Effect of Beta-Blocker Use on Exercise Heart Rate Gradient and Reclassification of Mortality Risk in Patients Referred for Exercise Testing

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Impairments in heart rate (HR) reserve and HR recovery are associated with mortality, and the combination of these two, termed exercise HR gradient (EHRG), is a better predictor than either alone. However, the confounding effect of beta-blockade on chronotropic impairment to exercise has not been fully explored; the aim of the present study was to evaluate the effect of beta blockade on EHRG. Participants were 2769 Veterans (58.7 ± 11.6 years) who underwent a maximal exercise test for clinical reasons. HR reserve and HR recovery were acquired and divided into quintiles and summed to provide an EHRG score. Net reclassification improvement (NRI) was performed to evaluate the impact of HR reserve, HR recovery and EHRG on all-cause mortality for patients with and without beta-blocker use. During a mean follow up of 10.9 ± 4.1 years, 657 patients died. Among patients without beta-blocker therapy, adding EHRG score to an established model including multiple baseline risk factors and exercise capacity resulted in an NRI of 14.3% (p <0.001). Adding HR recovery instead of EHRG score yielded an NRI of 11.5% (p <0.001), whereas HR reserve had no significant NRI among patients without beta-blocker therapy. In contrast, among participants on beta-blocker therapy, the addition of HR reserve, HR recovery, or EHRG score did not result in any significant reclassification. In conclusion, EHRG was superior to both HR reserve and HR recovery in predicting mortality and provides significant reclassification of risk but only among patients not taking beta-blockers. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;130:152−156)

Over the last 3 decades, the association between the heart rate (HR) response to exercise, HR recovery, and all-cause mortality has been extensively described.[1−7] Evidence has shown that a higher resting HR,[3] lower maximum HR,[8] lower HR reserve,[9] impaired HR recovery,[10,11] and decreased HR variability[12] have all been associated with higher all-cause and cardiovascular mortality. Patients taking beta blockers have a reduced maximal HR and a slower HR in recovery from exercise (8, 10-11), and most studies have excluded patients taking these agents. Duarte and colleagues[13] recently proposed a novel index combining HR reserve and HR recovery (termed the Exercise Heart Rate Gradient, or EHRG) as a predictor all-cause mortality in a relatively healthy Brazilian population and reported that this index was a better discriminator of mortality risk than HR reserve and HR recovery alone. However, the utility of EHRG in a population at comparatively high risk for CVD among patients on beta-blockade therapy is unknown. The purpose of the current study was therefore to analyze the effect of beta-blockade on the chronotropic, recovery, and EHRG response to exercise in a sample of subjects referred for an exercise test for clinical reasons.

Methods

The study population consisted of 2769 Veterans (2656 [95.9%] men; mean age 58.8 ± 11.6 years) from the Veterans Exercise Testing Study (VETS) cohort.[14] VETS[14,15] is an ongoing, prospective evaluation of Veteran subjects referred for exercise testing for clinical reasons. Patients who had undergone a maximal exercise treadmill test (ETT) between 1987 and 2014 at the VA Palo Alto Health Care System were included in the study. All subjects signed an informed consent before undergoing their exercise test and medical history was abstracted from the Veterans Affairs Computerized Patient Record System (CPRS).

Historical information included previous myocardial infarction by history or presence of Q waves, heart failure, hypertension (blood pressure ≥140/90 mm Hg), hypercholesterolemia (>200 mg/dl, statin use, or both), claudication, chronic obstructive pulmonary disease, cancer, renal disease, type 2 diabetes mellitus (DM2), stroke, smoking status (never, former, and current), and use of cardiac/antihypertensive medications.

Subjects underwent symptom-limited treadmill testing using an individualized ramp treadmill protocol.[16] All tests were performed to maximal voluntary exhaustion or to standard criteria for termination, including moderately severe angina, >2.0 mm horizontal or downsloping ST depression, a sustained decrease in systolic blood pressure, or serious

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rhythm disturbances. The Borg 6-20 perceived exertion scale was used to quantify degree of effort.[17] Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping.[18,19] Blood pressure was taken manually, and exercise capacity (in peak metabolic equivalents [METs]) for each participant was calculated based on treadmill speed and grade using standardized American College of Sports Medicine equations.[18] No test was classified as indeterminate, medications were not withheld, and age-predicted maximal target heart rates were not used as end points. The exercise tests were performed, analyzed, and reported using a standard protocol incorporating a computerized database with definitions and measurements prospectively defined.[20]

A standard 12-lead electrocardiogram (ECG) was continuously monitored and heart rate was digitally recorded. Resting HR was obtained after a minimum of 5 minutes in the supine position before the test, and the highest HR obtained during the test was considered maximal HR. After the test, subjects were placed in the supine position and HR at 2 minutes recovery was recorded. HR reserve was calculated as: HR maximum − HR at rest; and HR recovery was determined by: HR maximum − HR at 2 minutes recovery. All HR values were expressed in beats per min.

The frequency distribution of HR reserve and HR recovery were divided into quintiles, with the lowest quintile (Q1) representing the highest risk group similar to that reported by Duarte et al.[13] The ranges of HR reserve and HR recovery in quintiles are shown in Table 1. EHRG was calculated by summing the quintile ranking of HR reserve and HR recovery (1 to 5 for each). EHRG scores thus ranged from 2 to 10, with a value of 2 representing those subjects who exhibited the lowest HR changes during the rest-exercise-rest transition (i.e., the lowest quintiles for both HR reserve and HR recovery).[13] Thus, EHRG reflects the magnitude of on- and off- heart rate transients to exercise and simply summing the number of quintiles represents a dimensionless score.

The primary endpoint was all-cause mortality. Vital status of each patient was ascertained by the Veterans Affairs CPRS. Follow-up was completed through December 2015.

All descriptive data are presented as mean ± standard deviation and categorical variables are presented in absolute numbers or as percentages. Comparisons of survivors vs nonsurvivors were performed using independent t-tests for continuous variables and chi-square tests for categorical variables. Survival analyses to determine independent predictors of all-cause mortality were performed using Cox proportional hazards analyses in a univariate model. Kaplan-Meier curves were used to illustrate survival stratified for EHRG scores 2, 3-4, 5-6, and 7-10.

To determine the impact of HR reserve, HR recovery and EHRG score on risk reclassification for all-cause mortality over the baseline model,[15] net reclassification improvement (NRI) was performed among participants. NRI has been proposed as an objective measure of improvement in risk prediction when a priori risk categories do not exist.[21] The degree of correct upward or downward absolute risk reclassification was measured to quantify the addition of EHRG to the baseline model. 1000 bootstrap samples were used for correction for overoptimism.

For all analyses, a probability value of p <0.05 was considered to be statistically significant. Statistical calculations were performed using SPSS (IBM SPSS Advanced Statistics, Version 20.0; IBM Corp, Armonk, New York) software or R (R Foundation for Statistical Computing, Vienna, Austria)

Results

Clinical characteristics of the cohort are shown in Table 2. Those who died were less fit (6.6 ± 2.7 vs 9.3 ± 3.1 METs, p <0.001), had lower EHRG scores (4.2 ± 1.8 vs 5.4 ± 1.9), lower HR recovery index (1.2 ± 0.5 vs 1.5 ± 0.9), lower HR recovery index (3.0 ± 1.6 vs 3.9 ± 1.4), and were more often treated with medications compared with survivors. Three hundred ninety three subjects (14.2%) were classified with an EHRG score of 2, considered the severely impaired category, whereas EHRG scores of 3-4 (23.2%), 5-6 (40.3%), 7-10 (22.4%) composed the impaired, borderline, and normal categories, respectively.

Overall, EHRG score (HR: 0.75, CI: 0.72−0.78, p <0.001) was a stronger predictor of all-cause mortality than HR reserve (HR: 0.48, CI: 0.41−0.58, p <0.001) or HR recovery (HR: 0.73, CI: 0.70−0.77, p <0.001). EHRG scores categorized in quartiles[2−6,7−10] were significantly associated with mortality (Figure 1). In the overall sample, compared with the highest EHRG score, a gradient for increased risk was observed as EHRG was lower (EHRG score 2: HR: 6.22, CI: 4.60−8.42, p <0.001; EHRG score 3-4: HR: 3.51, CI: 2.60−4.74, p <0.001; EHRG score 5-6: HR: 2.32, CI: 1.73−3.18, p <0.001). Among subjects not on beta-blockade therapy, log-rank analysis of EHRG scores was statistically significant (p <0.001). Compared with the highest EHRG score, a gradient for increased risk was observed as EHRG was lower (EHRG score 2: HR: 6.97, CI: 4.82−10.09, p <0.001; EHRG score 3-4: HR: 3.60, CI: 2.51−5.16, p <0.001; EHRG score 5-6: HR: 2.53, CI: 1.80−3.56, p <0.001).

Category-free NRI results for patients not taking beta-blockers are presented in Table 3 and those taking beta-blockers are shown in Table 4. Adding EHRG score to an established model including baseline risk factors and exercise capacity resulted in an NRI of 14.3% (p <0.001) among patients not on beta-blocker therapy. In contrast, among patients on beta-blocker therapy the addition of HR reserve, HR recovery, or EHRG score did not result in any significant NRI.

Table 1
Cutoff values for heart reserve and heart rate recovery quintile

Quintile	HR reserve (bpm)	HR recovery (bpm)
First (1 EHRG score points)	24-80	0-27
Second (2 EHRG score points)	81-94	28-33
Third (3 EHRG score points)	95-104	34-39
Fourth (4 EHRG score points)	105-113	40-45
Fifth (5 EHRG score points	114-151	46-87

HR reserve = HR maximum − supine HR at rest.
HR recovery = HR maximum − 2-minutes supine HR recovery.

Table 2
Patients characteristics

	Whole study group (n = 2769)	Survivors (n = 2112)	Non Survivors (n = 657)	p-Value*
Men	2656 (95.9%)	2008 (95.1%)	648 (98.6%)	<0.001
Age (years)	58.78 ± 11.59	56.74 ± 10.97	65.31 ± 11.12	<0.001
Follow-up (years)	10.88 ± 4.09	11.84 ± 3.58	7.80 ± 4.11	<0.001
BMI (kg/m^2)	29.27 ± 5.39	29.40 ± 5.36	28.83 ± 5.44	.025
Exercise capacity (METs)	8.65 ± 3.23	9.28 ± 3.10	6.62 ± 2.74	<0.001
EHRG score	5.11 ± 1.96	5.40 ± 1.91	4.18 ± 1.80	<0.001
HR reserve index	1.43 ± 0.86	1.52 ± 0.93	1.15 ± 0.48	<0.001
HR recovery index	3.67 ± 1.49	3.87 ± 1.39	3.03 ± 1.60	<0.001
Risk factors				
History of CVD	2571 (92.8%)	1944 (92.0%)	627 (95.4%)	.003
History of hypertension	1546 (55.8%)	1125 (53.3%)	421 (64.1%)	<0.001
History of dyslipidemia	1302 (47.0%)	1017 (48.2%)	285 (43.4%)	.032
History of drugs	169 (6.1%)	134 (6.3%)	35 (5.3%)	.341
History of alcohol abuse	271 (9.8%)	200 (9.5%)	71 (10.8%)	.314
History of diabetes	549 (19.8%)	375 (17.8%)	174 (26.5%)	<0.001
Current Smoking	549 (19.8%)	379 (17.9%)	170 (25.9%)	<0.001
Medication				
Beta-blocker	729 (26.3%)	476 (22.5%)	253 (38.5%)	<0.001
ACE	900 (32.5%)	624 (29.5%)	276 (42.0%)	<0.001
Antihypertensive	411 (14.8%)	296 (14.0%)	115 (17.5%)	.028
Diuretics	438 (15.8%)	312 (14.8%)	126 (19.2%)	.007
Statins	919 (33.2%)	682 (32.3%)	237 (36.1%)	.072

BMI = body mass index, MET = metabolic equivalent, CI = confidence interval, ACE = angiotensin-converting enzyme, CVD = cardiovascular disease.

* Comparing patients who censored to those who did not censor by an independent t test or chi-square if appropriate.
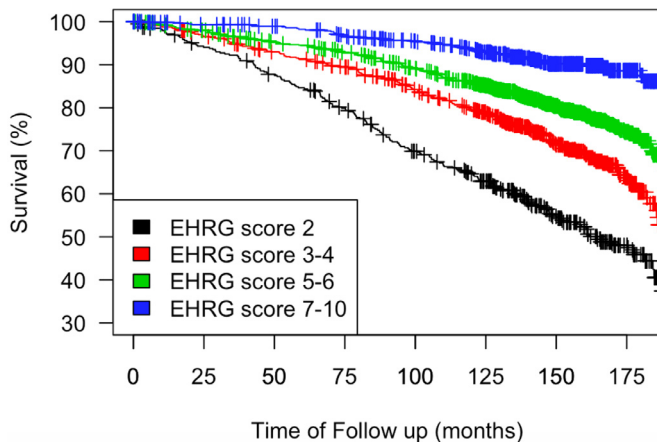

Figure 1. Kaplan-Meier curves for survival stratified according to quartiles of EHRG scores.

Discussion

We observed that HR reserve, HR recovery, and a novel composite variable, EHRG, were significant predictors of mortality in a heterogeneous sample of subjects referred for exercise testing for clinical reasons. In addition, EHRG provided significant NRI for risk of all-cause mortality, but only among subjects not on beta-blocker therapy. Among subjects on beta-blocker treatment, neither EHRG, HR reserve or HR recovery resulted in significant NRI in comparison to baseline parameters and exercise capacity. When stratified by quartiles (Figure 1), log-rank tests suggest that EHRG was an overall powerful discriminator of risk. EHRG remained a strong predictor of mortality when fully adjusted for conventional risk factors. The reclassification improvement observed was superior to that of HR reserve or HR recovery alone among participants without beta-blocker usage. However, the reclassification improvement was not statistically significant for EHRG or either of the HR indices alone among those on beta-blockade therapy.

Table 3
Category-free net reclassification improvement (patients without beta-blocker usage)

Model	Overall NRI			Event NRI	Non-event NRI
	Estimate	Confidence interval	p-Value		
BRF	Reference	Reference	Reference	Reference	Reference
BRF + HR reserve	2.9%	-0.018 - 0.131	0.454	-6.3%	9.2%
BRF + HR recovery	11.5%	0.035 - 0.210	**<0.001**	7.3%	4.2%
BRF + EHRG score	14.3%	0.056 - 0.263	**<0.001**	9.9%	4.3%

Baseline risk factors are age, body mass index, hypertension, hyperlipidemia, cardiovascular disease, smoking, diabetes and exercise capacity. BRF = baseline risk factors; NRI = net reclassification improvement.

Table 4
Category-free net reclassification improvement (patients with beta-blocker usage)

Model	Overall NRI			Event NRI	Non-event NRI
	Estimate	Confidence interval	p-Value		
BRF	Reference	Reference	Reference	Reference	Reference
BRF + HR reserve	1.8%	-0.016 - 0.117	0.993	-4.3%	6.0%
BRF + HR recovery	5.4%	-0.047 - 0.325	0.582	6.0%	-0.6%
BRF + EHRG score	6.7%	-0.049 - 0.326	0.497	6.9%	-0.2%

Baseline risk factors are age, body mass index, hypertension, hyperlipidemia, cardiovascular disease, smoking, diabetes and exercise capacity. BRF = baseline risk factors; NRI = net reclassification improvement.

HR at rest and in response to exercise is reflections of autonomic balance and has been explored extensively over several decades in relation to health outcomes.[22,23] In addition, combinations of the HR response to exercise and recovery have been shown to more strongly predict mortality than either alone[22]; however, to our knowledge, only one study[13] has integrated resting, exercise, and recovery HRs into a single index. EHRG integrates the dynamic changes of exercise HR transients into a single index that is easily applied. The current results extend the findings of Duarte and colleagues[13] by assessing EHRG in a clinically-referred sample, separately analyzing participants with and without beta-blocker usage, and applying a relatively novel method of quantifying change in risk, termed NRI. In contrast to the earlier study of Duarte and colleagues,[13] our participants underwent a maximal exercise test for clinical reasons, many of whom had a history of cardiovascular disease and extensive medication use including beta blockers. NRI is a relatively new analysis that provides clinically meaningful improvement in risk reclassification achieved with the addition of a risk marker to an established risk model or risk factor.[21] The additional risk reclassification by adding EHRG among patients not on beta blocker therapy suggests that 14% of subjects were correctly reclassified beyond other HR indices and exercise capacity, which are well-established markers of risk.

A salient finding was that significant reclassification occurred by adding EHRG to other HR metrics only among subjects not on beta blockade therapy. Patients taking beta blockers have both an impaired capacity to increase heart rate during exercise and a slower HR recovery after exercise, and their use has clouded the interpretation of HR responses and their application for risk stratification among patients taking these agents.[22,24−26] Although criteria have varied, in general, achieving lower than 80% of heart rate reserve and a decrease of less than 12 beats at 1 minute or 22 beats at 2 minutes in recovery have been considered chronotropic incompetence and an abnormal heart rate recovery response, respectively.[22,24−28] Some studies have reported that there is no difference between participants with or without the use of negative chronotropic agents,[24] whereas others have reported a significant impact of beta blockade on these responses.[22,25,26] We observed that among participants on beta-blocker therapy, EHRG had no significant NRI. Among subjects not on beta blockade, adding EHRG to an established model provided a net reclassification improvement of 14.3%. However, among patients taking beta-blockers, neither EHRG score, nor the other HR indices significantly predicted mortality.

Our sample consisted largely of males (95.9%); thus, the results may not be applicable to women. And over 92% of subjects had some form of CV disease. Whether EHRG functions as well in asymptomatic apparently healthy subjects is unknown. In addition, the quintiles for HR reserve and HR recovery responses lack universal standards and therefore, variation in results may occur depending on different criteria or the population studied (particularly HR recovery time point, recovery position, and presence or absence of a cool down cycling or treadmill walking period).[10,27,28]

In conclusion, EHRG significantly predicts mortality and provides net reclassification improvement for risk of all-cause mortality among patients referred for exercise testing without beta-blocker usage. Whereas further studies are required to validate EHRG and the impact of beta-blockade, it appears to have important potential for risk-stratifying patients with or at high risk for CVD.

Disclosures

There are no conflicts of interest to report. No funding was associated with this study.

1. Jensen MT, Marott JL, Allin KH, Nordestgaard BG, Jensen GB. Resting heart rate is associated with cardiovascular and all-cause mortality after adjusting for inflammatory markers: The Copenhagen City Heart Study. *Eur J Prev Cardiol* 2012;19:102–108.
2. Sandvik L, Erikssen J, Ellestad M, Erikssen G, Thaulow E, Mundal R, Rodahl K. Heart rate increase and maximal heart rate during exercise as predictors of cardiovascular mortality: a 16-year follow-up study of 1960 healthy men. *Coron Artery Dis* 1995;6:667–679.
3. Woodward M, Webster R, Murakami Y, Barzi F, Lam T-H, Fang X, Suh I, Batty GD, Huxley R, Rodgers A. The association between resting heart rate, cardiovascular disease and mortality: evidence from 112,680 men and women in 12 cohorts. *Eur J Prev Cardiol* 2014;21:719–726.
4. Jouven X, Empana J-P, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;352:1951–1958.
5. Ricardo DR, de Almeida MB, Franklin BA, Araújo CGS. Initial and final exercise heart rate transients: influence of gender, aerobic fitness, and clinical status. *Chest* 2005;127:318–327.
6. Custodis F, Reil J-C, Laufs U, Böhm M. Heart rate: a global target for cardiovascular disease and therapy along the cardiovascular disease continuum. *J Cardiol* 2013;62:183–187.
7. Freeman J V, Dewey FE, Hadley DM, Myers J, Froelicher VF. Autonomic nervous system interaction with the cardiovascular system during exercise. *Prog Cardiovasc Dis* 2006;48:342–362.
8. Jouven X, Escolano S, Celermajer D, Empana J-P, Bingham A, Hermine O, Desnos M, Perier MC, Marijon E, Ducimetière P. Heart rate and risk of cancer death in healthy men. *Little J* 2011;6:e21310.

9. Cheng Yiling J, Caroline A. Macera TSC and SNB. Heart rate reserve as a predictor of cardiovascular and all-cause mortality in men. *Med Sci Sport Exerc* 2002;34:1873–1878.

10. Savonen KP, Kiviniemi V, Laaksonen DE, Lakka TA, Laukkanen JA, Tuomainen T-P, Rauramaa R. Two-minute heart rate recovery after cycle ergometer exercise and all-cause mortality in middle-aged men. *J Intern Med* 2011;270:589–596.

11. 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;132:552–555.

12. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256–262.

13. Duarte CV, Myers J, de Araújo CGS. Exercise heart rate gradient: a novel index to predict all-cause mortality. *Eur J Prev Cardiol* 2014;22:629–635.

14. 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.

15. Myers J, Nead KT, Chang P, Abella J, Kokkinos P, Leeper NJ. Improved reclassification of mortality risk by assessment of physical activity in patients referred for exercise testing. *Am J Med* 2015;128:396–402.

16. Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M, Froelicher VF. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol* 1991;17:1334–1342.

17. Borg G. Borg's perceived exertion and pain scales. *Hum Kinet* 1998.

18. Riebe D, Ehrman JK, Liguori G, Magal M. *ACSM's Guidelines for Exercise Testing and Prescription*. 2018.

19. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, Coke LA, Fleg JL, Forman DE, Gerber TC, Gulati M, Madan K, Rhodes J, Thompson PD, Williams MA. Exercise standards for testing and training. *Circulation* 2013;128:873–934.

20. Shue P FV. EXTRA: An expert system for exercise test reporting. *J Non-Invasive Test* 1998;II−4:21–27.

21. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;30:11–21.

22. Myers J, Tan SY, Abella J, Aleti V, Froelicher VF. Comparison of the chronotropic response to exercise and heart rate recovery in predicting cardiovascular mortality. *Eur J Cardiovasc Prev Rehabil* 2007;14:215–221.

23. Araújo C. Fast "ON" and "OFF" heart rate transients at different bicycle exercise levels. *Int J Sports Med* 1985;06:68–73.

24. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. *J Am Coll Cardiol* 2003;42:831–838.

25. 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;341:1351–1357.

26. 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.

27. Shetler K, Marcus R, Froelicher VF, Vora S, Kalisetti D, Prakash M, Do D, Myers J. Heart rate recovery: validation and methodologic issues. *J Am Coll Cardiol* 2001;38:1980–1987.

28. Gorelik DD, Hadley D, Myers J, Froelicher V. Is there a better way to predict death using heart rate recovery? *Clin Cardiol* 2006;29:399–404.