









ORIGINAL RESEARCH

Role of Heart Rate Recovery in Chronic Heart Failure: Results From the MyoVasc Study

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BACKGROUND: Cardiac autonomic dysfunction is associated with heart failure (HF). Reduced heart rate recovery (HRR) indicates impaired parasympathetic reactivation after physical activity. Heart rate recovery 60 seconds after peak effort (HRR₆₀) is linked to autonomic dysfunction, but data on its relevance across HF phenotypes are scarce. This study aimed to identify clinical determinants of HRR₆₀ in an HF cohort and assess its relationship with clinical outcomes.

METHODS: Data from the MyoVasc study (NCT04064450; N=3289) were analyzed. Participants underwent standardized clinical phenotyping including cardiopulmonary exercise testing. HRR₆₀ was defined as the heart rate decline 60 seconds after exercise termination. Clinical determinants of HRR₆₀ were evaluated using multivariate regression, whereas Cox regression analyses assessed all-cause death and worsening of HF.

RESULTS: The analysis sample comprised 1289 individuals (median age, 66.0 [interquartile range {IQR}, 58.0–73.0] years, 30.4% women) ranging from stage B to stage C/D according to the universal definition of HF. Age, sex, smoking, obesity, peripheral artery disease, and chronic kidney disease were identified as determinants of HRR₆₀. HRR₆₀ showed a strong association with all-cause death (hazard ratio [HR]_{HRR60 [10 bpm]}, 1.56 [95% CI, 1.32–1.85]; $P < 0.0001$) and worsening of HF (HR_{HRR60 [10 bpm]}, 1.36 [95% CI, 1.10–1.69]; $P = 0.0052$) independent of age, sex, and clinical profile. Sensitivity analysis showed a stronger association with worsening HF in HF with preserved left ventricular ejection fraction ($P_{\text{interaction}} = 0.027$).

CONCLUSIONS: HRR₆₀ was associated with clinical outcome in chronic HF. Because it showed a stronger association with outcomes in HF with preserved ejection fraction, future research should consider phenotype-specific differences.

Key Words: all-cause death ■ autonomic dysfunction ■ heart failure ■ heart rate recovery ■ prognosis ■ worsening of heart failure

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Globally, nearly 38 million people suffer from heart failure (HF),¹ with an estimated prevalence between 1% and 2% among adults in developed countries.² Acute HF is the leading cause of hospitalization in older patients in Europe and the United States.³ Due to the aging of the society and advances in medical therapy, HF prevalence is expected to rise.

Autonomic dysfunction (AD) is a key characteristic of the HF.⁴ Observations from neurological disorders show that AD affects the cardiovascular system, leading to symptoms such as orthostatic hypotension.⁵ Cardiac neurotransmission have been reported to directly impact physiological functions of the heart (eg, chronotropy, dromotropy, lusitropy, and inotropy).⁶ An

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RESEARCH PERSPECTIVE

What Is New?

- Heart rate decline 60 seconds after exercise termination showed a strong association with clinical outcome in a contemporary heart failure (HF) cohort across the left ventricular ejection fraction spectrum.
- HF phenotype-specific differences on the association of heart rate decline 60 seconds after exercise termination and worsening of HF were identified.

What Question Should Be Addressed Next?

- Future research should investigate the phenotype-specific differences observed in this study by investigation of both new-onset of HF as well as worsening of symptomatic HF. Integration of multilayered data on heart rate variability, subclinical disease measures, and molecular omics data may contribute to advance our understanding of specific autonomic dysfunction-related processes involved in HF pathophysiology.

Nonstandard Abbreviations and Acronyms

AD	autonomic dysfunction
ATC	Anatomical Therapeutic Chemical
CPET	cardiopulmonary exercise testing
CVRF	cardiovascular risk factors
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HRR	heart rate recovery
HRV	heart rate variability

aging-related decline of parasympathetic, sympathetic, and fibers in the left ventricle of mice lead to reduced heart rate variability (HRV).⁷ In subjects with diabetes, cardiovascular autonomic neuropathy resulted in arterial hypertension, impaired HRV, and exercise intolerance.⁸ Diabetic cardiovascular autonomic neuropathy was associated with increased morbidity and mortality.⁹ Cardiovascular AD has been associated with cardiac remodeling¹⁰ and has been demonstrated to negatively impact HF outcome.¹¹

Individuals with HF commonly showed a reduced heart rate recovery (HRR) after exercise, indicating a reduced postexercise parasympathetic reactivation as¹² part of cardiac AD. Sympathovagal interaction during

postexercise recovery contributed to decreased HRR in HF.¹³ In a sample of healthy adults, HRR 60 seconds after peak effort (HRR₆₀) was associated with an elevated risk of all-cause mortality.¹⁴ Reduced postexercise HRR can result from various mechanisms. A study on individuals with HF revealed that inefficient oxygen use during cardiopulmonary exercise testing (CPET) led to increased anaerobic metabolism dependence. This created a larger oxygen deficit, causing prolonged VO₂ recovery delay during CPET. Notably, this delayed oxygen (VO₂) recovery was identified as a predictor of clinical outcomes in patients with HF.¹⁵ In a small HF cohort, HRR₆₀ was a predictor of all-cause mortality independent of CPET markers and left ventricular ejection fraction (LVEF).¹⁶ Another study of 712 individuals with a reduced LVEF of ≤45% also confirmed that HRR predicts mortality independent of age, gender, New York Heart Association class, LVEF, and body mass index.¹⁷ However, evidence on the determinants of HRR in individuals ranging from pre-HF to chronic HF and its relevance for HF outcome is limited.

The aim of the present study was to evaluate the spectrum of HRR, to assess clinical and medical determinants, and to investigate the association of HRR with clinical outcome in a large contemporary HF sample.

METHODS

Data Availability Statement

Data are not made available for the scientific community outside the established and controlled workflows and algorithms. To meet the general idea of verification and reproducibility of scientific findings, we offer access to data at the local database in accordance with the ethics vote on request. Interested researchers can make their requests to the coordinating principal investigator of the MyoVasc study (Dr. Philipp Wild, MD, MSc; philipp.wild@unimedizin-mainz.de).

Study Design and Study Population

The MyoVasc study is a prospective cohort study on HF conducted at the University Medical Center Mainz in Germany. The MyoVasc study was approved by the local ethics committee, and all study procedures adhere to the standards of good clinical practice and the Declaration of Helsinki. Informed consent has been obtained from all study participants. A total of 3289 participants aged 35 to 84 years underwent baseline examination between 2013 and 2018. The study population was of predominantly White mid-Western European ancestry and included individuals with the full spectrum of HF phenotypes according to the universal definition and classification of heart failure.¹⁸ Inclusion criteria can be found in the study flowchart (see [Figure S1](#)).

The study was registered at clinicaltrials.gov (NCT04064450). Rationale and study design of the MyoVasc study have been published elsewhere.¹⁹

Data Assessment

Participants underwent a comprehensive examination at the MyoVasc study center performed by trained study physicians and certified medical-technical assistants. Examinations included acquisition of anthropometric data, resting electrocardiography, transthoracic echocardiography, and CPET. Information about cardiovascular risk factors (CVRF), comorbidities, and current Anatomical Therapeutic Chemical (ATC) classification-coded medication was assessed via structured computer-assisted interviews, available patient files, examination, and blood sampling. Detailed definitions of comorbidities and CVRF can be found in the supplemental appendix (see [Supplemental Methods](#)).

Cardiopulmonary Exercise Testing

CPET was performed on a VIAsprint bicycle ergometer using adjusted World Health Organization-25 or World Health Organization-50 protocols depending on the participants' fitness levels. The GE KISS system and GE CardioSoft (version 6.71) were used for electrocardiographic measurements. Ventilatory measures were assessed using the Jaeger MS-CPX system. Ventilatory thresholds were calculated with modified Wasserman curves in JLab software (version 5.72.1.77).

HRR₆₀ was defined as the difference between maximum heart rate and heart rate at 60 seconds after termination of exercise. Due to the automatic electrocardiographic-based heart rate assessment, a tolerance of 60 seconds with a margin of ± 4 seconds was allowed to determine individual HRR₆₀. The same procedure was followed to determine HRR at 10, 20, 30, 40, 90, 120, and 180 seconds after peak exercise. Concurrently, manual point blood pressure measurements were taken, and both systolic and diastolic blood pressure recovery were calculated. CPET was performed according to standard operating procedures, based on the joint statement of the American Thoracic Society and the American College of Chest Physicians on cardiopulmonary exercise testing.²⁰ During CPET, the occurrence of arrhythmias (ie, paroxysmal supraventricular tachycardias and ventricular extrasystoles) were counted.

Echocardiography

Standardized transthoracic echocardiography was performed by trained physicians on an iE33 echocardiography system using an S5-1 sector array transducer (Philips Healthcare, Hamburg, Germany). Measurements of cardiac structure and function were

performed according to current guidelines.²¹ Offline analysis was performed using an image archiving and communication system (Xcelera; Philips Healthcare).

Assessment of Clinical Outcome

For evaluation of clinical outcomes, annual computer-assisted telephone interviews with subsequent validation of end points via source data (eg, medical records) and independent adjudication were performed. Information on survival was retrieved by quarterly checks with registration offices. Death records were obtained for the adjudication of cardiac death. All information on end points was coded according to the *International Classification of Diseases, Tenth Revision (ICD-10)* system. The primary end point of the MyoVasc study was worsening of HF defined as composite of ambulatory or inpatient treatment for worsening of HF and cardiac death. Details on study end points have been described elsewhere.¹⁹

Statistical Analysis

For this analysis, individuals who did not undergo CPET as well as individuals with >50% pacemaker stimulation or no sinus rhythm during the resting ECG or a heart transplantation, healthy individuals, and individuals at risk of HF (stage A according to the Universal Definition of HF)¹⁸ were excluded from the analysis sample. Spearman correlation analyses were performed between different HRR measures ranging from 10 to 180 seconds after peak exercise, and HF biomarkers (eg, age, body mass index, peak oxygen uptake [peak VO₂], NT-proBNP [N-terminal pro-B-type natriuretic peptide]) to systematically evaluate which HRR measure was most relevant for all subsequent analyses (see [Figure S2](#)). HRR₆₀ was carried forward for subsequent analyses.

Baseline characteristics were stratified based on the median value of HRR₆₀, dividing the analysis sample into 2 groups. Continuous variables are described by median (Q1–Q3) and tested with the *U* test. Discrete variables are described through relative and absolute frequencies, and χ^2 tests were performed to test for difference. To identify drugs affecting HRR, all pharmacological subgroups, as defined according to the third level of the ATC classification system, taken by at least 10 participants, were used as predictors in single linear regression analysis adjusted for age and sex, with standardized log-transformed HRR₆₀ as the dependent variable. Afterward, medication groups with an influence on HRR₆₀ (ie, a *P* value below the Bonferroni threshold of *P*=0.0007) was used as a predictor in a multivariate linear regression model, with HRR₆₀ as the dependent variable to retrieve the coefficients that were subsequently used in a linear equation to compute a score reflecting the impact of medication on

HRR₆₀ (see [Table S1](#)). The score was used in further analyses.

To identify clinical determinants of HRR₆₀, multivariate linear regression models with HRR₆₀ as the dependent variable, with adjustment for age, sex, CVRF (ie, arterial hypertension, diabetes, smoking, obesity, dyslipidemia, and family history of myocardial infarction/stroke), comorbidities (ie, history of myocardial infarction, stroke, coronary artery disease, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease, deep vein thrombosis, pulmonary embolism, and chronic kidney disease), and the medication score were used. Clinical determinants affecting HRR₆₀ were considered for subsequent analyses.

To examine the relationship between HRR₆₀ and clinical outcome (ie, all-cause mortality and worsening of HF), Kaplan-Meier curves and cumulative incidence plots were generated, respectively. To analyze the association of HRR₆₀ with all-cause death and sudden cardiac death (SCD), Cox regression models with HRR₆₀ (10 bpm) as the predictor with stepwise adjustment for possible confounders such as age, sex, identified clinical determinants, and the medication score were used. For worsening of HF, Cox competing risk models (with death as the competing event) with HRR₆₀ (10 bpm) as the predictor were used, respectively.

Sensitivity analyses with adjustment for age, sex, and NT-proBNP as surrogate for HF severity were performed to evaluate whether the relationship of HRR₆₀ and clinical outcome was dependent on the severity of HF. To investigate potential differences in the association between HRR₆₀ and clinical outcomes, we conducted separate analyses of HF subgroups: those with heart failure with reduced ejection fraction (HFrEF) and those with heart failure with preserved ejection fraction (HFpEF). HFrEF was defined as HF stage C/D with an LVEF <50%, whereas HFpEF was characterized by HF stage C/D with an LVEF ≥50%. We used Cox regression analysis and Cox competing risk analysis, adjusted for age and sex, to examine these relationships. To identify *P* for interaction, a Cox regression model with the variables age, HFrEF, HRR₆₀, HRR₆₀*HFrEF, and age was calculated for each end point. The optimal cutoff value of HRR₆₀ for outcome prediction was identified using the Youden index (see [Table S2](#)). Due to the exploratory character of the study, *P* values were interpreted as a continuous measure of statistical evidence. No testing of hypotheses was performed. The software R (version 4.2.1) was used for all statistical analyses.

RESULTS

Sample Characteristics

The analysis sample with available data on HRR comprised 1289 individuals ranging from pre-HF (stage

B) to chronic heart failure (stage C/D). In the analysis sample, 30.4% of the individuals were women, and the median age was 66.0 (interquartile range [IQR], 58.0–73.0) years. Median LVEF was 55.8% (IQR, 48.7–61.2), median left ventricular early mitral inflow velocity to early diastolic mitral annulus velocity ratio was 8.5 (IQR, 6.5–11.4), and median concentration of NT-proBNP was 173.0 pg/mL (IQR, 83.9–370.0). Heart failure (stage C/D) was present in 57.1% (736/1289) of the analysis sample. A comprehensive display of baseline characteristics including guideline-recommended HF therapy can be found in [Table S3](#).

Evaluation of HRR Measures and Relationship to Clinical Profile

HRR correlated strongly with NT-proBNP and peakVO₂, at 60 seconds after peak exercise strain. At later time points the correlation only increased marginally (see [Figure S2](#)). HRR₆₀ was carried forward for subsequent analyses. In univariate analyses, lower values of HRR₆₀ indicated a higher frequency of cardiovascular risk factors and comorbidities ([Table 1](#)). Participants with an HRR₆₀ below the median (≤19 bpm) showed the highest burden of CVRF. Major comorbidities such as atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, history of stroke or transient ischemic attack, peripheral artery disease, and venous thromboembolism were most frequently observed in individuals with a lower HRR₆₀. The number of individuals with New York Heart Association functional class ≥2 occurred most frequently in participants with an HRR₆₀ below the median. The study sample showed an inverse relationship between HRR₆₀ and resting heart rate. Additionally, individuals with higher HRR₆₀ generally had a higher maximum heart rate, higher performance [watt], greater peak VO₂, and longer exercise duration. In summary, HRR₆₀ showed a direct relationship with cardiopulmonary fitness. Further CPET characteristics by the median of HRR₆₀ can be found in the [Table S4](#).

Clinical Determinants of HRR₆₀

In total, 71 medication groups, classified according to the third level of the ATC classification system, were used as predictors in single linear regression analyses with HRR₆₀ as the dependent variable, with adjustment for age and sex. Sixteen medication groups were considered significantly important for HRR₆₀ (see [Table S1](#)) and were used to compute the medication score. [Figure 1](#) shows the relationship between the clinical profile and HRR₆₀. A multivariate model was used to identify clinical determinants of HRR₆₀. In short, age ($\beta = -1.72$ [95% CI, -2.27 to -1.16]; $P < 0.0001$), sex ($\beta = -1.41$ [95% CI, -2.62 to -0.21]; $P = 0.022$), diabetes ($\beta = -1.43$ [95% CI, -2.78 to -0.09]; $P = 0.037$), obesity ($\beta = -2.64$ [95% CI, -3.80 to -1.47]; $P < 0.0001$), smoking ($\beta =$

Table 1. Sample Characteristics by the Median of HRR₆₀

Characteristic	≤ Median (HRR ₆₀ ≤19bpm)	> Median (HRR ₆₀ >19bpm)	P for trend
Sample size (n)	689	600	
Demographics			
Sex (women)	30.5% (210/689)	30.3% (182/600)	1.00
Age, y	68.0 [60.0–74.0]	65.0 [56.0–71.0]	<0.0001
HF characteristics			
HF stages, stage B (pre-heart failure)	34.0% (234/689)	53.2% (319/600)	<0.0001
HF stages, stage C/D (heart failure)	66.0% (455/689)	46.8% (281/600)	<0.0001
NYHA functional class ≥2	42.2% (290/688)	16.0% (96/599)	<0.0001
NT-proBNP (pg/mL)	195.15 [92.92–455.17]	149.00 [72.00–276.83]	<0.0001
LVEF (%)	55.2 [47.7–60.9]	56.6 [50.4–61.9]	0.0024
E/E'	9.06 [6.62–12.20]	8.16 [6.34–10.71]	<0.0001
Clinical profile			
Arterial hypertension	77.9% (537/689)	69.5% (417/600)	0.00059
Atrial fibrillation	22.1% (152/689)	14.8% (89/600)	0.00097
Chronic kidney disease	19.2% (132/689)	11.5% (69/600)	0.00016
COPD	18.4% (114/618)	10.8% (60/558)	0.00021
Coronary artery disease	48.0% (331/689)	43.0% (258/600)	0.073
History of myocardial infarction	33.2% (229/689)	30.2% (181/600)	0.25
Diabetes	30.8% (212/689)	14.8% (89/600)	<0.0001
Dyslipidemia	79.5% (548/689)	70.8% (425/600)	0.00035
Family history of MI/stroke	25.8% (178/689)	20.8% (124/597)	0.035
History of stroke	10.2% (70/689)	6.5% (39/600)	0.021
History of venous thromboembolism	10.3% (71/689)	5.8% (35/599)	0.0043
Deep vein thrombosis	8.4% (58/689)	5.3% (32/599)	0.037
Pulmonary embolism	4.9% (34/689)	2.5% (15/599)	0.028
Obesity	38.0% (262/689)	21.2% (127/600)	<0.0001
Peripheral artery disease	9.4% (65/689)	2.8% (17/600)	<0.0001
Smoking	29.3% (202/689)	19.7% (118/600)	<0.0001
Intake of HR-modifying medication*			
Yes	73.7% (508/689)	57.3% (344/600)	<0.0001
No	26.3% (181/689)	42.7% (256/600)	<0.0001

Continuous variables are described by median (interquartile range), and Mann-Whitney *U* tests were performed to test for difference. Discrete variables are described through relative and absolute frequencies, and χ^2 tests were performed to test for difference. Detailed definitions of comorbidities and cardiovascular risk factors can be found in the [Supplemental Methods](#). ATC indicates Anatomical Therapeutic Chemical; COPD, chronic obstructive pulmonary disease; E/E', early mitral inflow velocity to early diastolic mitral annulus velocity ratio; HF, heart failure; HR, heart rate; HRR₆₀, heart rate recovery 60 seconds after peak effort; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*HR-modifying medication consists of antiarrhythmics class I and III (ATC C01B), β -receptor blocking agents (ATC C07), cardiac glycosides (ATC C01A), and ivabradine (ATC C01EB17).

= -2.89 [95% CI, -4.16 to -1.63]; $P < 0.0001$), chronic kidney disease ($\beta = -2.46$ [95% CI, -3.96 to -0.95]; $P = 0.0014$), history of stroke ($\beta = -2.51$ [95% CI, -4.35 to -0.67]; $P = 0.0077$), and peripheral artery disease ($\beta = -3.48$ [95% CI, -5.62 to -1.33]; $P = 0.0016$) were identified as significant determinants.

Relationship of HRR₆₀ and Clinical Outcome

Clinical relevance of HRR₆₀ was analyzed by investigating its relationship with clinical outcome. In the present analysis, a total of 251 deaths were recorded during a

median follow up time of 8.84 years (IQR, 7.11–10.00). For worsening of HF, 181 events and 134 competing events were recorded during a median follow-up time of 4.00 years (IQR, 2.32–4.00). Kaplan-Meier survival analysis showed an inverse relationship between HRR₆₀ and the occurrence of all-cause death (see [Figure 2A](#)). The incidence for all-cause death was higher for individuals with a HRR₆₀ below the median (<19bpm) (P for difference <0.0001). As indicated in [Figure 2B](#), a similar finding was found for the relationship between HRR₆₀ and worsening of HF, with the highest frequency of events in individuals with an HRR₆₀ <19bpm (Gray's test $P < 0.0001$).

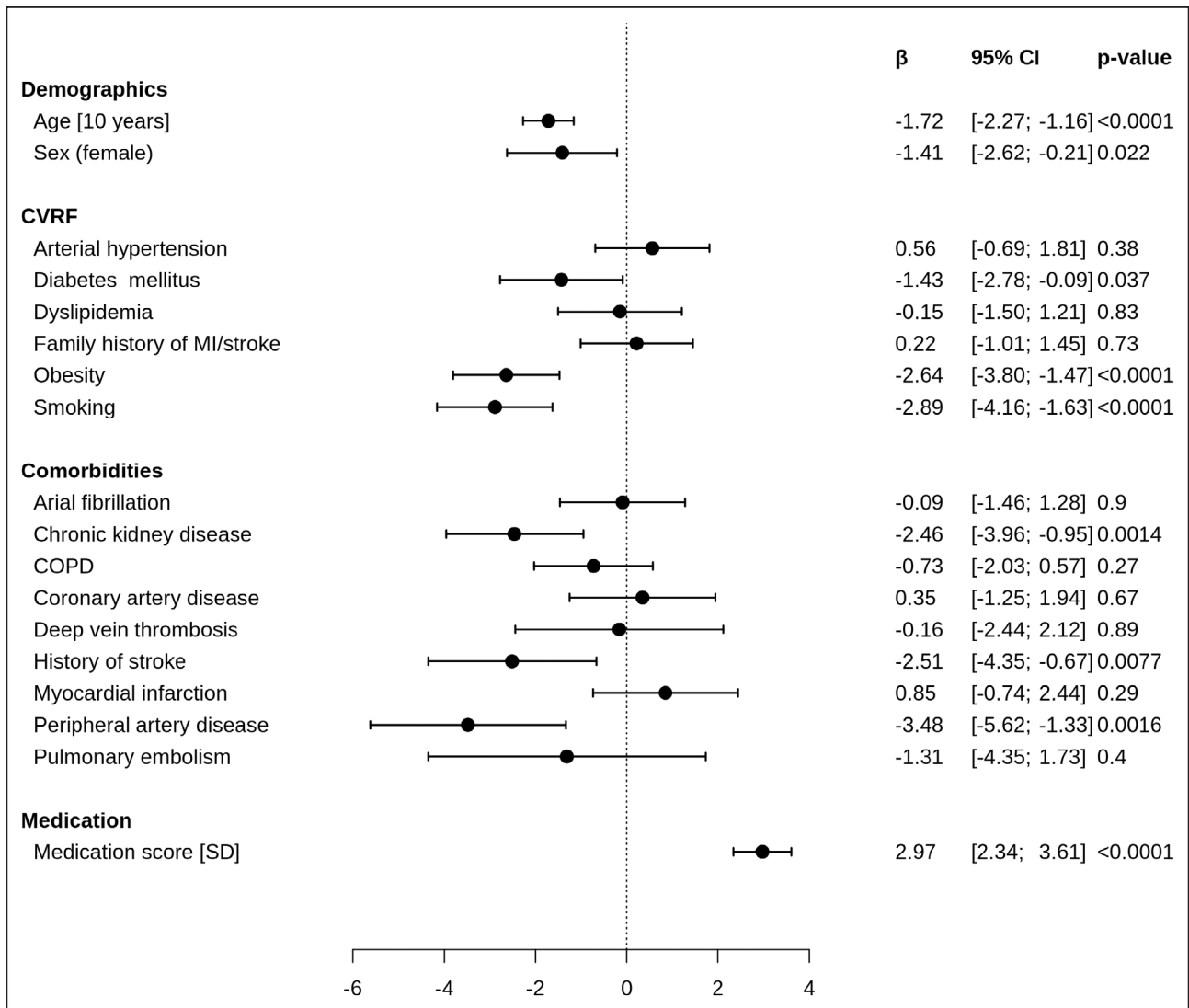


Figure 1. Clinical determinants of HRR₆₀.

Multivariate linear regression model for HRR₆₀ (bpm) as dependent variable with adjustment for age, sex, CVRF, comorbidities, and medication score. Detailed definitions of cardiovascular risk factors and comorbidities can be found in the Supplemental Methods. COPD indicates chronic obstructive pulmonary disease; CVRF, cardiovascular risk factors; HRR₆₀, heart rate recovery 60 seconds after peak effort; and MI, myocardial infarction.

In Cox regression analysis, HRR₆₀ was associated with all-cause death independent of age and sex (hazard ratio [HR]_{HRR60 [10 bpm]}, 1.97 [95% CI, 1.69–2.30], *P*<0.0001). This finding was robustly confirmed after additional adjustment for clinical determinants of HRR₆₀ (HR_{HRR60 [10 bpm]}, 1.56 [95% CI, 1.32–1.85]; *P*<0.0001) (see Table 2). For worsening of HF, Cox regression analysis demonstrated that HRR₆₀ is a strong and robust predictor independent of age and sex (HR_{HRR60 [10 bpm]}, 1.60 [95% CI, 1.30–1.97]; *P*<0.0001), as well as clinical determinants (HR_{HRR60 [10 bpm]}, 1.36 [95% CI, 1.10–1.69]; *P*=0.0052). For SCD, Cox regression analysis showed that HRR₆₀ is a strong and robust predictor independent of age and sex (HR_{HRR60 [10 bpm]}, 1.80 [95% CI, 1.06–3.07]; *P*=0.031). After additional adjustment

for clinical determinants, results did not remain robust (HR_{HRR60 [10 bpm]}, 1.44 [95% CI, 0.990–2.30]; *P*=0.13).

For all end points, additional adjustment for medication confirmed the consistency of results (Table S5). Sensitivity analyses adjusted for age, sex, and NT-proBNP demonstrated that the relationship between HRR₆₀ and all-cause death (HR_{HRR60 [10 bpm]}, 1.66 [95% CI, 1.42–1.93]; *P*<0.0001) and worsening of HF (HR_{HRR60 [10 bpm]}, 1.26 [95% CI, 1.05–1.51]; *P*=0.013) were both independent of NT-proBNP as a surrogate for HF. In addition, outcome analyses for HRR₆₀ with adjustment for different CPET variables were performed. In Cox regression analyses adjusted for age, sex, resting heart rate, and maximum heart rate, HRR₆₀ was associated with all-cause death (HR_{HRR60 [10 bpm]}, 1.36 [95% CI,

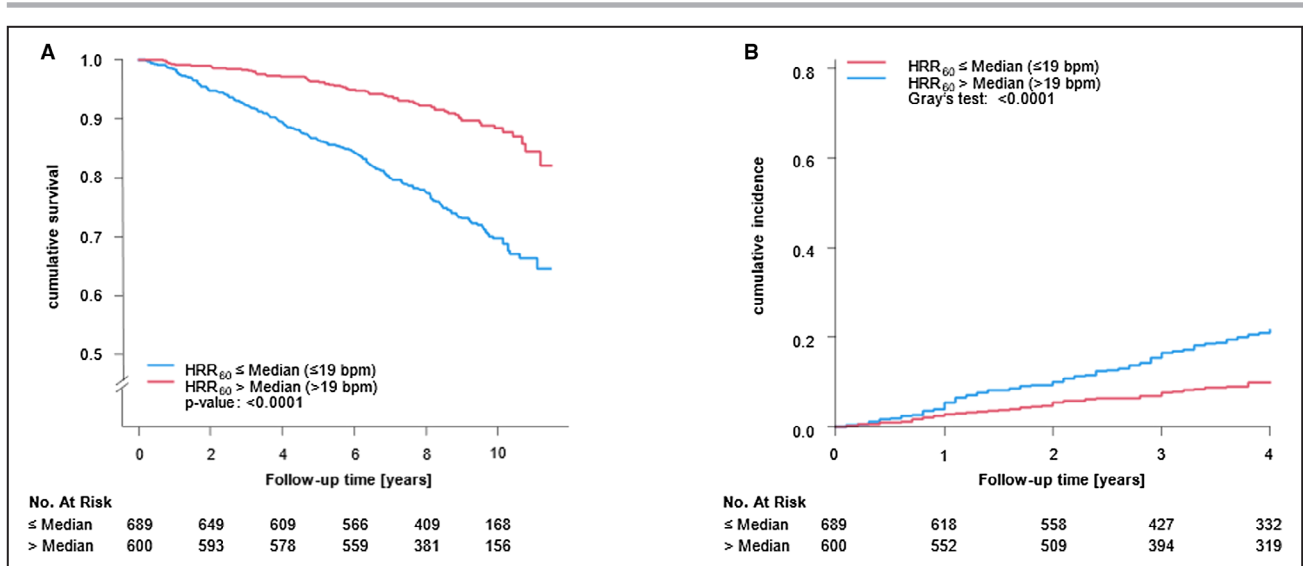


Figure 2. Clinical outcome by HRR₆₀ quartiles. **A**, Event-free survival by the median of HRR₆₀. Event-free survival during a median follow-up time of 8 years (IQR, 6.47–9.00) is displayed for stages B to C/D according to the universal definition and classification of HF. **B**, Worsening of HF by the median of HRR₆₀. The cumulative incidence of worsening of HF during a median follow-up time of 4 years (IQR, 2.32–4.00) is displayed for stages B to C/D. HF indicates heart failure; HRR₆₀, heart rate recovery 60 seconds after peak effort; and IQR, interquartile range.

1.09–1.68], $P=0.0054$). However, no significant association between HRR₆₀ and the end points worsening of HF and SCD was found.

Analyses with adjustment for age, sex, maximum oxygen uptake (peak VO₂), and minute ventilation/carbon dioxide production identified HRR₆₀ as an independent predictor of all-cause death (HR_{HRR60 [10 bpm]}, 1.47 [95% CI, 1.21–1.79]; $P<0.0001$) and SCD (HR_{HRR60 [10 bpm]}, 1.02 [95% CI, 1.17–3.26]; $P=0.010$) but not worsening of HF (HR_{HRR60 [10 bpm]}, 1.19 [95% CI, 0.96–1.49]; $P=0.12$). This study used the Youden index to determine the most effective HRR cutoff value for predicting clinical outcomes (see Table S2). An HRR₆₀ of ≤16 bpm was the optimal threshold for identifying patients at higher risk of adverse events.

Phenotype-Specific Sensitivity Analyses

Next, phenotype-specific analyses for clinical outcome were performed. As demonstrated in Figure 3, multivariate Cox regression adjusted for age and sex

identified HRR₆₀ as a strong predictor for all-cause death in both phenotypes (HFpEF: HR_{HRR60 [10 bpm]}, 1.98 [95% CI, 1.53–2.57]; $P<0.0001$; HFrfEF: HR_{HRR60 [10 bpm]}, 1.71 [95% CI, 1.34–2.17]; $P<0.0001$). There was no statistically significant difference on effect size estimates (P for interaction=0.50). For worsening of HF, Cox analysis of competing risks revealed a phenotype-specific relevant difference in effect size; a nearly 1.6-times stronger association of HRR₆₀ was found for subjects with HFpEF (HR_{HRR60 [10 bpm]}, 1.81 [95% CI, 1.25–2.62]; $P=0.0018$) compared with individuals with HFrfEF (HR_{HRR60 [10 bpm]}, 1.14 [95% CI, 0.94–1.38], $P=0.18$; P for interaction=0.027).

DISCUSSION

The study investigated clinical relevance of cardiac AD as measured by HRR in a large-scale, contemporary sample of individuals with HF across the spectrum of LVEF. Different times of HRR were evaluated, and

Table 2. Heart Rate Recovery as Predictor of Clinical Outcome in HF

Outcome	Model 1: adjusted for age and sex		Model 2: additional adjustment for clinical profile*	
	Hazard ratio HRR ₆₀ , 10 bpm [95% CI]	<i>P</i> value	Hazard ratio HRR ₆₀ , 10 bpm [95% CI]	<i>P</i> value
All-cause death	1.97 [1.69–2.30]	<0.0001	1.56 [1.32–1.85]	<0.0001
Worsening of HF	1.60 [1.30–1.97]	<0.0001	1.36 [1.10–1.69]	0.0052
Sudden cardiac death	1.80 [1.06–3.07]	0.031	1.44 [0.90–2.30]	0.13

Multivariate Cox regression analysis in individuals with stage B to stage C/D HF with all-cause death, worsening of HF, and sudden cardiac death, respectively, as dependent variable and HRR₆₀ (bpm) as predictor. HF indicates heart failure; and HRR₆₀, heart rate recovery 60 seconds after peak effort.

*Clinical profile included clinical determinants of HRR₆₀ (ie, diabetes, smoking (past 7 y), obesity, history of stroke, peripheral artery disease, and chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m²).

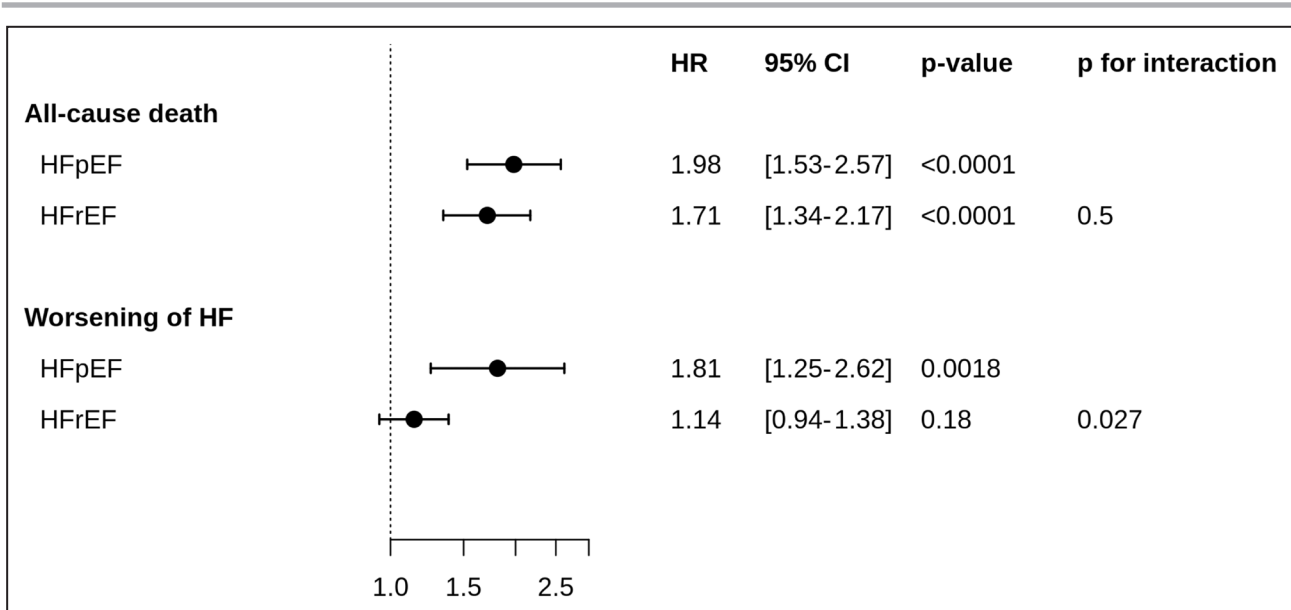


Figure 3. Prediction of clinical outcome by HRR₆₀ according to HF phenotypes.

Forest plot depicting clinical outcome in HF phenotypes with all-cause mortality and worsening of HF as the dependent variables and HRR₆₀ (bpm) as the predictor in the Cox regression model with adjustment for age and sex. HFpEF was defined as individuals with stage C/D HF with an LVEF ≥50%. HFrEF was defined as stage C/D HF with LVEF <50%. HF indicates heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; HR, hazard ratio; HRR₆₀, heart rate recovery 60 seconds after peak effort; and LVEF, left ventricular ejection fraction.

HRR₆₀ was identified as best predictor for HF biomarkers (see Figure S2). Clinical and medical determinants of HRR₆₀ were systematically identified in an unbiased approach and subsequently considered for evaluating the interplay between HRR₆₀ and its clinical relevance. HRR₆₀ was found to robustly predict both all-cause death and HF-specific outcomes independent of a large panel of potential confounders. Although this finding was present for HF individuals with both reduced and preserved LVEF, the substantially higher risk in subjects with HFpEF indicates potential phenotype-specific implications for the role of cardiac AD in HF. In addition, HRR₆₀ was identified as an independent predictor of SCD in Cox regression analysis adjusted for age and sex. However, after additional adjustment for clinical determinants, the results did not remain significant. This can be explained by the low occurrence of SCD in the analysis sample.

As shown in Table S4, HRR₆₀ and HR_{rest} shared an inverse relationship, whereas HRR₆₀ and HR_{max} showed a direct relationship. Nevertheless, there was no clinically relevant difference in HR_{rest} between individuals below and above the median of HRR₆₀ (75 versus 71 bpm). In addition, heart rate-lowering therapy was more frequent in individuals with a reduced HRR₆₀. This circumstance and a shorter exercise duration may explain the lower HR_{max}. However, adjustments were made for the medication taken. To the best of our knowledge, the present analysis represents 1 of the largest prospective observational cohort studies on individuals suffering from HF

who underwent comprehensive CPET examination. The present analysis sample represents all phenotypes of HF ranging from stage B to C/D according to the universal definition of HF. In contrast to previous studies, no participants were excluded based on the intake of certain medications with possible influence on HRR. Instead, drugs with an impact on HRR₆₀ were identified. Medication associated with HRR₆₀ presented a negative influence on HRR. Drugs for cardiac therapy but also for the treatment of diabetes or lung diseases were identified to be associated with HRR₆₀. This finding raised the hypothesis that they may also serve as proxies for lifetime exposure to underlying diseases, which have been reported to be linked to impaired cardiac AD¹³ or to reduced cardiorespiratory fitness and thereby also resulting in reduced HRR.

This study identified specific clinical determinants of HRR as a proxy for cardiac AD. Clinical determinants of HRR₆₀ included age, sex, diabetes, smoking, obesity, history of stroke, peripheral artery disease, and chronic kidney disease. Diabetes is especially known to cause polyneuropathy. It is regarded as the main trigger for secondary AD.²² Added to diabetes, obesity also increases the risk of cardiovascular autonomic neuropathy.⁸ All of the mentioned determinants had a negative impact on HRR and were considered in outcome analyses. These findings support the hypothesis of Nonaka et al that CVRF are closely linked to the development of HF and AD.²³

HRR₆₀ was identified as a robust predictor of clinical outcome comprising all-cause death and worsening of

HF in individuals with HF. Several studies have investigated the optimal cutoff values for abnormal HRR in predicting clinical outcomes. Although Watanabe et al suggested that a reduction of ≤ 18 bpm after exercise was abnormal,²⁴ and Cole et al identified 12 bpm as the optimal cutoff for predicting mortality,¹⁴ we identified ≤ 16 bpm to be the optimal cutoff for prediction of clinical outcome. This finding provides a more tailored approach to risk stratification in the HF population, as it considers the specific cardiovascular dynamics of these patients.

Research has shown that systolic blood pressure usually declines to baseline within 5 to 6 minutes after maximal exercise in healthy individuals. Maximum oxygen uptake (peak VO_2), percentual heart rate decline at 1 and 3 minutes, correlated with systolic blood pressure recovery at 1 and 3 minutes.²⁵ A delayed systolic blood pressure recovery was associated with an increased cardiovascular risk.²⁶ To gain a broader knowledge on different recovery kinetics of HRR_{60} , blood pressure recovery was analyzed (see Data S1). In contrast to previous studies, systolic blood pressure recovery was not associated with clinical outcome. This might be due to a lower data density for specific time points of blood pressure recovery.

In addition, we analyzed the relationship of arrhythmias and HRR_{60} (see Data S2). However, due to a low burden of arrhythmias during CPET in the selected sample, no valid analysis was possible.

To better understand the HRR kinetics we analyzed, we calculated the time it takes to reach 50% of the total HRR and named it HRR half-life. However, in Cox regression analyses, it was not associated with clinical outcome (see Table S6).

Measures of HRV can be used to identify AD.²⁷ A systematic analysis of HRV markers also identified acceleration and deceleration capacity to be the strongest predictors for all-cause death in individuals with HF independent from CVRF, comorbidities, and medication.²⁸ Individuals with diabetic cardiovascular autonomic neuropathy presented an increased morbidity and mortality due to an increased risk of arrhythmias and sudden cardiac death.²⁹ Moreover, the EURODIAB Prospective Complications Study identified autonomic and peripheral neuropathy to have a stronger association with all-cause mortality than traditional cardiovascular risk factors.³⁰

Another novel finding of the analysis is that HRR_{60} is also a strong predictor for worsening of HF and all-cause death independent from the gold-standard HF biomarker NT-proBNP. It is known that peak VO_2 and minute ventilation/carbon dioxide production slope assessed via CPET are predictors of HF-related outcome.³¹ In our analysis, HRR_{60} showed an association with clinical outcome independent of peak VO_2 and minute ventilation/carbon dioxide production slope. Our findings suggest

that HRR_{60} is a good complementary marker for prediction of clinical outcome via CPET, especially when gas exchange parameters are not available. This implies that CPET, and especially the evaluation of HRR_{60} , provides additional value for outcome prediction to NT-proBNP, which is often used in the management of patients with HF. Especially on the prediction HF-specific outcome, the assessment of HRR_{60} merits specified attention, because HRR is commonly available as a standard readout in CPET of clinical routine.

HF phenotypes show similar all-cause mortality rates but differ in worsening of HF. HFpEF is more strongly associated with worsening HF compared with HFrEF. This suggests HF phenotype influences disease progression more than mortality risk. A significant interaction between phenotype and the hazard ratio was found only for worsening of HF. Known key components of HFpEF are AD³² and a chronic proinflammatory state,³³ which can be directly associated with autonomic nerve damage. These findings strengthen the concept of differential underlying pathophysiology for the development and progression of HFrEF and HFpEF, respectively. In this context, obesity as major risk factor for the development of HFpEF merits attention given its proinflammatory state contributing to disease pathophysiology.³³ Moreover, this finding also raises the hypothesis of whether the effects of obesity and diabetes on HF development are associated with different mechanistic effects via differential impairment of cardiac AD in HFpEF and HFrEF. It will be interesting to also integrate other measures of cardiac AD for future investigations (eg, measures of HRV), which have been reported to be relevant in development and progression of HF.²⁸ Against the limited body of evidence, this work raises important new questions on potential phenotype-specific differences in our current understanding of the HF syndrome, including both experimental studies exploring disease mechanisms and longitudinal clinical studies, allowing further study of the relationship between cardiac AD and (sub-)clinical disease states.

Strengths and Limitations

The major strengths of the present study comprise the large sample size and deep clinical phenotyping and outcome adjudication. Moreover, the sample provides data on the spectrum of HF, and its sample size allows for comparative analyses between HF subtypes, which has not yet been comprehensively addressed. It is also the first study to evaluate potential clinical determinants of HRR_{60} . Nevertheless, some limitations also merit consideration. First, one must mention that the analyses conducted were data-driven. Therefore, the study is explorative in nature. The analyses were focused on HRR serving as surrogate parameter for cardiac AD.

However, HRR_{60} is primarily associated with parasympathetic reactivation. However, this parameter does not capture other potential factors contributing to reduced HRR, such as inefficient oxygen usage or increased anaerobic metabolism, which were not assessed in this study. Furthermore, conducting a comparative analysis between healthy individuals with a similar comorbidity burden and those with specific HF phenotypes could provide valuable insights into phenotype-specific differences in HRR kinetics. This approach would enhance our understanding of how various HF subtypes affect postexercise cardiac response, potentially leading to more tailored diagnostic and treatment strategies. The interpretation of the derived cutoff value for HRR_{60} merits caution, because further research is needed (eg, validation in independent data sets) to evaluate predictive capacity and generalizability. The evaluation of blood pressure recovery was conducted at 60 seconds post-peak effort. However, the data set for blood pressure recovery was more limited compared with HRR data due to the use of intermittent spot measurements rather than continuous monitoring. This approach may have missed important information about blood pressure recovery dynamics. Although continuous invasive blood pressure monitoring could offer detailed insights into recovery kinetics and transient fluctuations postexercise, its implementation in standard study settings is impractical and ethically challenging. The associated risks outweigh the potential benefits, especially for studies involving healthy individuals or those with stable cardiovascular conditions. It cannot go unmentioned that other CPET measures may provide additional information in this context. Outcome analyses were adjusted for the CPET parameters to account for possible confounders. Data assessment in the MyoVasc study will enable integration of additional dimensions (eg, HRV) in future investigations. Last, the relationship between impaired HRR_{60} and clinical outcome was demonstrated in this study, but the underlying mechanisms of HRR have not yet been deciphered. However, the MyoVasc database offers the potential to conduct multidimensional data analysis integrating longitudinal clinical and molecular data, which may help to gain a better understanding of relevant processes involved in HF pathophysiology.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods S1
Data S1–S2
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