The importance of heart rate response during myocardial perfusion imaging

Jeroen J. Bax, MD, PhD, and Victoria Delgado, MD, PhD

Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

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Myocardial perfusion imaging with single photon emission computed tomography (SPECT) is an established technique for the diagnosis of suspected coronary artery disease (CAD). Clinically even more important is the use of SPECT perfusion imaging for prognosis and risk stratification. Important parameters have been derived from SPECT imaging including the extent of scar tissue and the extent and severity of ischemia.[1] In addition, various other prognostic variables have been identified, such as transient ischemic dilatation of the left ventricle (LV), and functional LV parameters including the LV ejection fraction (LVEF, at rest and stress) and LV volumes. Particularly, Sharir et al[2] evaluated 1,680 patients and demonstrated that the post-stress LVEF provided incremental prognostic value over perfusion abnormalities. The incremental value of adding LVEF was most pronounced in patients with mild-moderate abnormal perfusion, where the annual cardiac death rate was 0.96% when the LVEF was ≥45%, but increased to 9.2% when the LVEF was <45%. Similarly, in patients with severe perfusion abnormalities but preserved LVEF, the annual cardiac death rate was 0.92% as compared to 5.7% in patients with reduced LVEF (<45%).

SPECT perfusion imaging is performed in conjunction with physical exercise or pharmacological stress, including both vasodilator stress (with dipyridamole or adenosine, and more recently adenosine A2A receptor agonists, such as regadenoson) and inotropic stress (with dobutamine).

Physical exercise is preferred, since it provides information on maximum exercise capacity, heart rate, and blood pressure response during exercise and heart rate recovery after exercise. All these parameters have been associated with prognosis. In general, perfusion imaging with pharmacological stress is associated with worse outcome, related to the inability to perform physical exercise.

OUTCOME AND EXERCISE-RELATED PARAMETERS

Myers et al[3] followed 6,213 consecutive men for 6.2 ± 3.7 years who were clinically referred for treadmill exercise testing. The annual mortality was 2.6%, and predictors included older age, lower maximum heart rate, lower maximum systolic/diastolic blood pressure, and lower exercise capacity. After adjustment for age, maximum exercise capacity (expressed in metabolic equivalents, METs) was the strongest predictor of death, both in normal subjects and in patients with cardiovascular disease. Recently, Kodama et al[4] performed a meta-analysis of the studies on the prognostic value of maximal aerobic capacity (n = 33 studies, 102,980 individuals with 6,910 deaths, and 84,323 individuals with 4,485 cardiovascular events), and showed that individuals with a maximal aerobic capacity of ≥7.9 METs had lower all-cause mortality and less cardiovascular events.

Resting heart rate has been recognized as a strong prognostic parameter with improved outcome after pharmacological lowering of heart rate.[5] Reduced increase in heart rate during exercise (referred to as chronotropic incompetence) has also been associated with worse outcome. Lauer et al[6] followed 1,575 men (mean age 43 years) without CAD, from the Framingham Offspring Study who underwent submaximal treadmill exercise testing. Different measures of chronotropic incompetence were evaluated, including failure to achieve 85% of the age-predicted maximum heart rate

Reprint requests: Jeroen J. Bax, MD, PhD, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2300 RC, Leiden, The Netherlands; *jbax@ision.nl, j.j.bax@lumc.nl*.

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and the actual increase in heart rate from rest to peak exercise. Failure to achieve target heart rate occurred in 21% of the individuals. During 7.7 years follow-up, there were 55 deaths (14 cardiac deaths) and 95 cases of incident CAD. Chronotropic incompetence predicted both mortality and CAD incidence.

Heart rate recovery is another variable that can be derived from exercise testing. It is defined as a delayed decrease in heart rate during the first minutes after graded exercise and is considered to reflect decreased vagal activity. In 2,935 patients who underwent exercise testing for suspected CAD, abnormal heart rate recovery was noted in 838 (29%) patients;[7] 14% had severe CAD on angiography. Both abnormal heart rate recovery and severe CAD were predictive of death, and when corrected for severity of CAD and LV function, heart rate recovery remained predictive of death.

PROGNOSTIC VALUE OF EXERCISE VARIABLES IN RELATION TO PERFUSION IMAGING

Lauer et al[8] evaluated 2,953 patients with known or suspected CAD, using exercise thallium-201 perfusion imaging; 91 patients died during 2 years follow-up. Perfusion defects were observed in 21% of patients. Chronotropic incompetence was noted in 1,078 patients. After adjustment for confounding variables (age, gender, thallium-201 perfusion defects), chronotropic incompetence was independently predictive of death.

In another study, Azarbal et al[9] evaluated 10,021 patients who underwent exercise SPECT perfusion imaging with follow-up of 719 ± 252 days; 234 deaths occurred, including 93 cardiac deaths. Chronotropic incompetence was noted in 42.8% of patients. Multivariate analysis indicated that the summed stress score on SPECT and chronotropic incompetence were predictive of all-cause mortality and cardiac death. SPECT perfusion imaging was the strongest predictor of cardiac death, followed by chronotropic incompetence.

Various mechanisms have been suggested to explain the relation between chronotropic incompetence and cardiac death.[9] It has been shown that chronotropic incompetence is related to CAD: patients with chronotropic incompetence have more perfusion defects and ischemia on SPECT perfusion imaging as compared to patients with a normal heart rate response. Still, chronotropic incompetence remained predictive for (cardiac) death after correction for CAD. Another explanation may be that chronotropic incompetence is a marker of autonomic dysfunction, which also relates to (cardiac) mortality.

PROGNOSTIC VALUE OF CHRONOTROPIC INCOMPETENCE IN PHARMACOLOGICAL STRESS PERFUSION IMAGING

Recently, it has become evident that a blunted heart rate response during vasodilator stress perfusion imaging also has prognostic value. Abidov et al[10] evaluated heart rate response during adenosine perfusion SPECT in 3,444 patients with follow-up of 2.0 ± 0.8 years. Cardiac death occurred in 6.5%. On multivariate analysis, a high resting heart rate and a low ratio of peak/rest heart rate were predictive of death. Moreover, addition of these variables provided incremental prognostic value over the perfusion data.

In the current issue of the Journal, Bellam et al[11] provide further evidence on the prognostic value of the heart rate reserve during vasodilator perfusion imaging. The authors have used positron emission tomography (PET) with rubidium-82 instead of SPECT. The data are collected from the PET Prognosis Multicenter Registry and included 2,398 patients undergoing vasodilator stress, with 64 cardiac deaths during 1.9 ± 0.9 years follow-up. The heart rate reserve was divided in tertiles ($\leq$4, 5-14, and $\geq$15 beats·minute^{-1}). Low heart rate reserve was associated with older age, male gender, beta-blocker use, and diabetes. A blunted heart rate response during vasodilator stress in patients with diabetes was earlier described by Bravo et al,[12] who compared the heart rate response during adenosine stress in 60 diabetic patients with 60 controls, all with normal perfusion on SPECT and normal LV function. The heart rate response was significantly lower in patients with diabetes. The prognostic value of this blunted heart rate response in diabetic patients was further explored in the population of the Detection of Ischemia in Asymptomatic Diabetes (DIAD) study.[13] In this study, 518 patients with diabetes underwent adenosine myocardial perfusion imaging; follow-up was obtained during 4.7 ± 0.9 years and 15 (3%) cardiac deaths or nonfatal myocardial infarctions occurred. Patients with a reduced heart rate response had a higher event rate as compared to patients with a normal heart rate response (8% vs 1%, $P < .01$). Both perfusion abnormalities and heart rate response were independently related with outcome. Importantly, patients with abnormal perfusion and reduced heart rate response had the highest event rate (38%), whereas patients with high heart rate response (independent of perfusion abnormalities) had low event rate (1%, $P < .001$). Adenosine produces an increase in heart rate, which most likely is related with sympathetic stimulation, and it has been suggested that reduced heart rate reserve is an expression of cardiac autonomic dysfunction as frequently observed in the elderly and in patients with diabetes.[14]

Bellam et al[11] also reported an association between a lower heart rate reserve with higher resting heart rate, use of diuretics, reduced LVEF (≤45%), and larger percentage abnormal myocardium at stress. These observations suggest that the reduced heart rate reserve could also be related to cardiac damage (scar formation and remaining LV function), but this could also have been related to impaired autonomic function. Interestingly, the heart rate reserve was not related to the extent of ischemia, and this requires further study.

Next, Bellam et al[11] described the relation between heart rate reserve and cardiac mortality: patients with high heart rate reserve had much lower mortality (0.8%) as compared to patients with low heart rate reserve (12.8%, $P < .0001$). Moreover, cardiac mortality was also related with the extent of abnormal myocardium at stress imaging. Specifically, patients with extensive perfusion abnormalities and reduced heart rate reserve were at high risk.

In conclusion, many studies have shown the prognostic value of chronotropic incompetence during physical exercise. There is now also increasing evidence that the heart rate response during vasodilator stress imaging provides important prognostic information and systematic inclusion of the heart rate response in the clinical report may further guide the clinician toward optimal risk stratification.

References

1. Hachamovitch R, Di Carli MF. Methods and limitations of assessing new noninvasive tests: Part II: Outcomes-based validation and reliability assessment of noninvasive testing. Circulation 2008;117:2793-801.
2. Sharir T, Germano G, Kavanagh PB, Lai S, Cohen I, Lewin HC, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 1999;100:1035-42.
3. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793-801.
4. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. J Am Med Assoc 2009;301:2024-35.
5. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A subgroup analysis of a randomised controlled trial. Lancet 2008;372:817-21.
6. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996;93:1520-6.
7. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341:1351-7.
8. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. J Am Med Assoc 1999;281:524-9.
9. Azarbal B, Hayes SW, Lewin HC, Hachamovitch R, Cohen I, Berman DS. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: Superiority over 85% of maximal age-predicted heart rate. J Am Coll Cardiol 2004;44:423-30.
10. Abidov A, Hachamovitch R, Hayes SW, Ng CK, Cohen I, Friedman JD, et al. Prognostic impact of hemodynamic response to adenosine in patients older than age 55 years undergoing vasodilator stress myocardial perfusion study. Circulation 2003;107:2894-9.
11. Bellam N, Veledar E, Dorbala S, Di Carli MF, Shah S, Eapen D, et al. Prognostic significance of impaired chronotropic response to pharmacologic stress Rb-82 PET. J Nucl Cardiol 2014. doi: 10.1007/s12350-013-9820-1.
12. Bravo PE, Hage FG, Woodham RM, Heo J, Iskandrian AE. Heart rate response to adenosine in patients with diabetes mellitus and normal myocardial perfusion imaging. Am J Cardiol 2008;102:1103-6.
13. Hage FG, Wackers FJ, Bansal S, Chyun DA, Young LH, Inzucchi SE, et al. The heart rate response to adenosine: A simple predictor of adverse cardiac outcomes in asymptomatic patients with type 2 diabetes. Int J Cardiol 2013;167:2952-7.
14. Hage FG, Iskandrian AE. Cardiovascular imaging in diabetes mellitus. J Nucl Cardiol 2011;18:959-65.