Clinical Research

Heart Rate Recovery After Exercise and Long-term Prognosis in Patients With Coronary Artery Disease

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ABSTRACT

Background: The long-term prognostic value of heart rate recovery (HRR) has been incompletely documented in patients with coronary artery disease (CAD). We sought to confirm the prognostic value of HRR in a large cohort with stable CAD.

Methods: From the Coronary Artery Surgery Study registry, a database of 24,958 patients with CAD who underwent cardiac catheterization between 1974 and 1979, we identified 4097 patients with baseline exercise stress testing data. HRR was measured at 3 minutes post exercise during a passive recovery. Clinical outcomes were evaluated according to HRR in both threshold and continuous models.

Results: Median long-term follow-up was 14.7 years (interquartile range, 9.8-16.2). HRR $<$ 46 beats per minute (Bpm) most appropriately differentiated nonsurvivors from survivors (area under receiver operating characteristic curve = 0.613) and was associated with an increased risk of all-cause death (adjusted hazard ratio = 1.15; P = 0.011). Increasing HRR was associated with a lower risk of all-cause (adjusted hazard ratio = 0.94 per 10 Bpm; 95% confidence interval, 0.91-0.97; P = 0.0005) and cardiovascular (CV) mortality (adjusted hazard ratio = 0.94 per 10 Bpm; 95% confidence interval, 0.90-0.98; P = 0.003).

Conclusions: HRR at 3 minutes independently predicts long-term all-cause and CV mortality in patients with stable CAD. Measurement of HRR at 3 minutes during passive recovery can be used as a complementary tool to identify patients with a higher total and CV risk.

RÉSUMÉ

Introduction : La valeur pronostique à long terme de la fréquence cardiaque de récupération (FCR) a été documentée de manière incomplète chez les patients ayant une maladie coronarienne (MC). Nous avons cherché à confirmer la valeur pronostique de la FCR chez une vaste cohorte ayant une MC stable.

Méthodes : À partir du registre CASS (Coronary Artery Surgery Study), une base de données de 24 958 patients ayant une MC qui ont subi un cathétérisme cardiaque entre 1974 et 1979, nous avons identifié 4 097 patients ayant des données de base à l'épreuve d'effort. La FCR a été mesurée 3 minutes après l'exercice durant une récupération passive. Les événements cliniques ont été évalués en fonction des modèles de FCR continu et avec seuil.

Résultats : Le suivi médian à long terme a été de 14,7 ans (écart interquartile, 9,8-16,2). La FCR $<$ 46 battements par minute (Bpm) a différencié de la manière la plus appropriée les non-survivants des survivants (l'aire sous la courbe caractéristique d'efficacité pour le récepteur = 0,613) et a été associée à une augmentation du risque de décès toutes causes confondues (risque relatif ajusté = 1,15; P = 0,011). L'augmentation de la FCR a été associée à un risque faible de mortalité toutes causes confondues (risque relatif ajusté = 0,94 par 10 Bpm; intervalle de confiance de 95 %, 0,91-0,97; P = 0,0005) et cardiovasculaire (CV) (risque relatif ajusté = 0,94 par 10 Bpm; intervalle de confiance de 95 %, 0,90-0,98; P = 0,003).

Conclusions : La FCR mesurée à 3 minutes est un prédicteur indépendant de la mortalité de toutes causes et CV à long terme chez les patients ayant une MC stable. La FCR mesurée à la 3ème minute de récupération passive peut être utilisée comme un outil complémentaire pour identifier les patients ayant un risque total et CV plus élevé.

Among the different heart rate (HR) prognostic variables provided by exercise testing (ET), heart rate recovery (HRR) has

been shown to be associated with total and cardiovascular (CV) mortality and/or morbidity in apparently healthy patients,[1-5] in patients with diabetes,[6] or in mixed populations with and without coronary artery disease (CAD).[7-14] The rise of HR during ET is considered to be a combination of increased sympathetic and decreased parasympathetic activation,[15] whereas the fall in HR immediately after exercise is considered to be a function of the reactivation of the parasympathetic nervous

system and subsequent withdrawal of the sympathetic nervous system.[10,15,16] Impaired autonomic regulation of CV function results in abnormal HRR, or a less pronounced decrease of HR immediately after exercise cessation, and is associated with a higher risk of CV events and/or sudden death.[4] As well, exercise training can improve HRR and reduce cardiac mortality in patients with myocardial infarction.[17]

Most studies examining the relationship between HRR and long-term outcomes were undertaken in subjects without underlying CV disease. However, in 3 previous studies with a significant proportion of patients with CAD,[7,8,11] HRR measured after 1 and/or 2 minutes of recovery was independently related to mortality after 5 to 8 years of follow-up and predicted the presence of CAD.[8] It is important to note that these studies used different methodologies, with HRR being measured either during active recovery[11] or in a supine position soon after exercise,[7,8] both of which methods can influence HRR.[18,19] The prognostic value of abnormal HRR and its link with long-term mortality and morbidity have not been studied adequately in patients with stable CAD. The objective of this study was to evaluate the long-term prognostic value of HRR (measured after 3 minutes of passive recovery) on total and CV mortality in a large and well-characterized population with CAD.

Methods

Patient population and follow-up

The Coronary Artery Surgery Study (CASS) registry includes 24,958 patients with suspected or proven CAD who were enrolled at one of 15 centres throughout North America between 1974 and 1979. Patients had annual scheduled follow-up until 1982, and afterwards vital status was obtained through a mail-in survey completed between 1989 and 1991. Vital status for nonresponders was obtained from the National Death Index for patients in the United States and by next of kin, medical records, and death certificates in Canada. Follow-up was complete for 96% of patients in the registry by the closing date of December 31, 1992. Patients without death records available were considered alive. CV mortality was defined according to the *International Classification of Diseases*, eighth revision (codes 390-458). From the CASS registry, we identified for inclusion in our study a total of 4097 patients with baseline exercise stress testing data.

Clinical variables

The clinical variables used were derived from the CASS registry and obtained at the time of enrollment in the study. They included age, gender, medical history of diabetes, hypertension, hypercholesterolemia and smoking, and β-blocker use. Additional variables studied were systolic and diastolic blood pressure, serum cholesterol, triglycerides, fasting plasma glucose, left ventricular ejection fraction, and extent of coronary disease. All blood marker measurements were performed at the time of blood collection from fresh samples. Left main artery disease was considered 2-vessel disease in the presence of a right-dominant coronary circulation and 3-vessel disease in the presence of a left-dominant coronary circulation. Coronary angiograms were interpreted by visual estimation in the CASS registry.

ET and HR measurements

ET was performed on a motor-driven treadmill according to a modified maximal Bruce protocol.[20] The stages at which exercise was started and stopped were recorded, as was the duration of the test. Grounds for discontinuation of the test were those of standard clinical practice as previously described.[20] All measurements were obtained at baseline ET. Peak or maximal HR was obtained with the patient standing on the treadmill at peak exercise. Postexercise HR was measured 3 minutes after completion of the modified Bruce protocol. HRR was calculated as maximum HR − postexercise HR after 3 minutes during a passive recovery period. Percentage HR reserve was computed as (maximal HR − resting HR)/(220 − age − resting HR) × 100. Maximal age-predicted HR was calculated as 220 − age. Exercise capacity (in metabolic equivalents) was estimated on the basis of the speed, slope, and time of exercise on the treadmill.[21]

Statistical analysis

Results are expressed as mean ± standard deviation or median (minimum, maximum) for continuous variables and as frequency (percentage) for categorical variables. Univariate analyses (1-way analysis of variance or Kruskal-Wallis test for continuous variables and Pearson χ^2 test for categorical variables were used to compare patients with normal HRR vs those with an abnormal HRR (based on the receiver operating characteristic [ROC] curve). Univariate Cox proportional hazards regression models were used to evaluate the influence of HRR on outcomes. Multivariate Cox regression models were also created adjusting for potential confounders (baseline characteristics, clinical variables). A ROC curve was generated to determine the value of HRR that best differentiated survivors from nonsurvivors. Kaplan-Meier curves with normal and abnormal HRR were constructed with the all-cause and CV time events. A P value < 0.05 was considered statistically significant. Statistical analyses were performed with SAS version 8.02 (SAS Institute Inc, Cary, NC).

Results

Baseline and angiographic characteristics

The ROC curve analysis of HRR vs both long-term all-cause and CV mortality identified a value of 46 beats per minute (Bpm) to most appropriately distinguish survivors from nonsurvivors (area under the curve for total mortality = 0.613; sensitivity = 0.568; area under the curve for CV mortality = 0.598; sensitivity = 0.564). Based on this analysis, we identified 2255 patients with a normal HRR ($\geq$ 46 Bpm) and 1842 patients with an abnormal HRR ($<$ 46 Bpm). Patients with abnormal HRR were older and had a greater prevalence of hypertension, dyslipidemia, diabetes, β-blocker use, and antihypertensive use and a greater extent of coronary disease than did patients with normal HRR (Table 1).

Exercise characteristics

Compared with patients with normal HRR, patients with an abnormal HRR ($<$ 46 Bpm) had lower exercise tolerance, resting HR, maximal HR, and maximal systolic blood pressure. They also had a lower mean HRR and HR reserve (Table 2).

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Table 1. Baseline characteristics according to heart rate recovery (HRR)

Characteristic	Patients with normal HRR (≥ 46 Bpm) (n = 2255) Mean ± SD	Patients with abnormal HRR (< 46 Bpm) (n = 1842) Mean ± SD	P ANOVA —
Age (years)	49.3 ± 8.3	53.2 ± 8.3	< 0.0001
Body mass (kg)	74.0 ± 13.3	75.4 ± 12.6	0.0357
BMI (kg/m^2)	25.6 ± 3.6	25.8 ± 3.5	0.0490
LVEF (%)	57.3 ± 12.6	56.8 ± 14.2	0.2249
Systolic BP (mm Hg)	132.3 ± 19.4	134.9 ± 21.3	0.0001
Diastolic BP (mm Hg)	82.0 ± 11.3	82.9 ± 11.9	0.0214
Serum total cholesterol (mg/dL)	231.5 ± 50.2	235.6 ± 50.8	0.0089
Serum triglycerides (mg/dL)	197.3 ± 117.7	210.6 ± 125.3	< 0.0001
Fasting plasma glucose (mg/dL)	95 (60-247)	98 (60-371)	< 0.0001
Medication, n (%)			
Antihypertensive treatment	119 (5.28)	164 (8.90)	< 0.0001
β-Blockers	764 (33.8)	819 (44.46)	< 0.0001
Aspirin	47 (2.0)	54 (2.9)	0.081
Antilipemic agents	109 (4.8)	87 (4.7)	0.869
Characteristic	n (%)	n (%)	
Male sex	1795 (79.6)	1502 (81.5)	0.119
Active smokers	1368 (60.6)	1059 (57.4)	0.039
Medical history of hypertension	562 (24.9)	628 (34.0)	< 0.0001
Family history of angina or MI	1030 (45.6)	803 (43.5)	0.079
Abnormal coronary angiogram	1806 (80.0)	1646 (89.3)	< 0.0001
Long-term death	661 (45.24)	800 (54.76)	< 0.0001
Extent of coronary disease			
0-vessel disease	689 (30.6)	356 (19.4)	< 0.0001
1-vessel disease	561 (24.9)	379 (20.6)	
2-vessel disease	525 (23.3)	481 (26.2)	
3-vessel disease	476 (21.1)	616 (33.6)	

Values are expressed as mean ± SD or in n and %, except for fasting plasma glucose, expressed as median with minimum and maximal values.

ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; Bpm, beats per minute; LVEF, left ventricle ejection fraction; MI, myocardial infarction; SD, standard deviation.

Outcomes

Continuous model. When evaluated as a continuous variable, increasing HRR was associated with a significant reduction in both long-term all-cause (adjusted hazard ratio = 0.94; 95% confidence interval [CI], 0.91-0.97; P = 0.0005 per 10-Bpm increment) and CV mortality (adjusted hazard ratio = 0.94; 95% CI, 0.90-0.98; P = 0.003 per 10-Bpm increment) during the median long-term follow-up period of 14.7 years (interquartile range, 9.8-16.2; Table 3).

Threshold model. In unadjusted models, HRR < 46 Bpm was associated with a higher risk of long-term all-cause and CV

death (Figs. 1 and 2; Kaplan-Meier survival curves). After age, sex, smoking, hypertension, total cholesterol, triglycerides, diabetes, weight, tolerance time, resting HR, β-blockers, and ejection fraction were adjusted for, HRR < 46 Bpm was associated with a 1.15-fold increase in the risk of all-cause death (adjusted hazard ratio = 1.15; 95% CI, 1.03-1.28; P = 0.011), while CV mortality tended to increase with HRR < 46 Bpm (adjusted hazard ratio = 1.12; 95% CI, 0.98-1.28; P = 0.084; Table 4).

Discussion

The principal findings of our study are that for continuous models, HRR at 3 minutes post exercise was an independent

Table 2. Exercise parameters according to heart rate recovery (HRR)

Exercise parameters	Patients with normal HRR (≥ 46 Bpm) (n = 2255) Mean ± SD	Patients with abnormal HRR (< 46 Bpm) (n = 1842) Mean ± SD	P ANOVA —
Metabolic equivalents	7.3 ± 2.8	5.5 ± 2.8	< 0.0001
Resting HR (Bpm)	72 ± 12	74 ± 14	< 0.0001
Exercise duration (seconds)	529 ± 201	393 ± 297	< 0.0001
Resting SBP (mm Hg)	133.0 ± 20.29	133.2 ± 21.6	0.799
Resting DBP (mm Hg)	83.2 ± 11.5	83.5 ± 12.1	0.466
Maximal HR (Bpm)	151 ± 21	121 ± 23	0.0001
Maximal SBP (mm Hg)	175.5 ± 28.7	165.2 ± 29.7	< 0.0001
Maximal DBP (mm Hg)	88.8 ± 14.6	87.6 ± 15.2	0.138
HRR (Bpm)	60 ± 11	32 ± 10	< 0.0001
HR reserve (%)	80 ± 18	52 ± 24	< 0.0001

ANOVA, analysis of variance; Bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation.

Table 3. Associations between heart rate recovery (HRR) and long-term mortality: continuous models

	Long-term all-cause mortality		Long-term CV mortality	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
HRR per 10-Bpm increment (unadjusted model)	0.85 (0.83-0.87)	0.0001	0.85 (0.82-0.88)	0.0001
HRR per 10-Bpm increment (adjusted model*)	0.94 (0.91-0.97)	0.0005	0.94 (0.90-0.98)	0.003

Bpm, beats per minute; CI, confidence interval; CV, cardiovascular.

*Adjusted for age, sex, smoking, hypertension, total cholesterol, triglycerides, diabetes, weight, tolerance time, resting heart rate, β-blockers, ejection fraction.

predictor of both long-term all-cause and CV mortality in a large CAD cohort. Similarly, in the threshold models, HRR < 46 Bpm at 3 minutes was independently associated with long-term all-cause mortality, while a statistical trend was noted for CV mortality. The novelty of this study is that it is the first to evaluate the prognostic value of HRR at 3 minutes post exercise. Furthermore, HRR was measured during a passive recovery with patients seated. We believe that measurement of HRR in this fashion is feasible and simple to perform in clinical practice and provides an additional risk stratification parameter.

There is currently no consensus regarding the most appropriate time and method to measure HRR. Because of the work of Cole et al. in men and women without CV disease,[9,10] measurement of HRR at 1 minute of recovery has become popular, with ≤ 12 Bpm used as the cut point for abnormal HRR. This cut point was found to confer a 2-fold increased risk of all-cause mortality among 2400 consecutive men and women referred for ET.[10] Two other studies in apparently healthy individuals[4,22] have compared the prognostic value of HRR measured at 1 and 2 minutes, with conflicting results. Shetler et al.[22] compared their own cut points at 1 minute (18-Bpm drop) and 2 minutes (42-Bpm drop) with those of previously published

studies that used cut points of 12 Bpm at 1 minute and 22 Bpm at 2 minutes.[9,10] They found that all cut points were able to predict all-cause mortality, although 22 Bpm at 2 minutes outperformed all other values (hazard ratio = 2.6; 95% CI, 2.4-2.8). In contrast, HRR measured at 1 minute (12-Bpm cut point) or 2 minutes (22-Bpm cut point) was not related to either total or CV mortality in the study of Morshedi-Meibodi et al.[4] Other studies in healthy subjects, however, confirm the prognostic value of HRR measured at 2 minutes.[9,13] Finally, Cheng et al.[6] demonstrated the prognostic value of HRR after 5 minutes of recovery in men with diabetes.

No previous studies have evaluated the potential utility of HRR measured at 3 minutes of recovery. Our results are consistent with other studies that measured HRR at 1 or 2 minutes in subjects with CAD. Among 2000 men with both ET and coronary angiography data and followed for 7 years, HRR at 2 minutes was better able to discriminate survivors from nonsurvivors (ROC area under curve = 0.67), was an independent predictor of total mortality ($P < 0.00001$) and was independently associated with angiographic severity of CAD ($P = 0.045$).[8] In addition, among 2900 consecutive patients referred for ET for suspected CAD and followed for 6 years, HRR at 1 minute (≤ 12 Bpm) was found to be an independent predictor
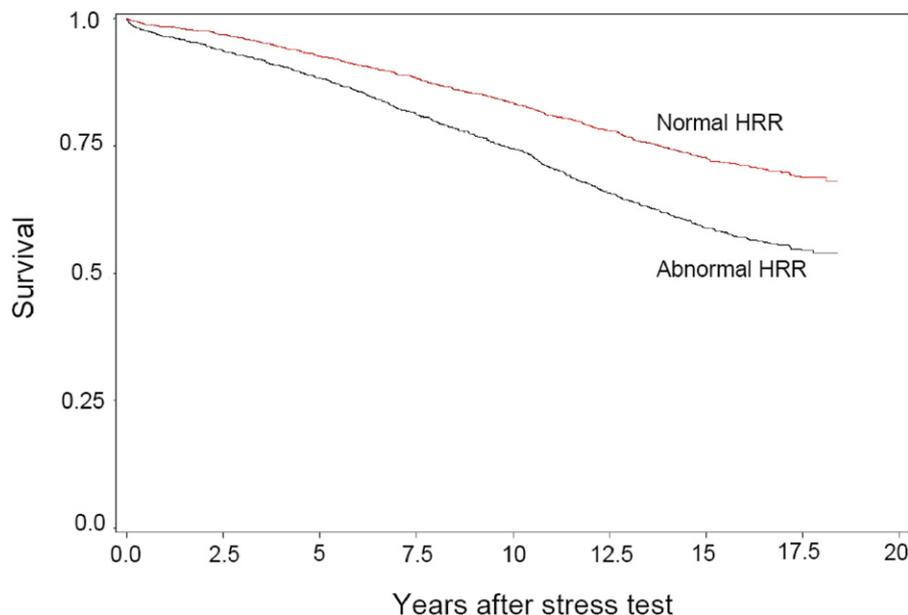

Figure 1. All-cause mortality. Kaplan-Meier survival curves according to normal heart rate recovery (HRR) (HRR ≥ 46 beats per minute) or abnormal HRR (HRR < 46 beats per minute) for all-cause mortality in patients with coronary artery disease. Analyses with the log-rank test including normal HRR and abnormal HRR and all-cause mortality rates were significant ($\chi^2 = 91.55$; $P < 0.0001$).
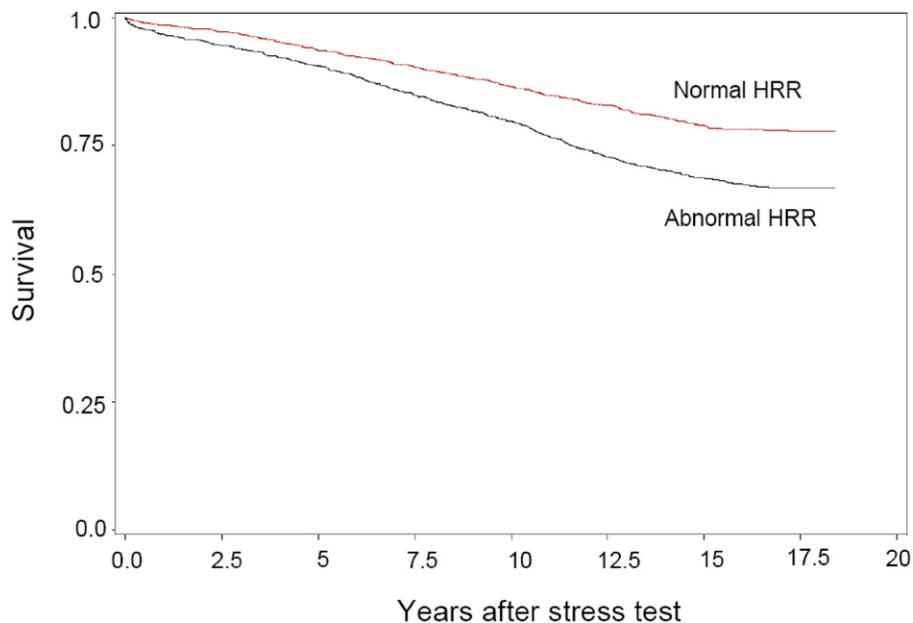
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Figure 2. Cardiovascular mortality. Kaplan-Meier survival curves according to normal heart rate recovery (HRR) (HRR ≥ 46 beats per minute) or abnormal HRR (HRR < 46 beats per minute) for cardiovascular mortality in patients with coronary artery disease. Analyses with the log-rank test including normal HRR and abnormal HRR and cardiovascular mortality rates were significant (χ^2 = 49.56; P < 0.0001).

of all-cause death (adjusted hazard ratio = 1.6; P < 0.0001) and angiographically severe CAD (adjusted hazard ratio = 1.14; P = 0.008).[11] Finally, Leeper et al.[7] found in their continuous model that HRR at 2 minutes was an independent predictor of total (adjusted hazard ratio 1.38; P < 0.001) and CV death (adjusted hazard ratio 1.32; P < 0.001) in CAD patients.

Although our data are consistent, our adjusted hazard ratios for mortality are somewhat lower (adjusted hazard ratio = 1.15 for all-cause mortality) than those observed in the previously cited literature. Several reasons may account for these differences. First, patients in the CASS registry were already high-risk subjects, 60% of whom were smokers and 50% of whom had multivessel CAD. Therefore abnormal HRR appears to have added little to their overall high-risk profile. Second, slow sympathetic withdrawal, which is the principal determinant of HRR during the latter part of the recovery period, may be less

associated with prognosis relative to the acute parasympathetic reactivation that primarily contributes to HRR during the first 2 minutes.[16,23] Third, the heterogeneity among study methodologies must be noted; various ET protocols and modalities such as treadmill[2,8,11-13,22] or cycling[24] were used. Furthermore, different types of recovery (active vs passive) were used during the ET protocols. All of these factors can in theory influence sympathetic and parasympathetic tone and HR during the recovery period,[18,19] and hence the link between HRR and prognosis. Studies measuring HRR at 1 minute post exercise generally did so during an active recovery or cooldown period, with patients continuing to walk for 1 to 2 minutes after peak exercise.[11] Such a protocol is not routinely recommended, however, given that a cooldown period may delay or eliminate the appearance of exercise-induced ST-segment depression.[25] Studies measuring HRR at 2 minutes post exercise used a passive recovery period, with participants immediately

Table 4. Multivariate Cox regression analysis for total and CV mortality (threshold model)

Variables	Total mortality		CV mortality	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age	1.04 (1.04-1.05)	< 0.0001	1.04 (1.03-1.05)	< 0.0001
Sex	0.55 (0.46-0.66)	< 0.0001	0.54 (0.43-0.68)	< 0.0001
Smoking	1.51 (1.35-1.68)	< 0.0001	1.50 (1.32-1.71)	< 0.0001
Hypertension	1.27 (1.14.1.42)	< 0.0001	1.43 (1.25.1.63)	< 0.0001
Total cholesterol	1.00 (1.00-1.00)	0.001	1.00 (1.00-1.00)	0.0002
Triglycerides	1.00 (0.99-1.00)	0.188	1.00 (0.99-1.00)	0.32
Diabetes	1.78 (1.53-2.06)	< 0.0001	1.77 (1.48-2.12)	< 0.0001
Weight	1.00 (0.99-1.00)	0.123	1.05 (0.99-1.01)	0.078
Exercise duration	0.94 (0.92-0.95)	< 0.0001	0.93 (0.91-0.95)	< 0.0001
Resting HR	1.00 (1.00-1.00)	0.022	1.00 (0.99-1.00)	0.12
β-Blockers	1.04 (0.93-1.15)	0.481	1.07 (0.94-1.22)	0.292
Ejection fraction	0.96 (0.96-0.97)	< 0.0001	0.95 (0.95-0.96)	< 0.0001
Abnormal HRR (< 46 Bpm)	1.15 (1.03-1.28)	0.011	1.12 (0.98-1.28)	0.084

Bpm, beats per minute; CI, confidence interval; CV, cardiovascular; HR, heart rate; HRR, HR recovery.

lying down in the supine position after peak exercise.[7,8,13,22] This type of protocol is more cumbersome and may be less comfortable for patients. HRR measured at 3 minutes during passive, seated recovery, as was performed in the CASS registry, therefore represents a simple, straightforward method for assessment of HRR and may be easily included into the routine clinical setting. Unfortunately, in the CASS registry database, HRR at 1 or 2 minutes was not available to enable us to simultaneously evaluate the prognostic value of HRR at multiple time points.

Our study also showed that patients with abnormal HRR had a higher resting HR and a lower maximal HR compared with those with normal HRR, suggesting not only reduced parasympathetic activity after maximal exercise but additional abnormalities of autonomic function. We should mention that patients with abnormal HRR had a higher rate of β-blocker use. However, conflicting results have been reported for the influence of β-blockers on HRR. Desai et al.[26] observed that HRR at 3 minutes was lower in CAD patients using β-blockers than in those not receiving this medication. In contrast, the use of β-blockers did not influence absolute HRR values at 1, 2, 3, or 5 minutes among patients referred for stress echocardiography in 2 other studies.[27,28] Furthermore, HRR, independent of the use of β-blockers, was shown to be a predictor of mortality in CAD patients.[8] Certain other medications may also influence HRR, including statins[29] and angiotensin-converting enzyme inhibitors.[30] However, a very low proportion of our patients were taking lipid-lowering therapy, and given the age of the registry, it is highly unlikely that antihypertensive therapy included any antagonists of the renin-angiotensin system.

Patients with abnormal HRR also had lower maximal HR and percentage HR reserve. One cannot exclude that these findings were due to a greater degree of chronotropic incompetence, disequilibrium of autonomic CV regulation at rest with relatively high sympathetic activity (higher resting HR among patients with abnormal HRR),[31,32] and/or a limitation of sympathetic activation during exercise.[14,27] These latter 2 abnormalities of autonomic CV function have also been linked to higher all-cause and CV risk.[31,32] Furthermore, low cardiorespiratory fitness per se may also contribute to impaired HRR, presumably through altered sympathovagal balance. Indeed, subjects with impaired HRR in the CASS registry did have lower exercise tolerance (Table 2). Certainly maximal HR at peak exercise and HR decay due to vagal reactivation in the postexercise period are dependent on exercise intensity, with greater values for these 2 parameters during more intense exercise relative to less intense exercise.[16] We assume that exercise intensity in both groups was maximal during ET. Cardiopulmonary ET with measurement of gas exchange would have allowed us to ensure this point; however, such tests were not performed in CASS.

The mechanisms linking abnormal HRR and mortality are not fully understood, but several contributing factors have been put forward. First, patients with CAD and abnormal HRR generally have more severe CAD,[8,11] a finding that we also observed in our cohort. Second, a previous study showed that patients with abnormal HRR have a greater degree of myocardial scar and myocardial ischemia on myocardial scintigraphy during exercise, which could also influence prognosis.[14,33] In our study, left ventricular function was normal and

similar among patients with and without abnormal HRR, suggesting that differences in the amount of scar tissue do not explain the mortality differences we observed between the 2 groups. Again, given that patients with abnormal HRR had a greater extent of CAD, it is plausible that they also had a greater ischemic burden, which may well have influenced prognosis. Hai et al. have suggested that persistent sympathetic activation following myocardial infarction may result in elevated myocardial oxygen consumption, unfavourable cardiac remodelling, and an increased propensity to ventricular arrhythmias that can ultimately lead to a higher risk of CV death.[17] Certainly, we cannot exclude that any of these factors may have contributed to the poorer prognosis in subjects with abnormal HRR, although patients in the CASS registry were not necessarily in the post–myocardial infarction period. Finally, abnormal HRR has also been associated with impaired endothelial function, which itself is predictive of future coronary events.[34]

Limitations of the current study include the fact that there have been considerable advances in the management of CAD since completion of this study. Nevertheless, our data demonstrate that the relationship between HRR and mortality is consistent with more recent data. Only approximately one-fifth of patients in the CASS registry underwent ET at baseline. It is unclear to us why this occurred. Despite this fact, our data are once again concordant with the large body of evidence showing the prognostic value of HRR in various patient populations. Strengths of our study include the well-characterized cohort, a large sample size, and the longest follow-up period among studies that have addressed this question.

In conclusion, HRR at 3 minutes post exercise during passive, seated recovery was an independent predictor of long-term all-cause and CV mortality in this large CAD cohort. HRR at 3 minutes is a simple parameter to measure and provides complementary information that may be used to assist in risk stratification. Further studies are required to determine whether treatment with lifestyle or pharmacologic interventions, including exercise training, diet, weight loss, and statins, may restore autonomic function and lead to normalization of HRR in CAD patients.

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Disclosures

The authors have no conflicts of interest to disclose.

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