applicable clinical value of routinely incorporating chronotropic response and heart rate recovery into stress test interpretation is that *they can be used alongside other exercise measures to easily and inexpensively identify low-risk patients*. For example, patients with a normal heart rate recovery and an exercise capacity that is at least average for age are at low risk for death (<1% per year), even if they also have nuclear perfusion abnormalities. Such patients need not be referred for imaging unless they have presumably anginal symptoms that are refractory to medical therapy. They can also be spared much anxiety and the potential side effects of polypharmacy. It should not be forgotten that identifying low-risk patients is arguably as important a function of risk stratification as identifying those at increased risk.

In summary, chronotropic incompetence and an abnormal heart rate recovery are two easy-to-measure exercise test variables that are powerful and independent predictors of mortality. They should be routinely incorporated into exercise test interpretation. Future research will be needed to determine how best these measures should be used in risk stratification and how to optimally reduce risk among patients who have these ominous findings.

### Suggested Reading

- Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality [see comments]. *N Engl J Med* 1999;341:1351–7.
- Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med* 2000;132:552–5.
- Diaz LA, Brunken RC, Blackstone EH, Snader CE, Lauer MS. Independent contribution of myocardial perfusion defects to

- exercise capacity and heart rate recovery for prediction of all-cause mortality in patients with known or suspected coronary heart disease. *J Am Coll Cardiol* 2001;37:1558–64.
- Ellestad MH. Chronotropic incompetence. The implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?) [editorial; comment]. *Circulation* 1996;93:1485–7.
- La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998;351:478–84.
- Lauer MS, Pashkow FJ, Larson MG, Levy D. Association of cigarette smoking with chronotropic incompetence and prognosis in the Framingham Heart Study. *Circulation* 1997;96:897–903.
- Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA* 1999;199:524–9.
- Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA* 2000;284:1392–8., USA
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