

# Resting Heart Rate and Heart Rate Reserve in Advanced Heart Failure Have Distinct Pathophysiologic Correlates and Prognostic Impact

## A Prospective Pilot Study

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- Objectives** The purpose of this study was to compare the prognostic impact of clinical and biomarker correlates of resting heart rate (HR) and chronotropic incompetence in heart failure (HF) patients.
- Background** The mechanisms and underlying pathophysiological influences of HR abnormalities in HF are incompletely understood.
- Methods** In a prospective pilot study, 81 patients with advanced systolic HF (97% were receiving beta-blockers) and 25 age-, sex-, and body-size matched healthy controls underwent maximal cardiopulmonary exercise testing with sampling of neurohormones and biomarkers.
- Results** Two-thirds of HF patients met criteria for chronotropic incompetence. Resting HR and HR reserve (HRR, a measure of chronotropic response) were not correlated with each other and were associated with distinct biomarker profiles. Resting HR correlated with increased myocardial stress (B-type natriuretic peptide [BNP]:  $r = 0.26$ ; pro A-type natriuretic peptide:  $r = 0.24$ ; N-terminal(NT)-proBNP:  $r = 0.32$ ) and inflammation (leukocyte count:  $r = 0.28$ ; high-sensitivity C-reactive protein assay:  $r = 0.25$ ). In contrast, HRR correlated with the neurohumoral response to HF (copeptin:  $r = -0.33$ ; norepinephrine:  $r = -0.29$ ) but not with myocyte stress or injury reflected by natriuretic peptides or hs-troponin I. Patients in the lowest chronotropic incompetence quartile ( $HRR \leq 0.38$ ) displayed more advanced HF, reduced exercise capacity, ventilatory inefficiency, and poorer quality of life. Over a median follow-up of 17 months, the combined endpoint of death or urgent transplant/assist device implantation occurred more frequently in patients with higher resting HR ( $>67$  beats/min) or lower HRR, with both markers providing additive prognostic information.
- Conclusions** Increased resting HR and chronotropic incompetence may reflect different pathophysiological processes, provide incremental prognostic information, and represent distinct therapeutic targets. (J Am Coll Cardiol HF 2013;1:259–66) © 2013 by the American College of Cardiology Foundation

Increased resting heart rate (HR) is a risk factor for mortality in patients with heart failure (HF) (1), and selective HR slowing improves outcomes, suggesting a causal relationship (2). However, inadequate HR responses during physiologic stress

may have adverse consequences as well (3). The failing heart displays limited ability to enhance stroke volume with exercise, making cardiac output responses exquisitely dependent upon cardioacceleration (4). Chronotropic incompetence (CI) thus contributes to exercise intolerance in HF (5,6) and is associated with increased risk of adverse events in the general population (7) and in some HF cohorts (8). The mechanisms underlying HF-related CI are incompletely understood (3). The influence of resting and exercise HRs on prognosis might be reflective

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of fundamentally different underlying pathophysiological influences. If that were the case, then resting HR and heart rate reserve (HRR, a measure of CI) would be expected to be

**Abbreviations  
and Acronyms****CI** = chronotropic  
incompetence**HF** = heart failure**HR** = heart rate**HRR** = heart rate reserve**LV** = left ventricle**MLHFQ** = Minnesota Living  
with Heart Failure  
questionnaire**NYHA** = New York Heart  
Association**RV** = right ventricle**VO<sub>2</sub>** = carbon dioxide  
production**VE** = minute ventilation**V<sub>O<sub>2</sub></sub>** = oxygen consumption

associated with separate clinical characteristics and biomarker profiles. Biomarkers of HF can be grouped into categories reflecting primarily inflammation, neurohumoral response, myocyte injury, and myocyte stress. Biomarker profiling can thus be useful for risk stratification and categorization and delineation of HF pathogenesis (9).

The current pilot study sought to explore the mechanisms and significance of altered HR modulation in HF by examining resting HR, HRR, catecholamine dynamics, and comprehensive biomarker profiles in healthy controls and in patients with advanced HF. Patients were followed

prospectively to identify how resting HR and HRR correlate with prognosis. We hypothesized that resting HR and HRR are prognostically relevant but are associated with unique clinical and biomarker profiles, suggesting fundamental differences in underlying pathophysiologies.

**Methods**

**Study subjects.** Patients with chronic (>6-month) stable advanced HF resulting from left ventricle (LV) dysfunction (ejection fraction [EF]: <40%), electively hospitalized at IKEM, Prague, for transplant eligibility evaluation or device implantation were screened, and those receiving stable, optimized medical therapy and in sinus rhythm were recruited. Patients with recent decompensation, reversible LV dysfunction (planned valve surgery, revascularization, or tachycardia-induced cardiomyopathy) were excluded. Healthy controls (hospital employees) free of medication or cardiovascular disease were recruited by advertisement to match age, gender, and body composition of the HF cohort. The protocol was approved by the ethics committee, and subjects signed informed consent.

**Protocol.** Prior to exercise, patients completed a Minnesota Living with Heart Failure questionnaire (MLHFQ) and anthropometric tests and echocardiography (Vivid-7; General Electric, Milwaukee, Wisconsin) were performed. LV function and dimensions were measured according to published recommendations (10). Right ventricle (RV) dimension was measured in the parasternal long-axis view perpendicular to the base of the septum. RV dysfunction (RVD) grade was based on tricuspid annular systolic excursion (TAPSE) and systolic velocity (Sm) using the following cutoff values: RVD0: TAPSE >20 mm, Sm >12 cm·s<sup>-1</sup>; RVD1: TAPSE, 16 to 20 mm; Sm, 9 to 12 cm·s<sup>-1</sup>; RVD2: TAPSE, 10 to 15 mm; Sm, 6 to 8 cm·s<sup>-1</sup>; RVD3: TAPSE, <10 mm; Sm <6 cm·s<sup>-1</sup>. Subjects then underwent symptom-limited upright

cycle ergometry (V<sub>max</sub> Encore29S; SensorMedics, Palo Alto, California) starting at 25 W, followed by 25-W stepwise 3-min increments until exhaustion. Rhythm was monitored by continuous 12-lead electrocardiography. Expired-gas analysis was used to measure minute ventilation (VE), oxygen consumption (VO<sub>2</sub>), and carbon dioxide production (VCO<sub>2</sub>). Peak VO<sub>2</sub> was determined as the highest VO<sub>2</sub> achieved. Functional capacity was stratified by peak VO<sub>2</sub> according to Weber criteria (11). Blood samples were taken prior to exercise by peripheral intravenous cannula (after >20 min in supine rest) and immediately after exercise termination.

Chronotropic responses were evaluated by heart rate reserve (HRR), calculated as the difference between peak exercise and resting HR, divided by the difference of age-predicted maximal and resting HRs (3). Age-predicted maximal HR was calculated by (220 – age) (3). Resting HR was derived from the supine resting recording prior to exercise. CI was defined using established criteria (HRR <0.62 on beta-blocker regimen or HRR <0.80) (5,6). The sinus node responsiveness index was calculated as (peak-resting HR)/(log peak-resting norepinephrine concentration) (12). Cutoff values for partitioning beta-blocker daily doses into low/middle/high (1–3) categories for carvedilol were ≤12.5/–/≥50 mg/day, ≤25/–/≥200 mg/day for metoprolol, and ≤2.5/–/≥10 mg/day for bisoprolol; other beta-blockers were not used in our patients.

**Biomarker assessment.** The following HF biomarkers were selected: C-reactive protein (CRP) as a marker of inflammation; catecholamines and C-terminal pro-vasopressin (copeptin) as a marker of neurohormones; troponin I as a marker of myocyte injury; and natriuretic peptides A and B (ANP, BNP, respectively) as markers of myocyte stress (9). Catecholamines in plasma were determined by radioimmunoassay (epinephrine CV: 13.6%; norepinephrine coefficient of variation (CV): 18.5%; Cat-Combi; DRG Instruments, Marburg, Germany). BNP was measured by chemiluminescent micro-particle immunoassay (CV 4.5%; Architect-BNP; Abbott). N-terminal proBNP was measured using pro-BNP assay (CV 2.7%), high-sensitivity CRP (hs-CRP) was measured using CRPHS assay (CV 1.3%), both were assayed using the Cobas6000 analyzer (Roche-Diagnostics, Indianapolis, Indiana). Copeptin (C-terminal pro-vasopressin, CV: 3.7%) and mid-regional ANP (proANP, CV: 2.5%) were measured using the Kryptor Compact analyzer (BRAHMS AG, Henningsdorf, Germany). Troponin I was measured using a novel ultrasensitive, single-molecule assay (detection limit of 0.2 pg·ml<sup>-1</sup>; imprecision of 10% at 9 pg·ml<sup>-1</sup>; Erenna hs-TnI; Singulex, Alameda, California). White blood cell count and routine chemistry tests were measured using LH750 (Beckman-Coulter, Miami, Florida) and Architect ci1600 (Abbott, Abbott Park, Illinois) analyzers.

**Statistical analysis.** Patients were prospectively followed, and the adverse outcome was defined by the combined endpoint of death, urgent heart transplantation, or ventricular assist device insertion. Because time to nonurgent transplant reflects donor availability rather than recipient's condition, those patients were

censored as having no outcome at the day of transplantation (13). Data were analyzed using SPSS version 19 software (IBM, Armonk, New York). To determine whether baseline clinical and biochemical levels differed between cases and controls, a chi-square test, unpaired *t*-test, or ANOVA and Scheffé's post hoc test was used. Changes within groups were tested with a paired *t*-test. Correlations between clinical and biochemical variables were assessed using the Pearson test. The influences of HR and HRR on prognosis were tested using a univariate Cox model. Because the relationship between HRR and risk is known to be nonlinear (16), the lowest quartiles of HRR (cutoff: 0.38) and resting HR (cutoff: 67 beats/min) were compared to the remainders of the samples, as previously reported in other studies (8,17). The combined effect of HR and HRR was tested with the

Cox model using a 4-group analysis and cutoff values as specified above.

## Results

**Baseline and exercise characteristics.** Patients were predominantly middle-aged men with advanced, chronic systolic HF (Table 1), receiving optimal medical therapy including beta-blockers in the majority (97%). Half of the patients had ischemic HF, 51% had defibrillators, and 23.4% had resynchronization defibrillators. Controls were of similar age, sex, and body composition and were free of medical therapy and comorbidities.

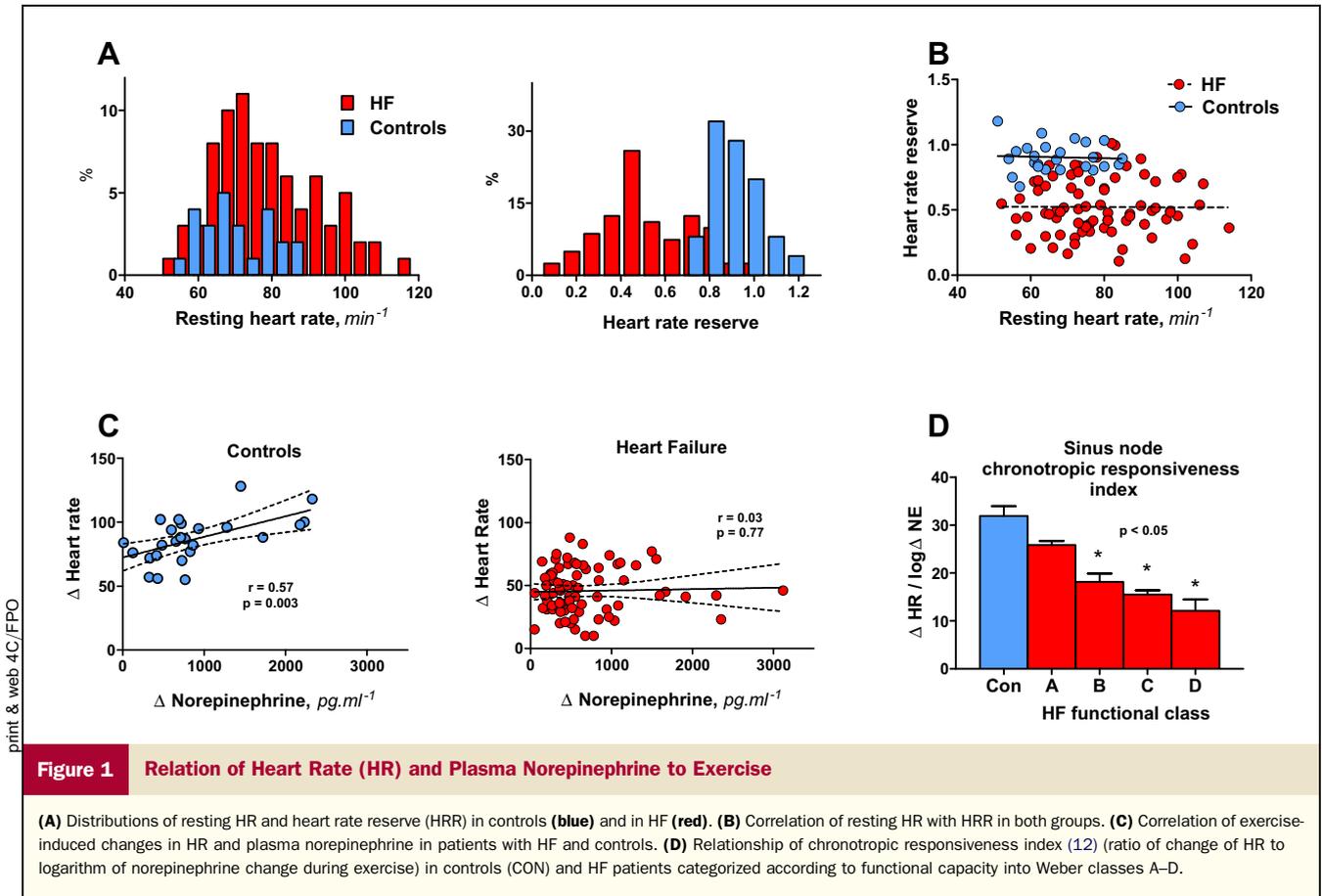
Patients with HF displayed markedly impaired exercise performance compared with controls, with lower peak

**Table 1** Clinical, Biochemical and Exercise Characteristics

Characteristic	Controls (n = 25)	HF (n = 81)	p Value
Age (yrs)	50.3 ± 7.8	52.4 ± 8.2	0.27
Male gender (%)	78.2%	85.2%	0.72
Body mass index (kg·m <sup>-2</sup> )	28.4 ± 2.5	27.4 ± 4.0	0.21
Ischemic HF cause (%)	—	51%	—
HF duration (yrs)	—	5.7 ± 6.7	—
MLHFQ (sum score)	0.9 ± 2.4	45.9 ± 23	<0.001
NYHA class	1 ± 0	2.7 ± 0.6	<0.001
Systolic/diastolic BP (mm Hg)	120 ± 16/84 ± 12	111 ± 18/72 ± 11	0.02/<0.001
LV ejection fraction (%)	60 ± 0	24 ± 6	<0.001
LV end-diastolic dimension (mm)	50 ± 5	71 ± 9	<0.001
RV end-diastolic dimension (mm)	27 ± 3	31 ± 6	<0.001
RV dysfunction grade (0–3)	0 ± 0	1.5 ± 1.0	<0.001
Beta-blocker therapy and dose (0–3)	—	97%, 1.43 ± 0.70	—
ACE /AT/AR blocker therapy (%)	—	82%/12%/84%	—
Furosemide therapy and daily dose (mg)	—	95%/89 ± 66	—
Type 2 DM known/treated (%)	0/0%	35%/24%	<0.001
<b>Laboratory parameters</b>			
Copeptin (pmol·l <sup>-1</sup> )	4.19 ± 4.9	16.9 ± 13.7	<0.001
NT-proBNP (pg·ml <sup>-1</sup> )	36.4 ± 25	1,952 ± 1,885	<0.001
ProANP (pmol·l <sup>-1</sup> )	47.6 ± 15	293 ± 156	<0.001
BNP (pg·ml <sup>-1</sup> )	21 ± 17	860 ± 799	<0.001
Leukocyte count (10 <sup>9</sup> ·l <sup>-1</sup> )	5.9 ± 0.9	7.2 ± 2.0	<0.001
hs-Troponin I (pg·ml <sup>-1</sup> )	2.82 ± 3.1	28.7 ± 9.5	<0.001
hs-CRP (mg·l <sup>-1</sup> )	1.35 ± 1.25	3.68 ± 3.19	<0.001
<b>Cardiopulmonary exercise</b>			
Systolic BP at rest/at peak exercise (mm Hg)	120 ± 16/194 ± 27	111 ± 18/124 ± 24	0.02/<0.001
Heart rate at rest/at peak exercise (min <sup>-1</sup> )	74 ± 9/161 ± 15	79 ± 12/125 ± 20	0.06/<0.001
HRR (%)	0.90 ± 0.11	0.52 ± 0.21	<0.001
Peak VO <sub>2</sub> (ml·kg <sup>-1</sup> ·min <sup>-1</sup> )	29 ± 15	15 ± 4	<0.001
VE/VCO <sub>2</sub> slope	24 ± 3	35 ± 10	<0.001
Peak respiratory quotient	1.13 ± 0.08	1.11 ± 1.0	0.34
Peak workload (W)	172 ± 50	74 ± 29	<0.001
Exercise duration (min)	20.6 ± 6.0	8.9 ± 3.5	<0.001
Epinephrine at rest/at peak exercise (pg·ml <sup>-1</sup> )	53 ± 38/114 ± 63	77 ± 55/103 ± 58	0.047/0.41
NE at rest/at peak exercise (pg·ml <sup>-1</sup> )	255 ± 135/1,138 ± 643	420 ± 325/1,089 ± 721	0.016/0.76
CI Δ HR/log Δ NE	31.9 ± 10.2	17.1 ± 7.0	<0.001

RV dysfunction was classified as absent (0), mild (1), moderate (2) or severe (3) based on tricuspid annular systolic excursion and tissue velocity, using cutoff values reported in the Methods. Beta-blocker daily dose was quantified as none (0), low (1), moderate (2), and high (3) using cutoffs specified in Methods. Values are means ± SD or proportions. A *t*-test or chi-square test was used for comparisons.

ACE = angiotensin-converting enzyme; ANP = A-type natriuretic peptide; AR = aldosterone receptor; AT = angiotensin receptor; BNP = B-type natriuretic peptide; BP = blood pressure; CI = chronotropic index; CRP = C-reactive protein; DM = diabetes mellitus; HF = heart failure; HR = heart rate; HRR = heart rate reserve; hs = high sensitivity; LV = left ventricle; NE = norepinephrine; NYHA = New York Heart Association; RV = right ventricle; VE = minute ventilation; VCO<sub>2</sub> = carbon dioxide production; VO<sub>2</sub> = oxygen consumption.



workload and  $\text{VO}_2$ , higher  $\text{VE}/\text{VCO}_2$  slope, higher resting HR, and markedly impaired chronotropic responses to exercise (Table 1, Fig. 1A). None of exercise parameters correlated with beta-blocker dose in HF patients. CI was present in a majority of HF patients (66%).

**Correlates of resting HR and chronotropic response.** In controls, HRR correlated with age, exercise duration, peak  $\text{VO}_2$ , and peak workload (Table 2). In HF patients, peak HR and HRR were strongly influenced by HF severity, in contrast to resting HR, which did not vary with severity (Online Fig. 1). In HF patients, HRR correlated directly with MLHFQ score, peak  $\text{VO}_2$ , maximal workload, and exercise duration; and HRR correlated inversely with  $\text{VE}/\text{VCO}_2$ , New York Heart Association (NYHA) class, RV diameter, and dysfunction grade. HRR was unrelated to resting HR (Fig. 1B), age, or beta-blocker dose. Resting HR was unrelated to MLHFQ or NYHA or Weber functional class, or to clinical or exercise parameters in HF. Patients in the lowest quartile of HRR ( $\leq 0.38$ ) were more likely to have diabetes and higher NYHA class and displayed lower peak  $\text{VO}_2$ , more pronounced hyperventilation (greater  $\text{VE}/\text{VCO}_2$  slope), and more RV dilation, despite similar age, resting HR, and LV dysfunction than the remainder of the HF cohort (Online Table 1).

**Catecholamines and biomarker profiles associated with resting HR and HRR.** In controls, the increase in HR with exercise was closely correlated with the increase in plasma

norepinephrine ( $r = 0.57$ ,  $p = 0.003$ ) (Fig. 1C); but in HF subjects, plasma norepinephrine levels were uncoupled with changes in HR ( $r = 0.03$ ,  $p = \text{non significant [NS]}$ ), suggesting diminished sinus node responsiveness to adrenergic stimulation. While resting norepinephrine levels increased slightly with more impaired functional class, exercise-related changes in plasma norepinephrine levels were not different than those observed in controls (Online Fig. 1). The sinus node responsiveness index was progressively more attenuated with increasing severity of HF (Fig. 1D).

Resting HR correlated with myocyte stress (BNP, proANP, and NT-proBNP) and inflammatory indexes (leukocyte count, hs-CRP) but not with the neurohormone copeptin (Table 2, Fig. 2). In contrast, HRR directly correlated with neurohormones (copeptin and norepinephrine) but was unrelated to myocyte stress (natriuretic peptides) or systemic inflammation. Both HR and HRR were unrelated to myocyte injury, as reflected by troponin assay results. Patients with severe CI had higher epinephrine and copeptin levels but similar natriuretic peptide levels than the remainder of the HF cohort (Online Table 1).

**Resting HR and HRR and prognosis.** Over a mean follow-up of 469 days (interquartile range: 273 to 764 days), 28 patients (34.6%) experienced an adverse event. Patients with low resting HR ( $\leq 67$  beats/min) had lower risk of adverse outcomes than those in the upper HR quartiles

**Table 2** Correlation Analysis of HR and HRR and Their Determinants in HF Patients and Controls

Characteristic	Controls		Heart Failure	
	Resting HR	HRR	Resting HR	HRR
Age	<b>0.18</b> (0.39)	<b>-0.47</b> (0.018)	-0.15 (0.17)	0.02 (0.83)
HF duration	—	—	0.03 (0.77)	<b>-0.30</b> (0.007)
Beta-blocker dose (0–3)	—	—	-0.14 (0.17)	<b>-0.12</b> (0.28)
MLHFQ score	-0.21 (0.32)	0.25 (0.22)	-0.08 (0.56)	<b>-0.33</b> (0.017)
LV diameter/ejection fraction	-0.19 (0.37) / -	-0.12 (0.84) / -	0.09 (0.42)/-0.14 (0.20)	-0.05 (0.65)/0.01 (0.97)
RV diameter/dysfunction grade (0–3)	0.01 (0.94) / -	-0.04 (0.69) / -	<b>0.23</b> (0.039)/0.13 (0.24)	<b>-0.24</b> (0.33)/ <b>-0.22</b> (0.05)
Exercise variables				
Peak V <sub>O<sub>2</sub></sub>	-0.26 (0.21)	<b>0.43</b> (0.013)	-0.10 (0.35)	<b>0.58</b> (<0.001)
VE/VC <sub>O<sub>2</sub></sub>	-0.12 (0.57)	0.01 (0.98)	-0.05 (0.68)	<b>-0.37</b> (0.001)
VE max	-0.38 (0.06)	<b>-0.55</b> (0.004)	-0.06 (0.57)	<b>0.23</b> (0.039)
Peak work load	<b>-0.40</b> (0.047)	<b>0.47</b> (0.019)	-0.05 (0.63)	<b>0.51</b> (<0.001)
Δ HR/log Δ delta NE	<b>-0.40</b> (0.047)	0.30 (0.15)	-0.20 (0.08)	<b>0.86</b> (<0.001)
Laboratory variables				
Epinephrine rest	0.22 (0.29)	0.12 (0.96)	0.14 (0.13)	-0.17 (0.13)
End	-0.31 (0.14)	<b>0.40</b> (0.048)	-0.02 (0.82)	-0.54 (0.64)
Delta	<b>-0.40</b> (0.045)	0.36 (0.075)	-0.19 (0.09)	0.13 (0.23)
Norepinephrine rest	0.36 (0.07)	-0.14 (0.563)	<b>0.34</b> (0.003)	<b>-0.29</b> (0.011)
End	-0.16 (0.65)	<b>0.46</b> (0.031)	<b>0.25</b> (0.027)	-0.09 (0.43)
Delta	-0.27 (0.41)	<b>0.47</b> (0.020)	0.13 (0.26)	0.05 (0.65)
Copeptin	-0.34 (0.12)	0.09 (0.69)	0.13 (0.26)	<b>-0.33</b> (0.003)
NT-proBNP	0.32 (0.13)	0.01 (0.99)	<b>0.32</b> (0.004)	0.01 (0.49)
BNP	-0.10 (0.63)	0.77 (0.71)	<b>0.26</b> (0.021)	-0.14 (0.23)
ProANP	0.29 (0.19)	-0.07 (0.76)	<b>0.24</b> (0.033)	-0.06 (0.60)
hs-CRP	0.06 (0.77)	0.11 (0.62)	0.25 (0.25)	-0.16 (0.89)
Leukocyte count	-0.06 (0.78)	0.12 (0.59)	<b>0.28</b> (0.012)	-0.12 (0.28)
hs-Troponin I	-0.24 (0.29)	-0.04 (0.86)	0.35 (0.76)	-0.01 (0.98)

The r values are Pearson correlation coefficients; p values are shown in parentheses. Values in boldface type indicate p < 0.05. RV dysfunction was classified as absent (0), mild (1), moderate (2), or severe (3), based on tricuspid annular systolic excursion and tissue velocity, using cutoff values reported in Methods. Beta-blocker daily dose was quantified as none (0), low (1), moderate (2), and high (3), using cutoffs specified in Methods.

Abbreviations are as in Table 1.

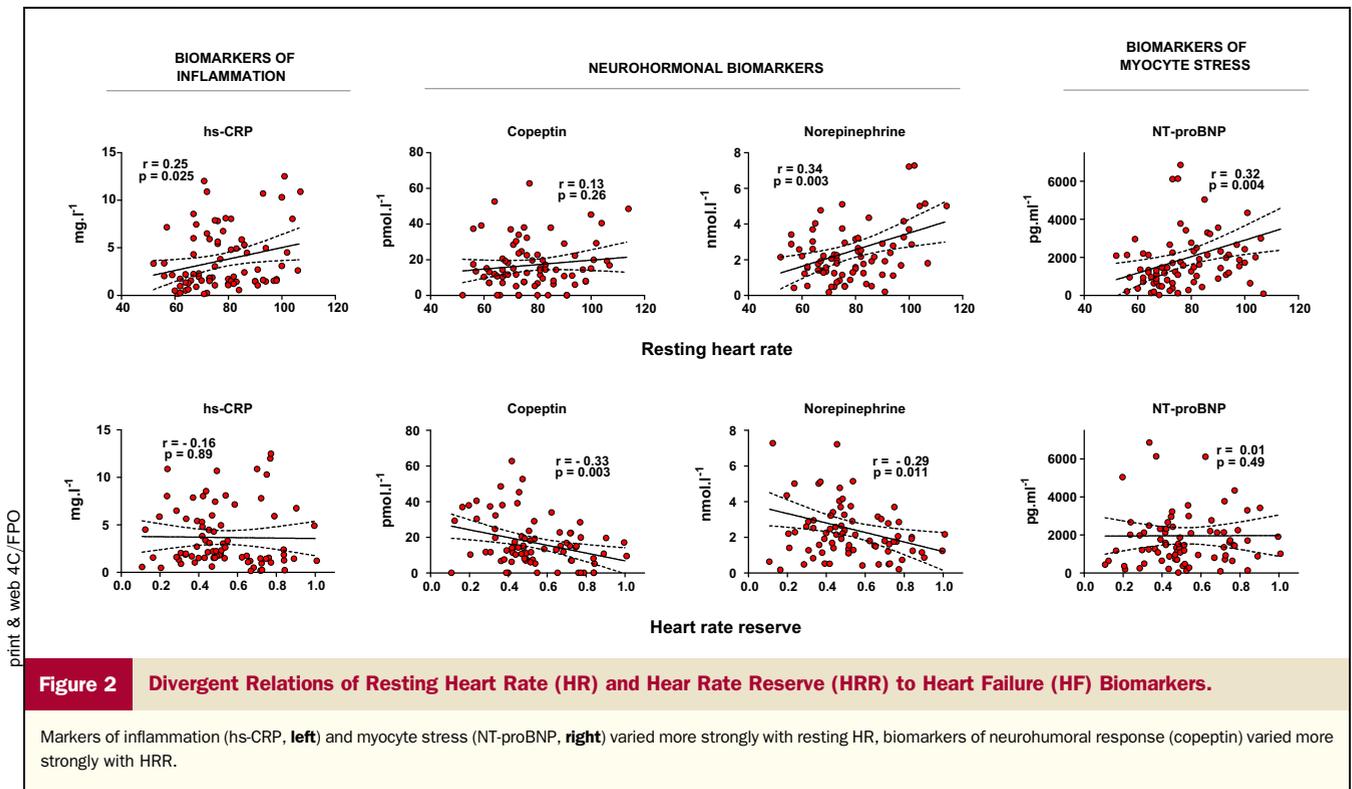
(hazard ratio: 0.24; 95% confidence interval [CI]: 0.11 to 0.53, p < 0.001) (Fig. 3). In contrast, patients in the lowest quartile of HRR (≤0.38) displayed increased risk (hazard ratio: 2.54; 95% CI: 1.18 to 5.48, p = 0.018). Combined quartile analysis of HR and HRR showed that each variable provided incremental prognostic information. In comparison to the group with lowest risk (low HR–high HRR), patients in the “low HR–low HRR” and “high HR–high HRR” groups had higher risk (hazard ratio: 3.36; 95% CI: 0.15 to 35, p = 0.36; and 4.42, 95% CI: 1.25 to 28, p = 0.018, respectively); the risk was highest if both parameters were abnormal (hazard ratio: 7.95; 95% CI: 2.01 to 53, p = 0.002).

## Discussion

This study examined chronotropic responses to exercise in chronic, advanced HF and how these responses are associated with adverse outcome while also exploring mechanisms that may underlie abnormal HR modulation in HF. Impaired chronotropic response to exercise was highly prevalent and was correlated with lower quality of life and reduced exercise capacity. Both increased resting HR and impaired HRR were predictive of adverse outcomes, but intriguingly, they were not correlated with each other, and each component was

associated with distinct clinical and neurohormonal profiles. CI was associated with typical neurohumoral responses to HF (increased copeptin and catecholamine levels). In contrast, resting HR correlated with markers of myocardial stress (natriuretic peptides) and those of systemic inflammation. The divergent relationships among biomarkers, resting HR, and chronotropic responses in HF have not been described and suggest that resting HR and HRR reflect discrete pathophysiologic processes and therapeutic targets.

**Relationships among resting HR, chronotropic responses, and biomarkers.** A higher resting HR was coupled with increased norepinephrine and natriuretic peptide levels. This association may be reflective of increased cardiac filling pressure causing stimulation of cardiac baroreceptors which stimulate cardiac sympathetic nerve activity. High filling pressure also increases diastolic wall tension, the main stimulus for natriuretic peptide secretion (14,15). Direct chronotropic effects of natriuretic peptides on the sinus node might contribute to HR acceleration (16). In addition, resting HR correlated with C-reactive protein and leukocyte count. The connection between inflammation and increased HR may be explained by HF-related attenuation of parasympathetic tone. Intriguingly, vagal tone tonically modulates not only HR but also systemic immune responses (17), and



vagal stimulation has pronounced antiinflammatory effects in experimental HF (18).

In contrast, HRR was unrelated to myocyte stress or inflammation, but it correlated positively with norepinephrine and copeptin levels, reflecting more intense neurohumoral stimulation. In a prospective HF cohort study, copeptin predicted adverse outcomes independent of natriuretic peptide levels (19). Elevated vasopressin in HF is primarily reflective of altered hemodynamics and reduced cardiac output (15,20) and corresponds to more impaired autonomic regulation (21). Using a novel ultrasensitive assay, we were able to detect cardiac troponin I in all subjects, including controls, but we observed no relationship to HR modalities, indicating that troponin leakage is unrelated to CI.

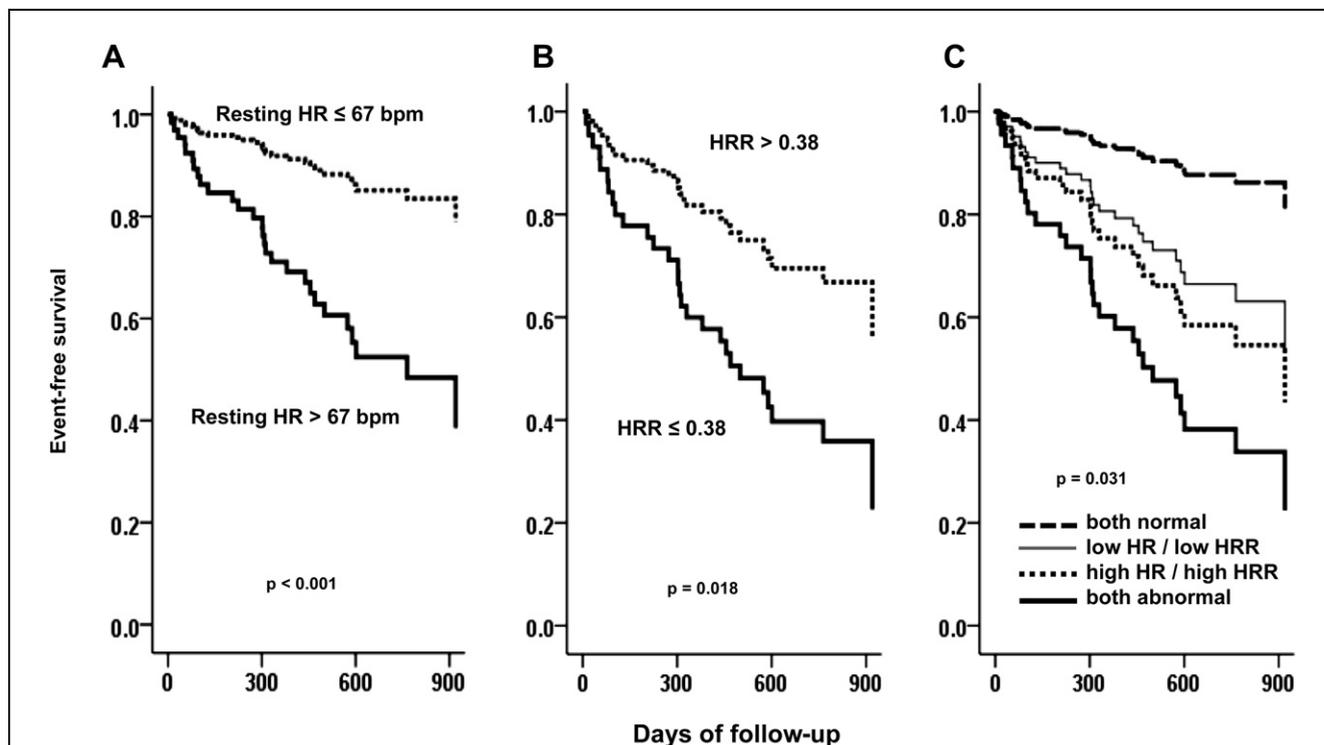
**HF-related CI.** The prevalence of CI in HF varies with the definition, drug therapy and disease stage (3). We observed a considerably higher prevalence of CI than that reported in less symptomatic cohorts with no or low beta-blocker use (6,22,23). Using CI criteria for beta-blocker-treated subjects without HF (HRR: <0.62) (24), we found CI was present in 66% of patients. Advanced CI (the lowest quartile of HRR: ≤0.38) was associated with markedly reduced quality of life, diminished exercise capacity, and increase risk of events. These findings speak against the notion that CI is a mere consequence of diminished exercise capacity in HF and point to a causal contribution (25).

In beta-blocker-treated subjects without HF, CI-related risk is markedly nonlinear and starts to increase below HRR of 0.6 to 0.7 (24). In a large study of beta-blocker-free

HF patients, only the lowest quartile of chronotropic index distribution (<0.51) was predictive of mortality, suggesting a threshold effect (8). With more advanced HF patients who were receiving beta-blockers as in our study, this threshold was further shifted towards lower HRR values. This nonlinearity also implies that CI is prognostically relevant for a certain subgroup of HF patients but not for all.

The influence of drugs and comorbidities on HF-related CI is incompletely understood, and our study provides additional insight (3). In an earlier study from the pre-beta-blocker era, HF patients demonstrated diminished sinus node responsiveness to norepinephrine, while the dynamics of catecholamines in plasma was preserved (11). Because chronic beta-blocker therapy attenuates plasma norepinephrine levels (26), diminished exercise-induced increases in catecholamines might contribute to CI in beta-blocker-treated HF patients. Our results argue against this possibility, because exercise-induced dynamics of plasma norepinephrine in HF subjects were similar to those in controls. Diminished sinus node responsiveness caused by β-adrenergic downregulation (11) and structural or functional remodeling of sinus node caused by the presence of HF (27) are likely explanations.

HRR correlated inversely with ventilatory efficiency (VE/VCO<sub>2</sub> slope), confirming previous observations (8,12), and less strongly with indexes of RV function. Ventilatory efficiency is a potent predictor of adverse outcome in HF (8). Reduced ventilatory efficiency can be a consequence of pulmonary perfusion/ventilation mismatch caused by low-exercise



**Figure 3** Prognostic Implication of Heart Rate (HR) Variables

The impact of resting HR (A), HRR (B), and a combination of both categorical variables (C) on event-free survival (combined endpoint of death without transplant, urgent heart transplantation, or mechanical assist device implantation). Univariate Cox model with cutoff values was based on quartile analysis. HRR = heart rate reserve.

cardiac output or of increased pulmonary vascular tone that may adversely impact RV function (28,29). The correlation between HRR and VE/VCO<sub>2</sub> slope can also reflect HR-related derangements in autonomic cardiorespiratory control, with enhanced ergoreflex and attenuated baroreflex signaling (30).

The issue of whether treatment of CI improves cardiac function or prognosis in HF is still a matter of debate and cannot be solved from these data. Because the predominant component of CI in HF appears to be irreversible (even with LV unloading [31]), rate-adaptive atrial pacing delivered during exercise may be necessary to restore normal chronotropic response (23,32). However, the impact of pacing-based strategy on symptoms and survival in HF remains to be tested.

**Study limitations.** The presented study is limited by its observational character, its relatively small sample size, and low event rate, precluding multivariate analyses. Data for rehospitalization were not available but could provide additional insight.

### Conclusions

The present study shows that CI is associated with more severe HF symptoms, reduced quality of life, impaired exercise capacity, and more intense activation of neurohumoral response in chronic systolic HF. In contrast, the

markers of myocyte stress (natriuretic peptides) were not associated with abnormal HRR but rather with increased resting HR, which also correlated with markers of systemic inflammation. While resting HR and HRR were not correlated with each other, each of them was associated with adverse outcomes, and each provided incremental prognostic information. These findings suggest that increased resting HR and attenuated chronotropic response reflect distinctive pathophysiologic processes, provide independent prognostic information, and represent separate therapeutic targets.

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**Key Words:** biomarkers ■ chronotropic incompetence ■ exercise ■ heart failure ■ heart rate.

 **APPENDIX**

**For a supplemental table and figure, please see the online version of this article.**