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Cardiovascular Reactivity to Mental Stress and Mortality in Patients With Heart Failure

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CME Objective for This Article: After reading this article, the reader should understand: 1) the normal response to acute mental stress in patients without heart failure; and 2) how cardiovascular reactivity to acute mental stress may refine clinical risk prediction in patients with systolic heart failure.

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Cardiovascular Reactivity to Mental Stress and Mortality in Patients With Heart Failure

ABSTRACT

OBJECTIVES This study examined whether blood pressure (BP) and heart rate responses to acute mental stress were associated with mortality in patients with heart failure (HF).

BACKGROUND HF is characterized by reduced contractility and impaired BP reactivity. Compared to exercise-induced physiological changes, the effects of mental stress on BP and heart rate in HF are not well understood.

METHODS Patients with systolic HF (N = 100, 26% female, mean 65 ± 12 years of age) underwent a structured public speech task, during which BP and heart rate were recorded. Stress-induced BP and heart rate reactivity were categorized as high (>75%), intermediate (25% to 75%), or low (<25%). Cox proportional hazards regressions were used to examine the predictive value of cardiovascular stress responses for mortality (median follow-up = 48.5 months), adjusting for age, implanted devices, and baseline BP and heart rate levels.

RESULTS At follow-up, 31 patients had died (31%). Mortality rates were 2 times higher (hazard ratio [HR]: 2.04; 95% confidence interval [CI]: 1.15 to 3.60; p = 0.014) among patients with the lowest diastolic BP responses (mean = −2.4 ± 5.4 mm Hg) to mental stress than among those patients with an intermediate diastolic BP response (mean = 7.3 ± 2.5 mm Hg), adjusting for covariates. High diastolic BP reactivity (mean = 16.3 ± 3.4 mm Hg) was not related to mortality (HR: 0.95; 95% CI: 0.55 to 1.66). Systolic BP responses showed a similar but nonsignificant association. Multivariate analyses showed that a high heart rate response (>6.3 beats/min) to acute mental stress was associated with a reduced mortality risk (HR: 0.40; 95% CI: 0.16 to 1.00; p = 0.051) compared to patients with intermediate responses.

CONCLUSIONS Low diastolic BP reactivity to mental stress is independently associated with all-cause mortality in patients with HF. Larger studies need to replicate this finding and examine the role of psychosocial variables.
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Heart failure (HF) with reduced left ventricular ejection fraction (LVEF) (systolic HF) is characterized by reduced cardiovascular responses to exogenous challenges, such as physical exertion, and reduced peripheral tissue perfusion. Left ventricular dysfunction is associated with compensatory sympathetic cardiac overactivation as reflected by an increased resting heart rate and higher plasma norepinephrine levels (1). Higher resting norepinephrine levels, in turn, have been associated with an increased mortality risk in HF (2).

Sympathetic overdrive may also explain the blunted autonomic nervous system responses to perturbation tests (handgrip, deep breathing, and orthostatic challenge), as the high sympathetic tone may reduce the capacity of the sinoatrial receptors to react to fluctuations in autonomic neural activity (3). Acute mental stress-induced heart rate and forearm blood flow responses are also attenuated in HF (4). Moreover, an attenuated chronotropic response to exercise has been associated with adverse outcome in healthy populations (5), as well as in patients with coronary artery disease (CAD) (6,7) and HF (8).

Cardiovascular responses to psychological challenge such as mental stress have prognostic significance in healthy individuals (9) and in patients with CAD. In patients with stable CAD, a relationship has been documented between high blood pressure (BP) responses and an increased incidence of cardiac events at follow-up (10,11), but no previous studies have examined the long-term adverse effects of BP and heart rate responses to mental stress in patients with systolic HF. Moreover, evidence suggests that the prognostic effects of "hyperreactivity" in CAD are not observed in advanced stages of cardiovascular disease. In fact, diminished cardiovascular and hormonal reactivity to psychological stress have been related to poor health outcomes in diverse populations (12), including patients with acute coronary syndrome (13). This suggests a bimodal risk profile, with both attenuated and hyper-reactive reactivity being associated with poor cardiovascular prognosis.

The current study examined the prognostic value of BP and heart rate reactivity to acute mental stress in patients with systolic HF. Poor BP responses to challenge can be associated with adverse outcome because hyporesponsiveness could reflect sympathetic depletion in systolic HF. Exaggerated BP responses to challenge may also be associated with adverse HF outcomes because of beta-adrenergic-mediated oxidative dysregulation and multiple exposures to stress-induced increases in afterload. We therefore hypothesized that a bi-modal risk profile would emerge such that HF patients with disproportionately low and high stress-induced BP responses to mental stress were at elevated mortality risk compared to patients with intermediate stress responses.

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METHODS

PARTICIPANTS. Patients with stable HF and reduced LVEF (<40% as measured by echo or nuclear imaging study) attending the outpatient HF clinic were enrolled between September 2006 and September 2008. Exclusion criteria were HF with preserved LV function (diastolic HF), >80 years of age, recent (<1 month) myocardial infarction (MI), other life-threatening diseases (e.g., cancer, end-stage renal disease), or insufficient understanding of spoken and written Dutch language. Medication (i.e., beta-blocking agents or renin-angiotensin-aldosterone system [RAAS] medication) was not withheld prior to study participation. The study was conducted according to the Helsinki declaration. All patients were cleared by their cardiologist prior to participating in the mental challenge protocol. Patients provided informed consent prior to participating in the study and were debriefed afterward.

PROTOCOL AND MEASURES. Patients were tested while they were in a sitting position and asked to rest quietly for 10 min prior to the task to collect baseline assessments. After the rest period, patients were instructed to prepare a 3-min speech about their personal strengths and weaknesses regarding social interactions. This preparation period took 3 min. Patients were instructed to speak in an honest and specific way about personal habits in, and difficulties with, social interaction. Patients spoke to the experimenter, who, the patients were told, was rating their performance. The content of the speech was recorded in terms of positive, negative, or mixed personally relevant topics. After this task was completed, patients were asked to rest quietly again for 10 min to assess recovery.

BLOOD PRESSURE AND HEART RATE. Patients were fitted with a BP monitor (model M5-1, Omron, Tokyo, Japan) (14) to assess BP and heart rate at a 2.5-min interval during rest, a 1.5-min interval during preparation and the speech task, and a 2.5-min interval during post-stress recovery.

MORTALITY. Survival status and cause of death were obtained from the medical records until 78 months (6.5 years) after the mental stress-testing assessments. The median follow-up time was 48.5 months (range 5 to 78 months; 95% confidence interval [CI]: 46.9 to 54.1). Survival status at follow-up was known for all patients. Cause of death was recorded and categorized as cardiac (i.e., MI, HF, arrhythmia, or sudden cardiac death) or noncardiac (i.e., pneumonia, cancer, or other causes). Because of the relatively small sample size, we did not discriminate between cardiac and noncardiac causes of death.

DEMOGRAPHIC AND CLINICAL VARIABLES. Demographic and behavioral variables included sex, age, level of education, marital status, smoking status, body mass index (BMI), and physical activity. The variables education and marital status were dichotomized (e.g., "at least high school education" vs. "less than high school education" and "married or living with spouse or partner" vs. "living alone or widowed or separated or divorced") for presentation purposes. Physical activity was assessed with a single question, "Are you physically active on a regular basis?" with a dichotomous answer option (yes/no). Clinical variables included LVEF, New York Heart Association (NYHA) functional class, cause of HF (ischemic vs. nonischemic), cardiac history (i.e., MI, percutaneous coronary intervention, coronary artery bypass graft surgery), arrhythmia, device implantations (pacemaker [univentricular and biventricular] and implantable cardioverter-defibrillator [ICD]), and medication use. Information about clinical variables was obtained from the medical records.

As part of a larger study, patients were also asked to fill out a psychological survey (at home, preceding the mental challenge test), including assessments of depression and anxiety and Type D, or distressed, personality (15,16). The sample size of the present study examining reactivity to mental stress was not sufficiently large to examine interactions among these contextual psychological factors and stress-induced reactivity for future mortality, so psychological background variables were used for descriptive purposes only in this study.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure
CAD = coronary artery disease
CI = confidence interval
HF = heart failure
HR = hazard ratio
MI = myocardial infarction
NYHA = New York Heart Association
LVEF = left ventricular ejection fraction
RAAS = renin-angiotensin-aldosterone system

STATISTICAL ANALYSES. Data are mean ± SD or N/n (%) as appropriate. For each study phase (rest, mental stress, and recovery) average BP and heart rate measurements were calculated and used for analyses. BP and heart rate reactivity were calculated by subtracting resting levels from stress levels and then were recoded based on the 25th percentiles (high = ≥75th percentile, intermediate = 25th to 75th percentile, and low = ≤25 percentile) and were also analyzed as continuous measures. We selected the reference group based on existing reports (17) that suggested the intermediate BP response was most comparable to an optimal and "normal" response to a speech task.

One-way ANOVA was used to analyze differences among response categories with respect to continuous patient variables, including psychological functioning and speech content, and average BP and heart rate levels, whereas Student *t* tests were used to analyze differences in continuous variables between deceased and surviving patients. Crosstabs with chi square tests were used to analyze differences with respect to discrete variables. Column proportions were compared using a z-test. Unadjusted and covariate-adjusted Cox proportional hazards regression models were used to examine the associations of BP and heart rate reactivity with all-cause mortality. Survival results are reported as hazard ratios (HRs) and 95% CIs. Covariates were entered simultaneously and included age, presence of implanted devices, and baseline BP or heart rate levels. Medication was not included as a covariate in the adjusted models, as almost all patients were prescribed angiotensin-converting enzyme (ACE)- or angiotensin receptor-inhibiting drugs and/or beta-adrenergic blocking agents. The proportional hazards assumption was met for all covariates. With respect to predictor variables, correlations of Schoenfeld residuals with time were nonsignificant (<0.16 for diastolic blood pressure [DBP] categories, <0.03 for systolic blood pressure [SBP]) categories, and <0.08 for heart rate categories), indicating an independence of these residuals with time. All analyses were performed using SPSS version 19.0 software (IBM Corp., Armonk, New York). A p value of <0.05 was considered statistically significant, and no correction for multiple comparisons was performed in the main regression analyses.

RESULTS

PATIENT CHARACTERISTICS. Clinical and demographic characteristics are presented in **Table 1**. The mean age was 66.6 ± 11.6 yrs, and the majority of patients was male (74%). The median time since HF diagnosis was 2.5 years (range 1.0 to 14.5 years, mean 3.3 ± 2.4 years). The LVEF was 31.8 ± 6.9%, and ischemia was the cause, and approximately one-half of the patients had an ischemic HF etiology. Approximately one-fourth of the patients were in NYHA functional class III, indicating that all patients are without symptoms at rest (**Table 1**). Comorbid conditions included hypertension (48%), renal disease (6%), diabetes mellitus (24%), peripheral arterial disease (7%), cerebrovascular disease (3%), paroxysmal atrial fibrillation (20%), and chronic obstructive pulmonary disease (COPD) (11%); 2 patients had left bundle branch block and none had atrioventricular block.

A total of 31 patients (31%) died during the follow-up period (median follow-up = 48.5 ± 18.2 months; range 5 to 78 months). A cardiac cause was identified in 15 patients. Mortality was related to older age (age difference of 5.2 years; t = −21; p = 0.04), whereas none of the other covariates predicted mortality (trends were found for comorbidities, use of ACE inhibitors or ARBs, and level of physical activity [Online Table 1]).

BLOOD PRESSURE AND HEART RATE RESPONSES TO MENTAL STRESS IN HEART FAILURE. On average, mental stress induced an increase in SBP (from 124.3 ± 19.0 mm Hg to 139.1 ± 21.9 mm Hg; p < 0.001; a difference [Δ] of 14.8 ± 11.7 mm Hg), in DBP (from 74.6 ± 10.2 mm Hg to 81.8 ± 10.5 mm Hg; p < 0.001; Δ = 7.1 ± 7.6 mm Hg), and heart rate (from 67.2 ± 10.8 beats/min to 70.8 ± 11.0 beats/min; p < 0.001; Δ = 3.6 ± 4.8 beats/min). Responses were divided into quartiles, with patients in the lowest quartile (reactivity cutoff values of ≤5.1 mm Hg for SBP, ≤2.3 mm Hg for DBP, and ≤0.5 beats/min for heart rate) characterized as "low" responders (mean ΔSBP = 1.0 ± 3.4 mm Hg; ΔDBP = −2.4 ± 5.4 mm Hg; and Δheart rate = −1.6 ± 3.2 beats/min). The 4th quartile was used to identify the "high" responders (mean ΔDBP = 16.3 ± 3.4 mm Hg, ΔSBP = 30.3 ± 7.1 mm Hg, and Δheart rate = 9.4 ± 3.9 beats/min). The BP and heart rate responses in the middle 2 quartiles (i.e., 25th to 75th percentiles: ΔDBP = 7.3 ± 2.5 mm Hg, ΔSBP = 13.9 ± 5.0 mm Hg; Δheart rate = 3.0 ± 1.8 beats/min) were considered intermediate responses and were used as references for comparing mortality rates between high and low responders. **Table 1** shows the association of low, intermediate, and high reactivity categories with the demographic, clinical, and medication variables, as well as speech content and psychological functions. Patients who were older displayed increased diastolic and systolic reactivity, and high-reactive patients less often had an ischemic HF cause (both BP and heart rate). Use of beta-adrenergic blocking agents

TABLE 1 Patient Characteristics Stratified By Response Category of Blood Pressure and Heart Rate

		Diastolic Blood Pressure			Systolic Blood Pressure			Heart Rate		
Parameter*	**TOTAL**	**Low**	**Intermediate**	**High**	**Low**	**Intermediate**	**High**	**Negative**	**Intermediate**	**High**
Demographics and health behaviors										
Deceased	31 (31%)	10 (40%)	11 (22%)	10 (40%)	9 (36%)	13 (26%)	9 (36%)	*4 (17%)*	*21 (41%)*	*6 (23%)*
Males	74 (74%)	19 (76%)	35 (70%)	20 (80%)	15 (60%)	40 (80%)	19 (76%)	17 (74%)	37 (73%)	20 (77%)
Age at stress task (yrs)	66.6 ± 11.6	**62.0 ± 12.4**	**67.1 ± 11.5**	**70.4 ± 9.8**	**64.7 ± 11.2**	**64.7 ± 12.3**	**72.4 ± 8.8**	67.9 ± 12.2	65.1 ± 11.5	68.5 ± 11.4
Education (≥high school)	43 (44%)	12 (52%)	21 (40%)	10 (40%)	8 (36%)	26 (52%)	9 (36%)	7 (32%)	23 (47%)	13 (50%)
Marital status (or partnered)	72 (72%)	18 (72%)	37 (74%)	17 (68%)	16 (64%)	40 (80%)	16 (64%)	19 (83%)	38 (75%)	15 (58%)
Smoking	22 (23%)	8 (35%)	11 (22%)	3 (12%)	9 (41%)	8 (16%)	5 (20%)	4 (18%)	10 (20%)	8 (31%)
BMI (kg/m^2)	27.9 ± 5.5	27.3 ± 6.7	28.4 ± 5.6	27.3 ± 3.4	27.1 ± 5.8	27.7 ± 4.3	28. ± 5.9	29.0 ± 6.2	26.7 ± 5.8	27.9 ± 4.8
Physically active	63 (63%)	15 (63%)	31 (63%)	17 (68%)	15 (68%)	30 (60%)	18 (72%)	13 (59%)	31 (63%)	19 (73%)
Clinical variables										
Ischemic cause	52 (52%)	*15 (60%)*	*29 (58%)*	*8 (32%)*	13 (52%)	28 (56%)	11 (44%)	*10 (44%)*	*32 (63%)*	*10 (39%)*
Cardiac history*	54 (54%)	14 (56%)	28 (56%)	12 (48%)	12 (48%)	29 (58%)	13 (52%)	**10 (44%)**	**34 (67%)**	**10 (39%)**
Devices†	13 (13%)	6 (24%)	5 (10%)	2 (8%)	*5 (20%)*	*8 (16%)*	*0 (0%)*	5 (22%)	7 (14%)	1 (4%)
Atrial fibrillation	20 (20%)	*4 (16%)*	*7 (14%)*	*9 (36%)*	3 (12%)	9 (18%)	8 (32%)	5 (22%)	8 (16%)	7 (27%)
≥2 comorbidities‡	27 (27%)	10 (40%)	11 (22%)	6 (24%)	9 (36%)	13 (26%)	5 (20%)	7 (30%)	14 (28%)	6 (23%)
NYHA functional class III	24 (24%)	4 (16)	14 (28)	6 (24)	6 (24)	15 (30)	3 (12)	*9 (39%)*	*10 (20%)*	*5 (19%)*
LVEF (%)	31.8 ± 6.9	30.6 ± 7.4	32.7 ± 6.6	31.0 ± 7.2	30.9 ± 7.2	32.1 ± 6.8	32.0 ± 7.1	32.0 ± 6.9	31.8 ± 7.3	31.5 ± 6.4
6-MWT distance (m)	284.6 ± 144.3	272.0 ± 160.6	283.3 ± 135.7	300.1 ± 147.1	279.6 ± 136.7	278.7 ± 145.8	300.6 ± 153.8	**213.9 ± 120.1**	**294.0 ± 153.9**	**322.0 ± 127.8**
Medications										
ACE inhibitors or ARBs	89 (89%)	23 (92%)	43 (86%)	23 (92%)	23 (92%)	43 (86%)	23 (92%)	22 (96%)	45 (88%)	22 (84%)
Beta-blockers	82 (82%)	21 (84%)	42 (84%)	19 (76%)	21 (84%)	40 (80%)	21 (84%)	20 (87%)	42 (82%)	20 (77%)
Digoxin	17 (17%)	3 (12%)	8 (16%)	6 (24%)	*3 (12%)*	*6 (12%)*	*8 (32%)*	1 (4%)	8 (16%)	8 (31%)
Diuretics	61 (61%)	15 (60%)	32 (64%)	14 (56%)	13 (52%)	34 (68%)	13 (52%)	16 (70%)	32 (63%)	13 (50%)
Psychotropic medication	15 (15%)	5 (20%)	7 (14%)	3 (12%)	4 (16%)	7 (14%)	4 (16%)	5 (22%)	9 (18%)	1 (4%)

Values are n (%) or mean ± SD. *History of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery. †Implanted devices, including pacemaker (uni- and biventricular) and implantable cardioverter-defibrillator. ‡Two or more of the following comorbidities: cerebrovascular disease, COPD, hypertension, diabetes, peripheral arterial disease, or renal disease. Significant differences between the respective diastolic and systolic blood pressure and heart rate response categories are in **bold**. Trends are visualized in *italic*.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; 6-MWT = 6-minute walk test; NYHA = New York Heart Association.

TABLE 2 Levels of Heart and Blood Pressure Stratified by Diastolic Blood Pressure and Heart Rate Response Category

	Diastolic Blood Pressure Reactivity			Heart Rate Reactivity		
	Low (n = 25)	Intermediate (n = 50)	High (n = 25)	Negative (n = 23)	Intermediate (n = 51)	High (n = 26)
Baseline levels						
Heart rate (beats/min)	69 ± 9	67 ± 10	66 ± 14	68 ± 12	69 ± 10	63 ± 11
DBP (mm Hg)	81 ± 12*‡	73 ± 9*§	72 ± 7*§	73 ± 9	76 ± 11	74 ± 10
SBP (mm Hg)	130 ± 22	122 ± 18	123 ± 17	122 ± 18	123 ± 19	128 ± 21
Stress levels						
Heart rate (beats/min)	69 ± 9	70 ± 14	71 ± 8	66 ± 11	72 ± 10	73 ± 13
DBP (mm Hg)	78 ± 13	81 ± 10	88 ± 8	80 ± 9	81 ± 11	85 ± 11
SBP (mm Hg)	135 ± 21†‡	135 ± 21†‡	150 ± 20†§	135 ± 18	137 ± 19	148 ± 28

Values are mean ± SD. All heart rate group differences in mean resting and stress levels were nonsignificant (ANOVA, corrected for multiple comparisons). *$p < 0.01$, †$p < 0.05$; comparison of column proportions using z scores: column proportions marked with ‡ are equal to other column proportions marked with ‡ and significantly different from column proportions marked with §, and vice versa.

DBP = diastolic blood pressure; SBP = systolic blood pressure.

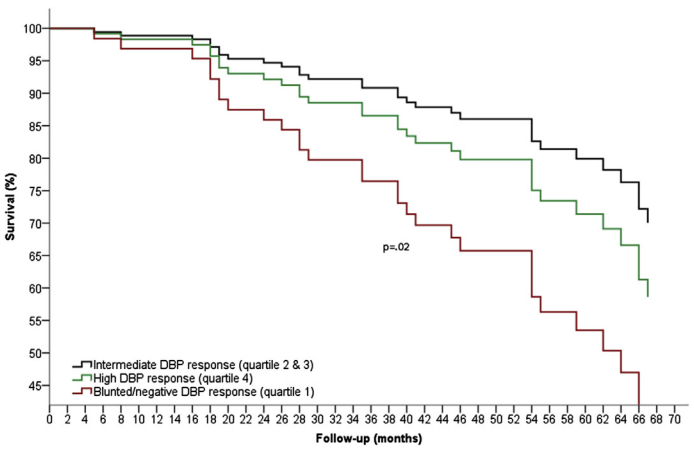
and ACE inhibitors or ARB was common (76% to 92%) and not related to an attenuated heart rate or BP response to mental stress (Table 1). Mean levels of baseline and stress levels of BP and heart rate stratified by response category are presented in Table 2.

BLOOD PRESSURE AND HEART RATE REACTIVITY AS A PREDICTOR OF MORTALITY. Figure 1 displays the adjusted cumulative hazard functions for the association between diastolic BP reactivity and survival. Multivariate analyses showed that patients with the lowest diastolic BP response (1st quartile) demonstrated an increased cumulative risk for all-cause mortality compared to intermediate responders (HR: 2.84; 95% CI: 1.15 to 7.00; p = 0.023). A high response (4th quartile) was unrelated to mortality (HR: 1.50, 95% CI: 0.63 to 3.54; p = 0.36) (Table 3). In this analysis, age and having an implanted device also displayed associations with increased mortality risk. Additional adjustment for baseline DBP did not change the results (HR: 2.79, 95% CI: 1.08 to 7.19; p = 0.032). Post-hoc analysis showed that patients in the lowest DBP response category died more frequently of cardiac causes (40%) than those in the reference category (18%).

The association between SBP reactivity and mortality showed a similar pattern, but this association was not significant (HR: 1.74; 95% CI: 0.74 to 4.10; p = 0.21).

Figure 2 shows the cumulative hazard functions for the association between heart rate reactivity and survival. Multivariate analyses showed that a high heart rate response (>6.3 beats/min) to acute mental stress was associated with a reduced mortality risk (HR: 0.40; 95% CI: 0.16 to 1.00; p = 0.051) compared to patients with intermediate responses. Patients who responded to mental stress with a drop in heart rate (i.e., the lowest 25th percentile, "negative heart rate response") also displayed a decreased mortality risk in comparison with the intermediate group (HR = 0.28; 95% CI: 0.09 to 0.87; p = 0.028) (Table 3). Post hoc analysis showed that the majority of patients in the high-reactivity group died of cardiac causes (67%), whereas the majority of the negative reactivity group died of noncardiac causes (75%). A higher baseline heart rate also was a significant predictor of mortality (HR: 1.04; 95% CI: 1.003 to 1.07; p = 0.03) in fully adjusted analyses. Adding baseline heart rate reduced the effect of high heart rate reactivity to not significant (HR: 0.46; 95% CI: 0.18 to 1.18; p = 0.11), whereas the protective effect of negative heart rate

FIGURE 1 Survival Curve, Stratified by Diastolic Blood Pressure Response



All-cause mortality is shown by follow-up months for the quartiles of change in diastolic blood pressure (DBP), for which the second and third quartiles have been merged. Quartile 1, which has the lowest change in DBP, has the highest mortality **(red line)**. The figure shows survival curves from the fully adjusted analysis, including the covariates age, implanted device, and baseline DBP.

reactivity remained significant (HR: 0.25; 95% CI: 0.08 to 0.76; p = 0.015). Regarding the topics patients talked about during the speech task, post-hoc analyses of speech content (Online Table 1) showed that 30% of the negative heart rate responders only spoke about positive personal characteristics, compared to 8% of the intermediate heart rate responders and to 19% of the high-reactivity group (p = 0.025). With respect to psychological measurements, no significant differences emerged (**Table 1**).

TABLE 3 Cox Proportional Hazards Analysis for Blood Pressure and Heart Rate With Time to Mortality

	Hazard Ratio	95% CI	p Value
Diastolic blood pressure			
4th quartile DBP response "high"	1.50	0.63–3.54	0.358
1st quartile DBP response "blunted"	2.84	1.15–7.00	0.023
2nd and 3rd quartile DBP response	Reference		
Age	1.05	1.004–1.09	0.033
Implanted device	2.54	0.93–6.94	*0.068*
Systolic blood pressure			
4th quartile SBP response "high"	0.97	0.39–2.44	0.955
1st quartile SBP response "blunted"	1.74	0.74–4.09	0.207
2nd and 3rd quartile SBP response	Reference		
Age	1.04	0.997–1.08	*0.07*
Implanted device	2.26	0.83–6.19	0.11
Heart rate			
4th quartile heart rate response "high"	0.40	0.16–1.00	*0.051*
1st quartile heart rate response "negative"	0.28	0.09–.87	0.028
2nd and 3rd quartile heart rate response	Reference		
Age	1.05	1.004–1.09	0.029
Implanted device	3.52	1.21–10.30	0.021

Italic values equal trend association (p < 0.10). Note: Cox proportional hazards results for the 4 quartiles of changes in DBP (ΔDBP), ΔSBP, and ΔHR, adjusted for age and implanted devices.
Abbreviations are as in Table 1.

DISCUSSION

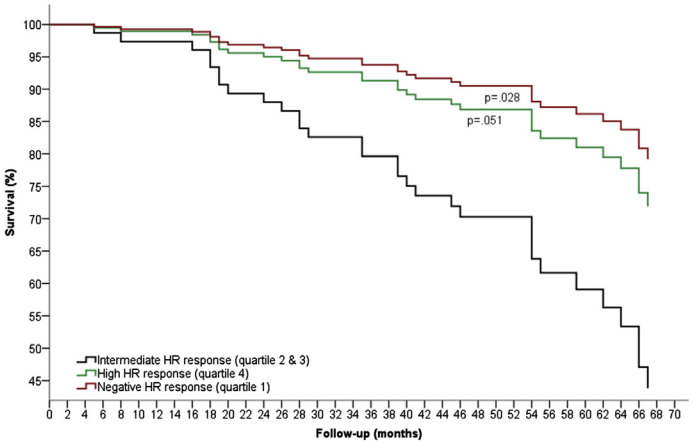
The current study examined the association of cardiovascular reactivity to acute mental stress with mortality in a subsample of a consecutive cohort of patients with systolic HF. Results demonstrated that blunted DBP reactivity to mental stress was independently associated with a higher mortality risk over the follow-up period, whereas hyperreactivity was not. No increased risk was observed in association with SBP responses.

Patients with HF and a reduced LVEF are characterized by increased sympathetic nerve traffic and elevated spillover of norepinephrine into systemic blood, combined with reduced vagal tone during rest (1,18), which results in tachycardia and decreased cardiac output. In response to exercise, BP and heart rate increases are metabolically driven to meet the muscles' oxygen demands and to maintain homeostasis with respect to, for example, temperature. In response to acute mental challenge, similar cardiovascular adjustments are observed, despite the absence of augmented metabolic demand (19). An optimal or "normative" stress response usually consists of vagal withdrawal, followed by an increase in sympathetic cardiac drive. The response to challenge in HF is characterized by below-normal chronotropic and inotropic responses as a consequence of left ventricular impairment, depletion of myocardial norepinephrine stores, a reduction in beta-adrenergic receptor density, and elevated systemic vascular resistance related to increased activity of the sympathetic and renin-angiotensin systems (3). In keeping with this pathophysiological response profile, patients in the current study exhibited on average relatively small responses to acute mental stress.

The current findings demonstrated that the lowest response quartile, exhibiting a blunted or even negative DBP response to mental stress, incurred an independent, increased mortality risk. This is in accordance with findings from a large study in patients with acute coronary syndrome, showing that low BP (<9 mm Hg DBP; <20 mm Hg SBP) and heart rate (<4 beats/min) responses to mental stress were associated with a 2-fold increased risk of future clinical events (13). Our findings are also in concordance with those of previous studies in patients with CAD and HF in which an attenuated cardiovascular response to exercise testing was associated with increased risk of mortality. An attenuated chronotropic response to exercise is associated with an adverse outcome in healthy populations (5) and in patients with CAD (6,7,20) and HF (8,21). Our results suggest that this phenomenon might extend to mental challenge, as an impaired diastolic response was associated with increased mortality risk. Low DBP responders were characterized by a younger age and seemed to be a little bit unhealthier, as a larger (but nonsignificant) percentage were smokers, had at least 2 comorbid somatic conditions, had a lower LVEF, and walked less distance on a 6-minute walk test (**Table 1**). Low DBP responders were also characterized by significantly lower levels of negative affectivity and slightly lower depression than intermediate responders (Online Table 1). Future research is needed to determine whether psychophysiological hyporeactivity to mental stress predicts HF progression and mortality independent of contextual psychological variables such as depression and personality factors.

It is important to examine the prognostic effects of cardiovascular reactivity measures in addition to the

FIGURE 2 Survival Curve, Stratified by Heart Rate Response



All-cause mortality is shown by follow-up months for the quartiles of change in heart rate (HR), for which the second and third quartiles have been merged. Quartile 4 patients, characterized by an intact heart rate response to stress **(green line)**, have better survival chances, just like the first quartile, characterized by a negative change in heart rate **(red line)**. The figure shows the survival curves from the adjusted analysis, including the covariates age and implanted device.

more common examination of the effects of resting levels, as different genes are involved in mounting the mental stress response than those responsible for resting levels (22). Our results indeed show a prognostic effect of reduced DBP reactivity in addition to the effect of resting levels, suggesting different underlying mechanisms may be responsible for these diverging effects.

A higher resting heart rate was predictive of earlier mortality in the adjusted model, which is consistent with a large body of evidence (23), and suggests a role for increased sympathetic tone in disease progression of systolic HF. Sympathetic over-activity might contribute to increased ventricular arrhythmias (24), increased inflammation, vascular alterations due to sequelae of poorer arterial compliance, and plaque disruption (25). Consistent with prior studies in chronotropic responses in HF, we found that preserved (high) heart rate response was associated with a reduced mortality risk (5,7). A heart rate response in the lowest quartile, indicating a drop in heart rate in response to stress, was also associated with better survival, which seems inconsistent with that in prior studies (5–8) and with their clinical presentation (**Table 1**).

The overlapping high heart rate and BP responses were 44% to 52%, and only 24% of the patients with a low heart rate response also had a low BP response. This suggests different physiological mechanism related to BP and heart rate responses (i.e., BP responses are related to endothelial function and heart rate responses to autonomic cardiac drive). Beta-adrenergic blockade might have been disproportionately present in the group with a drop in heart rate in response to stress (87% vs. 82% prescriptions in the reference group), but the high prevalence of beta-adrenergic blocking agents precluded statistical analysis with sufficient statistical power. Moreover, post hoc analysis showed that although beta-blockers did affect the level of heart rate ($p < 0.05$), there were no differences in heart rate response between beta-blocker users and nonusers. Exploratory analyses showed that this finding alternatively might be explained by the observation that among patients characterized by a drop in heart rate, a higher percentage elected to specifically talk only about their positive characteristics (Online Table 1), potentially influencing their level of experienced stress. Another possibility is disengagement with the task, because of motivational or performance-related issues or task difficulty (26). Finally, the inability for the sympathetic nervous system to mount a response may produce a net negative result with respect to heart rate. Because the vagal nerve is also impaired in HF (27,28), individual differences in the ratio of vagal versus sympathetic impairments might explain the current results.

Physiological reactivity studies in patients with HF have focused primarily on the hemodynamic response to physical challenge (i.e., exercise in relation to outcome) and have neglected reactivity to mental stress). In patients with impaired systolic function (LVEF ≤30), Akimboboye et al. (29) demonstrated that mental stress is a stronger trigger of myocardial ischemia than physical exertion. Cardiovascular reactivity may act as a mediating mechanism in the relationships of psychological risk factors such as depression, anxiety, perceived stress, and type D personality with future mortality in cardiovascular patient populations.

The present findings indicate that more information is needed about role of psychosocial contextual variables such as depression and perceived stress in the observed associations between cardiovascular reactivity and increased mortality risk.

STUDY LIMITATIONS. The results of the current study should be viewed in light of some limitations. The limited sample size resulted in restrictions on the number of covariates that could be included in the multivariate models and our focus on all-cause and not cardiovascular mortality. Due to limited power, we were unable to discern the potential mediating effects of cardiovascular stress reactivity in

explaining the association between psychological function and mortality. Because of the adverse events risk in this elderly HF sample, we did not withdraw medication (i.e., beta-blocking and RAAS agents), as is usually done in mental stress reactivity studies in patients with stable CAD. Confounding by medication effects, and thus disease severity, might serve as an alternative explanation for the results, as hemodynamic and cardiac reactivity to mental stress is known to be blunted by antihypertensive medication (30). In HF patients, no previous study has examined the effects of beta-blocker use on heart rate responses to mental stress. Nevertheless, almost all patients were taking these medications, and post hoc analyses that included these medication variables showed that the risk associated with low reactivity was independent of medication use and that the effect of the beta-blocker was equal across response categories. Another limitation is the lack of an exercise test which would have enabled a direct comparison between exercise and mental stress responses. Finally, in the years in which our data were collected, device implantation was not as common as it is presently, which explains the relatively low number of devices implanted in the current sample. Strengths of the study are the relatively long follow-up period and the standardized administration of the mental stress challenge.

CONCLUSIONS

We found that diminished DBP responses to acute mental stress were associated with an increased risk of earlier mortality in patients with chronic HF, independent of clinical covariates and resting diastolic BP. For SBP, a similar but more modest risk pattern emerged. This study suggests that blunted reactivity to acute mental stress might add to the risk stratification of HF patients and expands the knowledge base about the biobehavioral mechanisms involved in HF progression. Clinically, these results suggest that suboptimal pressor responses to acute psychosocial stressors are a prognostic factor in HF. Novel interventions are needed to target both the behavioral aspects of acute reactivity to stress and the pharmacological approaches that reestablish an adequate BP response to acute challenges such as mental stress and physical exertion in patients with HF.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Blunted blood pressure responses to acute mental stress may add to the clinical risk profile of heart failure patients.

TRANSLATIONAL OUTLOOK: Future trials should evaluate the prognostic impact of interventions targeting both the behavioral aspects of stress reactivity and the pharmacological aspects of adequate blood pressure responsivity to mental stress and physical exertion in patients with HF.

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KEY WORDS acute mental stress, blood pressure, heart failure, heart rate, reactivity

APPENDIX For a supplemental table, please see the online version of this article.

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