Prognostic Value and Clinical Usefulness of the Hemodynamic Gain Index in Men

Baruch Vainshelboim, PhD[a,b,*], Peter Kokkinos, PhD[c], and Jonathan Myers, PhD[b]

Although hemodynamic responses to exercise have been studied for decades, comprehensive and definitive prognostic markers are lacking. The present study aimed to assess the association between a new hemodynamic index and all-cause mortality in men. Treadmill exercise testing was performed between 1987 and 2012 in 11,455 men aged 58.5 ± 11 years who were prospectively followed for 9.8 ± 5.8 years. Heart rate (HR) and systolic blood pressure (SBP) responses were used to develop a hemodynamic gain index (HGI) = [(HRpeak × SBPpeak) − (HRrest × SBPrest)]/(HRrest × SBPrest). Multivariable Cox hazard models adjusted for established cardiometabolic diseases, risk factors, cardiorespiratory fitness, and medications were analyzed for HGI and all-cause mortality. During the follow-up, 2,804 participants (24.5%) died, and mean HGI was 1.68 ± 0.83 bpm/mm Hg. In a continuous model, every 1 unit higher in HGI was associated with a 23% (hazard ratio 0.77, 95% confidence interval 0.71−0.82, p <0.001) reduced risk of mortality. In a categorical model, compared with participants <25th percentile (HGI <1.1), participants who were between the 25th and 50th (HGI 1.1−1.59), 50th to 75th (HGI 1.6−2.1) and >75th percentile (HGI >2.1) exhibited 12%, 24%, and 36% reductions in mortality risk (p trend <0.001), respectively. The inverse association between HGI and death was significant across wide-range of age groups and among participants with varied chronic conditions. In conclusion, these novel findings indicate that higher HGI is inversely and independently associated with lower risk of all-cause mortality in men, suggesting its potential prognostic value for risk stratification in clinical and research settings. **(Am J Cardiol 2019;124:644−649)**

Exercise testing is a well-established clinical procedure, providing valuable diagnostic and prognostic information for patients with a wide spectrum of chronic conditions. Cardiorespiratory fitness (CRF) and hemodynamic responses during exercise testing are the core variables for evaluation of functional capacity, diagnosis of cardiovascular disease, and overall prognosis.[1−3] Despite the evolution in exercise testing applications, knowledge regarding the prognostic utility of hemodynamic responses (heart rate [HR] and blood pressure) has changed very little.[1−4] Chronotropic incompetence, hypotension, and impaired HR recovery are well-known abnormal hemodynamic responses associated with cardiovascular disease and poor prognosis.[1−4] Although these established hemodynamic responses endorsed by exercise testing guidelines, they reflect different physiologic attributes during an exercise test, and provide only partial and compartmental information on the hemodynamic response.[1,2,5] Given that many clinical and research centers primarily use a standard exercise test without metabolic or invasive assessments,[6] an inexpensive, simple, practical, and sensitive comprehensive hemodynamic marker could potentially be useful to optimize hemodynamic assessment and enhance risk stratification from an exercise test. Therefore, in the present study we aimed to assess the association between a newly developed hemodynamic index and all-cause mortality in a prospective cohort of men.

Methods

The cohort was drawn from the Veterans Exercise Testing Study from the VA Palo Alto Health Care System (n = 9,877) and the Exercise Testing and Health Outcomes Study from the VA Washington DC Medical Center (n = 2,591). In brief, these cohorts are ongoing, prospective evaluations of Veteran participants referred for exercise testing for clinical reasons such cardiometabolic risk factors, signs or symptoms suggestive of cardiovascular disease, or known cardiometabolic disease. The study designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes. The study was approved by the respective Institutional Review Boards at each institution, and all participants gave their written informed consent before undergoing the exercise test. All participants who underwent the exercise tests in these centers between 1987 and 2012 were considered for inclusion in the study. Of 12,468 participants who completed a baseline evaluation, 1,013 participants were excluded from the analysis; women (n = 624), those with less than 1 month follow-up (n = 29) and those with conditions that prevented

[a]Master of Cancer Care Program, School of Health Sciences, Saint Francis University, Loretto, Pennsylvania; [b]Cardiology Division, Veterans Affairs Palo Alto Health Care System/Stanford University, Palo Alto, California; and [c]Washington DC Veterans Affairs Medical Center, Washington, District of Columbia. Manuscript received February 13, 2019; revised manuscript received and accepted May 13, 2019.

The study was conducted at the Cardiology Division, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, and Washington DC Veterans Affairs Medical Center, Washington DC.

See page 649 for disclosure information.

*Corresponding author: Tel: (814) 472-2704; fax: (814) 472-3140.

E-mail address: baruch.v1981@gmail.com (B. Vainshelboim).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.05.015

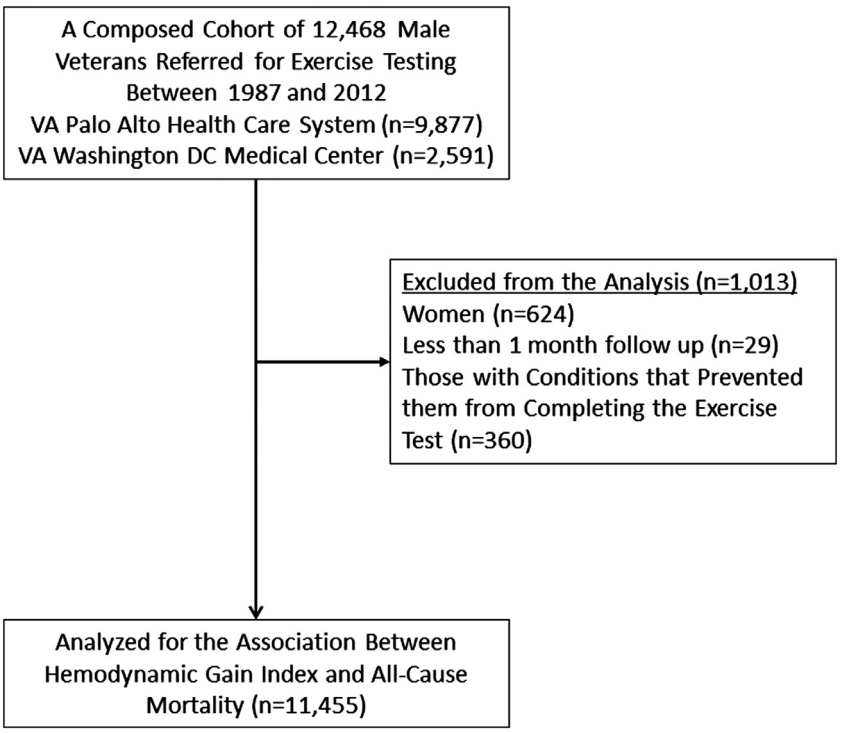

Figure 1. Flowchart of study design.

them from completing the exercise test (orthopedic or neurological reasons or those that required emergent intervention) (n = 360). A total of 11,455 male Veterans were included in the analysis who were followed for a mean of 9.8 ± 5.8 years (Figure 1). Clinical information on diagnoses, risk factors and health behaviors (smoking, alcohol, and drug abuse) were collected at the time of the exercise test using the Veterans Affairs Computerized Patient Record System (CPRS) and self-report health history.

Participants underwent symptom-limited treadmill exercise testing according established guidelines.[5,7] An individualized treadmill ramp protocol was utilized at the VA Palo Alto Health Care System and a Bruce protocol was used at the VA Washington DC Medical Center. A 12-lead electrocardiogram, HR, manual blood pressure and Borg 6-20 perceived exertion rating were continuously recorded throughout the tests and standard criteria for test termination were used.[5,7] Participants were instructed to continue their regular medication regimen on the testing day and exercise to volitional fatigue in the absence of clinical indications for stopping. CRF expressed in METs was calculated from peak treadmill speed and grade for the individualized ramp protocol, and exercise time for the Bruce protocols, utilizing the well-established metabolic equations from the American College of Sports Medicine.[5]

The hemodynamic gain index (HGI) was developed using HR and systolic blood pressure (SBP) responses from the exercise tests. The following equation was constructed: $HGI = ([HRmax \times SBPmax] - [HRrest \times SBPrest])/(HRrest \times SBPrest)$. Several validation processes conducted were as follows: (1) correlation analysis with CRF, a well-established prognostic marker for mortality and overall health[6]; (2) assessment of the risk association with a hard outcome (all-cause mortality); (3) adjustment of the risk models for many potential confounders to assess the independent association with mortality; and (4) a stratified analysis by age groups and clinical conditions.

The Veterans Affairs CPRS was used for capturing all-cause mortality as the primary outcome. Previous reports have demonstrated that the Veterans Affairs death records are relatively complete compared with those from other sources, such as the Social Security Administration[8] and they have good agreement (kappa = 0.82−0.91) with state death records.[9] Death records were carefully reviewed by qualified medical personal who were otherwise blinded to treadmill test results and other study information. International Classification of Diseases ninth and tenth edition codes were utilized to capture death cases. The vital status for each participant was ascertained as of August 2016.

SPSS (IBM, Chicago, Illinois) version 23 was used for statistical analyses. The significance level was set at $p < 0.05$. Demographic, clinical, and physiological data of the participants are presented as mean ± standard deviation for continuous variables and in percentages for categorical variables. Descriptive statistics using quartiles of <25th, 25th to 50th, 50th to 75th, >75th percentiles were used for categorical analysis of HGI. Participants' data were compared between the quartiles using analysis of variance for continuous variables and chi-square tests for categorical variables. The risk association between HGI and all-cause mortality was analyzed using a Cox proportional hazard model. The continuous and categorical models were adjusted for age, family history of heart diseases, body mass index, smoking status (never, former, and current),

hypertension (SBP ≥140 and or diastolic blood pressure ≥90 mm Hg or antihypertensive therapy), dyslipidemia (total cholesterol ≥200 or low-density lipoprotein cholesterol ≥130 or high-density lipoprotein cholesterol <40 mg/dl or on lipid-lowering medications),[5] diabetes, presence of cardiovascular disease, β blockers, calcium channel blockers, statins, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, diuretic drugs, and CRF. Kaplan-Meier survival curves and log-rank tests were utilized for comparisons between the HGI quartiles. The proportional hazards assumption was evaluated graphically for HGI percentiles and confirmed using the scaled Schoenfeld residuals. In order to address the potential reverse causality bias, a secondary analysis was performed after excluding participants who had less than 2 years follow-up. Pearson's correlations were conducted between HGI and CRF and exploratory analysis was performed for the risk association between maximal rate pressure product (HR × SBP) and death using a Cox proportional hazard model. Data report and presentation were followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[10]

Results

The sample included 11,455 men, aged 58.5 ± 11.2 years. Demographic, clinical, and physiological characteristics of the participants are presented in Table 1. During 9.8 ± 5.8 years follow-up, 2,804 participants died. Both in continuous and categorical models, higher HGI were associated with lower risk of all-cause mortality (Figures 2 and 3; Tables 2 and 3). The inverse association between HGI and death was significant in subgroups of participants with obesity, hypertension, dyslipidemia,

Table 1
Demographic and clinical characteristics of the cohort

Clinical history and demographics	Entire cohort (n = 11,455)	HGI <25th percentile (n = 2,944)	HGI 25 to 50th percentiles (n = 2,888)	HGI 50 to 75th, percentiles (n = 2,435)	HGI >75th percentile (n = 3,188)	p Value
Age (years)	58.5 ± 11.2	62.3 ± 10.5	59.8 ± 10.6	57.3 ± 10.8	54.5 ± 11.1	<0.001
Body mass index (kg/m^2)	28.9 ± 5.6	28.4 ± 5.7	29 ± 5.3	29 ± 5.5	29.1 ± 5.9	<0.001
Clinical history						
Family history of coronary artery disease	20.4%	20.3%	20.5%	21.4%	19.5%	0.377
Hypertension	53.3%	60.1%	57.8%	51.3%	44.6%	<0.001
Dyslipidemia	25.8%	18.1%	25.1%	26.5%	33.7%	<0.001
Obesity (body mass index ≥30)	35.6%	32.6%	36.7%	36.9%	36.5%	0.001
Any cardiovascular disease	17.2%	29.2%	18.4%	13.6%	7.3%	<0.001
Any pulmonary disease	7%	8.9%	7.6%	5.8%	4.7%	<0.001
Diabetes	48.7%	56.4%	55.8%	48.1%	35.5%	<0.001
Smoking	15.1%	13.2%	17.4%	13.2%	17.4%	<0.001
Pack/years	16.3 ± 26.7	17.4 ± 28.8	15.9 ± 24.5	15.4 ± 26.6	16.1 ± 26.5	0.259
Hemodynamics						
Resting heart rate (bpm)	75.3 ± 14.3	81.3 ± 16	79.5 ± 13.6	74.8 ± 11.5	67 ± 10.3	<0.001
Peak heart rate (bpm)	140.3 ± 23.6	120.6 ± 21.4	137.5 ± 20.1	147.3 ± 18.8	156 ± 17.4	<0.001
Percent of predicted maximal heart rate (%)(220-age)	84.2 ± 13	73.9 ± 12.9	83.2 ± 11.6	88.2 ± 10.3	92.3 ± 9.2	<0.001
Resting systolic blood presure (mm Hg)	129.9 ± 19.4	136.5 ± 22	133.8 ± 19	128.8 ± 17	122.2 ± 15.4	<0.001
Resting diastolic blood presure (mm Hg)	80 ± 17	81.2 ± 12	81.5 ± 18.5	79.9 ± 11.5	77.5 ± 22.2	<0.001
Peak systolic blood presure (mm Hg)	178.6 ± 28.3	160.6 ± 27.7	178.3 ± 24.4	184.7 ± 23.9	193.3 ± 24.5	<0.001
Peak diastolic blood presure (mm Hg)	85 ± 20	82.4 ± 20.4	85.8 ± 24	85.4 ± 14.5	86.3 ± 19	<0.001
Hemodynamic gain index (bpm/mm Hg)	1.68 ± 0.83	0.77 ± 0.23	1.35 ± 0.15	1.84 ± 0.14	2.74 ± 0.56	<0.001
Cardiorespiratory fitness (METs)	8.5 ± 3.4	5.93 ± 2.6	8 ± 2.8	9.4 ± 2.9	10.8 ± 3.1	<0.001
Medications						
Any drugs affecting hemodynamics	51%	62.4%	53.1%	47.6%	41.5%	<0.001
Antihyperlipidemias Drugs	17.3%	11%	16.2%	17.3%	24.5%	<0.001
Deaths (n/%)	2,804/24.5%	1,279/43.2%	792/27.2%	442/18.2%	295/9.3%	<0.001
Follow up time (years)	9.8 ± 5.8	10.2 ± 5.9	10.2 ± 5.7	10.2 ± 5.9	8.6 ± 5.7	<0.001

Data presented as means ± standard deviations or % for categorical variables. HGI = hemodynamic gain index.

Hypertension was defined as systolic blood pressure ≥140 and or diastolic blood pressure ≥90 mm Hg or antihypertensive therapy, dyslipidemia was defined as total cholesterol ≥200 and or LDL cholesterol ≥130 and or HDL cholesterol <40 mg/dL or on lipid-lowering medication.[5]

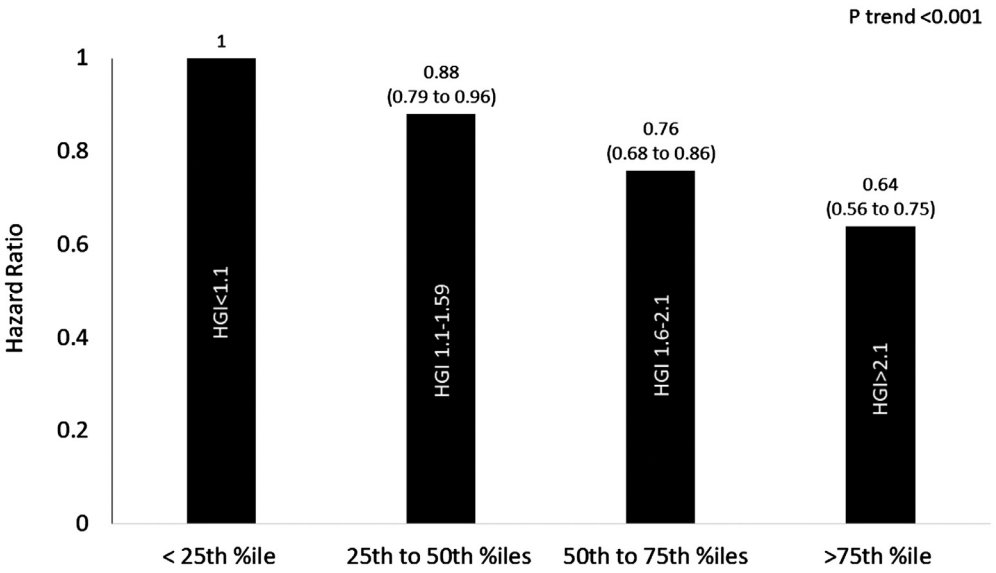

Figure 2. Hazard ratios of hemodynamic gain index percentiles and all-cause mortality in men. HGI = hemodynamic gain index.

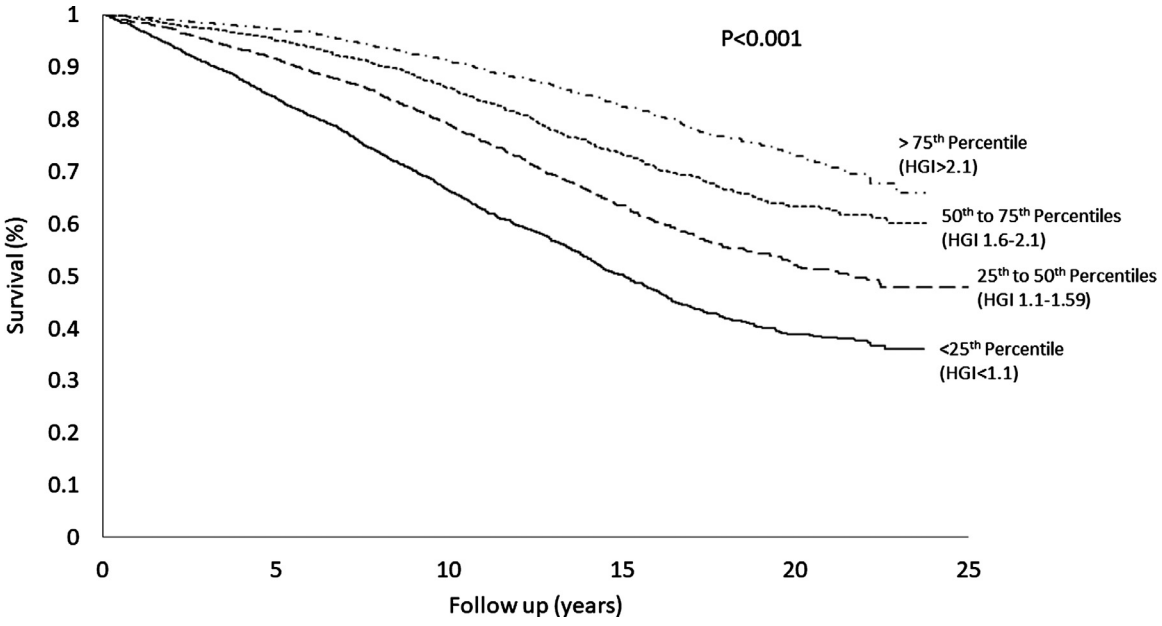

Figure 3. Survival curves of hemodynamic gain index percentiles in men. HGI = hemodynamic gain index.

cardiovascular disease, diabetes, those who were on medications affecting hemodynamics, and smokers as well as in each age decade between 40 and 79 years (Tables 2 and 3). After exclusion of those with less than 2 years follow-up, HGI remained a significant predictor of mortality both in continuous and categorical models. The hazard ratio and 95% confidence interval for the continuous model was 0.77, (0.72−0.83), p <0.001. The hazard ratios and 95% confidence interval for the categorical model were 0.90 (0.81−0.98), 0.77 (0.67−0.87), and 0.65 (0.56−0.76), p trend <0.001. The correlation between HGI and CRF was r = 0.54, R^2 = 0.29, p <0.001 (Table 2). Both in bivariable and multivariable hazard models, maximal rate pressure product (HR × SBP) alone was not associated with mortality.

Discussion

In the present study, we aimed to assess the prognostic value of a newly developed hemodynamic index in a large cohort of men. Using HR and SBP responses to exercise testing, we developed a new index (HGI) and conducted clinical and statistical validation. The novel findings demonstrated that higher HGI is inversely and independently associated with lower risk of all-cause mortality. HGI remained a strong predictor of mortality even after

Table 2
Correlation coefficients and hazard ratios of hemodynamic gain index and cardiorespiratory fitness in subgroups of the cohort

Condition/parameter / analysis	Obesity (n = 3,890)	Hypertension (n = 6,154)	Dyslipidemia (n = 2,989)	Any CVD (n = 1,979)	Diabetes (n = 5,617)	Medications affecting hemodynamics (n = 5,891)	No medications affecting hemodynamics (n = 5,636)	Smokers (n = 1,741)	Entire cohort (n = 11,455)
HGI (bpm/mm Hg)	1.68 ± 0.8	1.58 ± 0.78	1.87 ± 0.84	1.3 ± 0.66	1.52 ± 0.72	1.56 ± 0.8	1.81 ± 0.84	1.6 ± 0.8	1.68 ± 0.83
Cardiorespiratory fitness (METs)	8 ± 3	7.9 ± 3.1	8.6 ± 2.9	7.4 ± 3.2	8.1 ± 3.3	7.9 ± 3	9.3 ± 3.6	7.7 ± 3	8.5 ± 3.4
Pearson's correlations	r = 0.51 p <0.001	r = 0.51 p <0.001	r = 0.49 p <0.001	r = 0.56 p <0.001	r = 0.55 p <0.001	r = 0.51 p <0.001	r = 0.54 p <0.001	r = 0.56 p <0.001	r = 0.54 p <0.001
HR 95%(CI) per 1- unit increase in HGI	0.73 (0.64-0.84) p <0.001	0.73 (0.66-0.8) p <0.001	0.75 (0.58-0.98) p = 0.035	0.82 (0.77-0.99) p = 0.038	0.82 (0.77-0.91) p <0.001	0.78 (0.70-0.86) p <0.001	0.75 (0.68-0.83) p <0.001	0.69 (0.56-0.86) p = 0.001	0.77 (0.71-0.82) p <0.001

CI = confidence intervals; CVD = cardiovascular disease; HGI = hemodynamic gain index; HR = hazard ratio; MET = metabolic equivalent.
The hazard ratio models were adjusted for age, family history of heart diseases, body mass index, smoking status, hypertension, dyslipidemia, diabetes, any cardiovascular disease, beta-blockers, calcium channel blockers, statins, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, diuretic drugs, and cardiorespiratory fitness.

adjusting for established chronic conditions, age, medications affecting hemodynamics, exclusion of those with less than 2 years follow-up, and CRF. This independent association along with the modest explained variability ($R^2 = 0.29$) between HGI and CRF, support the potential additional prognostic value of HGI beyond CRF. Given that many clinical and research settings have limited resources where metabolic or other advanced hemodynamic assessments are not available, these findings have potentially important clinical implications for risk stratification of patients referred for exercise testing. The simplicity of calculating the index and the powerful prognostic value of HGI provide potential for its application in clinical and research settings.

The current results are consistent with the available body of knowledge with respect to hemodynamic responses to exercise and mortality risk.[1−3] Our findings strengthen this knowledge, and add a novel index which comprehensively evaluates the hemodynamic response that could complement the existing prognostic markers. Although several hemodynamic markers have been associated with adverse cardiovascular outcomes, each has limitations.[1,2,5] For instance, achieving a maximal HR <85% of age-predicted, the first minute of HR recovery <12 bpm and a hypotensive SBP response during exercise reflect different hemodynamic abnormalities and are measured at separate time points during the exercise test. These variables express only a fractional hemodynamic response to an exercise test and lack the integration of both HR and blood pressure responses into one comprehensive metric.[1,2,5] HGI offers a more integrated evaluation of HR and blood pressure responses to exercise in a single index. In addition, HGI provides a noninvasive and sensitive evaluation of cardiovascular function during exercise that is independently associated with mortality.[4]

Several physiological mechanisms may explain these results. The product of HR and SBP (rate−pressure product) is an indirect measure of myocardial oxygen consumption and overall cardiac function.[4,7,11] Rate pressure product is an accepted metric for determining an ischemic threshold for exercise training in cardiac rehabilitation, and is associated with cardiac function and prognosis in patients with coronary artery disease.[4,5,7] HGI in the present study utilized the net gain (from rest to maximal exercise) in rate pressure product divided by resting values, a method that has a strong physiological rationale for assessing the responsiveness (net gain) in cardiovascular function. The index objectively reflects the net capacity of the cardiovascular system to generate forceful blood flow for meeting the physiological demands of maximal aerobic exercise. It is a mechanistic reflection of the pumping capability of the heart as well as compliance of the vasculature in response to physiological stimuli. Overall, the higher the HGI, the better the cardiovascular function. In contrast, a low HGI may suggest a noninvasive evaluation of stiffness of the myocardium and the vascular system.[4,7,11,12] Exercise testing guidelines acknowledge that abnormal resting and maximal HR and SBP responses are associated with increased risk of cardiovascular disease and mortality, which the proposed index effectively expresses in a single and simple metric.[1,2,5,7]

Table 3
Hazard ratios of hemodynamic gain index and cardiorespiratory fitness by different age groups

Age group (years) / parameter /analysis	20-29 (n = 106)	30-39 (n = 434)	40-49 (n = 1,822)	50-59 (n = 3,488)	60-69 (n = 3,604)	70-79 (n = 1,560)	≥80 (n = 247)
HGI (bpm/mm Hg)	2.4 ± 0.84	2.2 ± 0.94	1.9 ± 0.84	1.73 ± 0.81	1.59 ± 0.8	1.3 ± 0.64	1.2 ± 0.63
Cardiorespiratory fitness (METs)	13.8 ± 3.5	12 ± 3.2	10.3 ± 3.4	8.9 ± 3	7.7 ± 3	6.4 ± 2.6	5.3 ± 2.1
Death events (n)	No death events	No death events	217	566	1,185	714	122
HR 95%(CI) per 1 unit increase in HGI	N/A	N/A	0.71 (0.58-0.86) p <0.001	0.53 (0.46-0.6) p <0.001	0.61 (0.56-0.67) p <0.001	0.6 (0.53-0.69) p <0.001	NS

CI = confidence intervals; HGI = hemodynamic gain index; HR = hazard ratio; MET = metabolic equivalent; N/A = not applicable; NS = not significant.
The hazard ratio models were adjusted for family history of heart diseases, body mass index, smoking status, hypertension, dyslipidemia, diabetes, any cardiovascular disease, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, diuretic drugs, and cardiorespiratory fitness.

The strengths of the present study include the application of noninvasive and easily assessable physiological variables (HR and SBP), a large sample size (n = 11,455) and extended prospective follow-up (approximately 10 years) for adverse outcomes. Mortality outcomes were verified through the Veterans Affairs computerized medical records system, which has been demonstrated to be comparatively accurate and complete.[8,9] The prognostic value of HGI was validated using several clinical and statistical methods. The study has also several limitations. First, Veteran participants are a unique population with a rich mixture of comorbidities that may have influenced the results by selection bias. Nevertheless, HGI aligns with a well-established body of knowledge of physiological responses and exercise testing guidelines.[1,2,5] Second, the study was limited to men, and the extent to which the findings apply to women needs to be examined in future studies. Finally, although the findings provide a strong and independent association between HGI and mortality outcomes, they do not demonstrate a cause and effect relation, and require additional validation in a separate cohort.

HGI is a powerful, simple, noninvasive, and practical prognostic marker requiring only HR and SBP responses to exercise. Higher HGI is inversely and independently associated with lower risk of all-cause mortality in men, regardless of the presence of established clinical conditions, risk factors, CRF levels and medications affecting hemodynamics. The current results suggest that HGI adds prognostic value beyond CRF, and has good potential for clinical and research applications. Future studies are needed to confirm these findings and assess changes in HGI over time and risk of health-related outcomes.

Acknowledgment

The authors thank Taryn Davidson for organizing the data file and to Tetyana Vainshelboim for helping with construction of figures.

Disclosures

The authors have no conflicts of interest to disclose.

1. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010;122:191–225.
2. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J. EACPR/AHA scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation* 2012;126:2261–2274.
3. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation* 2016;133:e694–e711.
4. American College of Sports Medicine. *ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription*. Baltimore: Lippincott Wiliams & Wilkins; 2010.
5. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014:456.
6. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisloff U, American Heart Association Physical Activity Committee of the Council on L, Cardiometabolic H, Council on Clinical C, Council on E, Prevention, Council on C, Stroke N, Council on Functional G, Translational B, Stroke C. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation* 2016;134:e653–e699.
7. 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, American Heart Association Exercise CR, Prevention Committee of the Council on Clinical Cardiology CoNPA, Metabolism CoC, Stroke N, Council on E, Prevention. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation* 2013;128:873–934.
8. Page WF, Mahan CM, Kang HK. Vital status ascertainment through the files of the Department of Veterans Affairs and the Social Security Administration. *Ann Epidemiol* 1996;6:102–109.
9. Dominitz JA, Maynard C, Boyko EJ. Assessment of vital status in Department of Veterans Affairs national databases. comparison with state death certificates. *Ann Epidemiol* 2001;11:286–291.
10. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med* 2007;147:W163–W194.
11. Farrell PA, Joyner MJ, Caiozzo VJ. *ACSM's Advanced Exercise Physiology*. 2nd ed Baltimore: Lippncott Williams& Wilkins; 2012.
12. Froelicher VF, Myers J. *Exercise and the heart*. 5th ed Philadelphia: Saunders Elsivier; 2006.