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Chemoreflex and Baroreflex Sensitivity Hold a Strong Prognostic Value in Chronic Heart Failure

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ABSTRACT

BACKGROUND Novel treatments targeting in baroreflex sensitivity (BRS) and chemoreflex sensitivity (CRS) heart failure (HF) are grounded on small prognostic studies, partly performed in the pre-beta-blockade era.

OBJECTIVES This study assesses the clinical/prognostic significance of BRS and CRS in a large cohort of patients with chronic HF on modern treatments.

METHODS Outpatients with chronic HF with either reduced (≤40%) or mildly reduced left ventricular ejection fraction (LVEF) (41% to 49%) underwent BRS (SD method) and CRS to hypoxia and hypercapnia (rebreathing technique) assessment and were followed up for a composite endpoint of cardiac death, implantable cardioverter-defibrillator shock, or HF hospitalization.

RESULTS A total of 425 patients were enrolled (65 ± 12 years of age, LVEF 32% [IQR: 25%-38%], 94% on beta blockers). Patients with decreased BRS (n = 96 of 267, 36%) had lower exercise tolerance and heart rate variability ($P < 0.05$), whereas those with increased CRS to both hypoxia and hypercapnia (n = 74 of 369, 20%) had higher plasma norepinephrine and central apneas across the 24-hour period ($P < 0.01$). During a median 50-month follow-up (IQR: 24-94 months), the primary endpoint occurred more often in patients with decreased BRS (log-rank: 11.64; $P = 0.001$), mainly for increased cardiac deaths/implantable cardioverter-defibrillator shocks, and in those with increased CRS (log-rank: 34.81; $P < 0.001$), mainly for increased HF hospitalizations. Patients with both abnormal BRS and CRS showed the worst outcome. Reduced BRS (HR: 2.76 [95% CI: 1.36-5.63]; $P = 0.005$) and increased CRS (HR: 2.91 [95% CI: 1.34-6.31]; $P = 0.007$) were independently associated with the primary outcome and increased risk stratification when added to standard HF prognosticators ($P < 0.05$).

CONCLUSIONS In subjects with HF on modern treatment, abnormal BRS and CRS are frequently observed. BRS and CRS elicit autonomic imbalance, exercise limitation, unstable ventilation, and predict adverse outcomes.
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The treatment of chronic heart failure (HF) is mainly based on neurohormonal antagonism acting downstream to block adrenergic and renin-angiotensin-aldosterone systems.[1] Despite optimal treatment, a significant neurohormonal escape is frequently observed in HF, contributing to adverse outcome.[2-4]

An alternative approach is to act upstream on dysfunctional visceral reflexes (ie, decreased baroreflex sensitivity [BRS] and increased chemoreflex

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sensitivity [CRS]) that are believed to cause sympathovagal imbalance and ventilation instability in HF.[5,6] Novel treatments have been developed for modulation of BRS and CRS; but to maximize efficacy and minimize side effects, the proper selection of patients is desirable.[7-10]

Notably, BRS/CRS therapies are grounded on dating back prognostic studies in relatively small populations, partly run during the pre-beta-blockade and pre-cardiac resynchronization therapy (CRT) era, that have been challenged by more recent findings.[11-16]

Nevertheless, we hypothesize that abnormal BRS and/or CRS may still be present in a relevant proportion of patients and may deserve a targeted approach; thus, we aimed to address their prevalence and clinical and prognostic significance in a population of patients with chronic HF on modern drug and device therapy.

METHODS

SUBJECTS AND STUDY DESIGN. Between January 2010 and December 2018, we prospectively screened outpatients with a left ventricular ejection fraction (LVEF) <50% on stable HF treatment from at least 6 months at Fondazione Toscana G. Monasterio (FTGM), Pisa, Italy.

Exclusion criteria were any condition of clinical instability including acute coronary syndrome, acute decompensated HF, or changes in HF treatment including CRT implantation in the 3 months before enrollment, severe renal and pulmonary disease, and therapy with morphine or derivates, theophylline, oxygen, or acetazolamide. The study protocol was approved by the Institutional Review Board of FTGM, and informed consent was obtained from all subjects.

All patients underwent neurohormonal evaluation, 2-dimensional Doppler echocardiography (Philips iE33), symptom-limited maximal cardiopulmonary exercise test (CPET) (Ergostik, Geratherm Respiratory), 24-hour electrocardiographic (ECG) recording (Elamedical) including measurements of heart rate variability (HRV) in the time domain in patients in sinus rhythm and <1,000 ectopic beats over 24 hours (Elamedical; signals digitized at a sampling rate of 250 Hz), and 24-hour cardiorespiratory monitoring (Somté, Compumedic) for detection of apneas.[4,17-19] Finally they also underwent BRS and CRS assessment.[13,20-22]

BRS ASSESSMENT. For patients in sinus rhythm, the evaluation of BRS was performed by the standard deviation method (BRS-SD).[20] BRS-SD is based on the ratio between the global rather than specific variabilities of the intervals between successive heartbeats or RR interval and systolic blood pressure. This method was developed and validated by Bernardi et al[20] against 6 established methods of BRS assessment, and showed prognostic significance in HF patients in a preliminary study.[21]

A supine recording of blood pressure (Finapres Medical Systems BV) and ECG lasting ≥5 minutes was obtained. All signals were acquired online at 500 Hz/signal. Data were analyzed after linear detrending, high-pass filtering at 0.025, and 0.05 Hz. Ectopic beats were recognized visually and corrected by linear interpolation. BRS-SD was then calculated as:

$$BRS-SD = \frac{SD\ of\ RR\ interval}{SD\ of\ systolic\ blood\ pressure}$$

CHEMOREFLEX SENSITIVITY ASSESSMENT. In a sitting position, patients breathed through a breath-by-breath spirometer and gas analyzer (Vmax, Sensormedics), while oxygen saturation (SaO_2) was recorded through a pulse oximeter (SET Radical, Masimo). All signals were acquired online at 500 Hz/signal. After a 5-minute baseline assessment in free breathing conditions, they were connected through a two-way non-rebreathing valve (Hans Rudolph) to a closed circuit (5 L, no gas within the bag) and performed in a random order the hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) trials (5 minutes of recovery between the 2 maneuvers).[13,22,23]

During the HVR test, end-tidal carbon dioxide ($etCO_2$) was kept constant to baseline values by passing a portion of the expired air into a scrubbing circuit before returning to the bag. The test was stopped when SaO_2 fell below 80% down to 70%, according to individual tolerance. HVR was calculated as the regression line between ventilation and SaO_2 (L/min/%SaO_2). During the HCVR test, PO_2 was kept constant to baseline values by adding O_2 to the circuit. The test was stopped when $etCO_2$ achieved 50 mm Hg or there was an increase 10 mm Hg from baseline, according to individual tolerance. HCVR was calculated as the regression between ventilation and $etCO_2$ (L/min/mm Hg).

FOLLOW-UP. Patients were followed up until December 2020 at the outpatient clinic of our hospital, and their outcome status was determined from the

ABBREVIATIONS AND ACRONYMS

AHI = apnea-hypopnea index
BRS = baroreflex sensitivity
CAI = central apnea index
CPET = cardiopulmonary exercise test
CRS = chemoreflex sensitivity
CRT = cardiac resynchronization therapy
eGFR = estimated glomerular filtration rate
HCVR = hypercapnic ventilatory response
HF = heart failure
HRV = heart rate variability
HVR = hypoxic ventilatory response
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
NT-proBNP = N-terminal pro-B-type natriuretic peptide
OSA = obstructive sleep apnea

TABLE 1 Clinical Features of Patients According to BRS

	All Patients (N = 267)	BRS ≥5.5 ms/mm Hg (n = 171, 64%)	BRS <5.5 ms/mm Hg (n = 96, 36%)
Clinical			
Age, y	63 ± 13	62 ± 13	65 ± 11
Males	207 (78)	130 (76)	77 (80)
BMI, kg/m^2	27 ± 4	26 ± 4	28 ± 5[a]
Ischemic etiology	116 (43)	69 (40)	47 (49)
NYHA functional class III-IV	36 (14)	19 (11)	17 (18)
Heart rate, beats/min	68 ± 9	68 ± 9	68 ± 10
Systolic blood pressure, mm Hg	118 ± 25	117 ± 25	120 ± 25
Comorbidities			
Hypertension	128 (48)	77 (44)	51 (53)
Dyslipidemia	134 (50)	85 (49)	49 (51)
Diabetes	69 (26)	39 (23)	30 (31)
COPD	29 (11)	15 (8)	14 (15)
Hb, g/dL	13.3 ± 1.6	13.4 ± 1.5	13.1 ± 1.6
eGFR, mL/min/1.73 m^2	79 ± 27	80 ± 27	78 ± 26
Echocardiography			
LAD, mm	44 ± 6	44 ± 7	45 ± 6
Severe MR	43 (16)	26 (15)	17 (18)
Diastolic dysfunction III	64 (24)	41 (24)	23 (24)
LVEDD, mm	61 (57-66)	62 (57-68)	61 (56-65)
LVESD, mm	51 (45-57)	52 (45-58)	51 (45-55)
LVEF, %	32 (35-38)	33 (26-38)	30 (25-38)
RVD, mm	27 (25-30)	27 (25-29)	28 (26-30)[a]
TAPSE, mm	19 (16-23)	20 (17-23)	18 (15-21)[a]
sPAP, mm Hg	37 (30-46)	37 (30-46)	34 (30-49)
CPET parameters			
Workload, W	90 (63-120)	90 (70-127)	82 (60-110)[a]
Peak VO_2/kg, mL/kg/min	14 (11-19)	15 (12-20)	13 (11-17)[a]
VE/VCO_2 slope	33 (28-39)	32 (28-39)	33 (29-39)
EOV	64 (24)	44 (26)	20 (21)
Neurohormonal activation			
NT-proBNP, ng/L	847 (375-1,691)	873 (373-1,721)	831 (370-1,670)
Norepinephrine, ng/L	392 (264-566)	362 (256-558)	433 (282-618)
Aldosterone, ng/L	100 (60-163)	98 (56-166)	101 (65-157)
Treatment			
Beta-blockers	248 (93)	156 (91)	92 (96)
ACEI/ARBs	235 (88)	147 (86)	92 (88)
ARNI	13 (5)	11 (6)	2 (3)
MRA	193 (72)	121 (71)	72 (75)
Furosemide	169 (63)	96 (56)	73 (76)[b]
ICD/CRT	55/37 (21/14)	33/22 (19/23)	18/19 (11/20)

Values are mean ± SD, n (%), or median (IQR). [a]$P < 0.05$ vs BRS ≥5.5 ms/mm Hg. [b]$P < 0.01$ vs BRS ≥5.5 ms/mm Hg.

ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; BRS = baroreflex sensitivity; CPET = cardiopulmonary exercise test; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; EOV = exertional oscillatory ventilation; Hb = hemoglobin; ICD = implantable cardioverter-defibrillator; LAD = left atrial diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; RVD = right ventricular diameter; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion; VE/VCO_2 = ventilation-to-carbon dioxide output; VO_2 = oxygen consumption.

medical records or telephone interviews with patients, their relatives, or general practitioners.

As the primary outcome, a combination of cardiac death (including HF progression, myocardial infarction, and sudden cardiac death), life-threatening ventricular tachyarrhythmias requiring appropriate implantable cardioverter-defibrillator (ICD) shock, and first hospitalization for acute HF was considered. As secondary endpoints, cardiac death, first HF hospitalization, and a combination of cardiac death and appropriate ICD shock were also individually considered.

STATISTICAL ANALYSIS. Statistical analysis was performed by using SPSS (version 25.0, 2017, IBM Statistics), and R software (version 3.4.0), and a 2-tailed $P \leq 0.05$ was considered significant.

Quantitative values were presented as mean ± SD, or median (IQR) (for values with non-normal distribution), whereas qualitative values were presented as numbers or percentages. Differences among groups were evaluated through the unpaired Student's *t*-test or Mann-Whitney U test, analysis of variance, or Kruskal-Wallis with Bonferroni post hoc correction, when appropriate. Discrete variables were compared by the chi square test with Yates' correction or the Fisher exact test.

The optimal cutoff values of CRS and BRS for risk prediction were identified through the maximally selected log-rank statistics, and Kaplan-Meier method was performed to build the survival curves.[24] The prognostic role of BRS and CRS for the primary and secondary endpoints was tested in a multivariable regression model adjusted for other acknowledged predictors of events in HF (namely, patients' age, ischemic HF etiology, LVEF, values of peak VO_2/kg and of VE/VCO_2 slope, estimated glomerular filtration rate [eGFR], and plasma N-terminal pro-brain natriuretic peptide [NT-proBNP]).

The Fine-Gray model for competing-risk analysis was used, considering overall mortality as a competing event for HF hospitalization and noncardiac mortality as a competing event for cardiac mortality. The incremental value for event prediction of BRS and CRS when added to the multivariable model was evaluated through the difference (Δ) in Harrell's C-statistic.

RESULTS

Of 612 patients originally screened, 425 patients were included in the study (93 were excluded for recent acute heart failure/acute coronary syndrome, 36 for recent CRT implantation, 58 for being on therapies potentially influencing ventilation) as described in Supplemental Table 1.

Patients (aged 65 ± 12 years) had a moderate-severe left ventricular (LV) systolic dysfunction

(LVEF: 32% [IQR: 25%-38%], 42% of ischemic etiology), with 77% having HF with reduced ejection fraction (HFrEF) and 23% HF with mildly reduced ejection fraction.

Despite optimal neurohormonal treatment (94% on beta blockers, 94% on either angiotensin converting-enzyme inhibitors/angiotensin receptor blockers [ACEI/ARBs] or angiotensin receptor-neprilysin inhibitors, and 74% on mineralocorticoid receptor antagonists) and device treatment (20%/18% with ICD/CRT), 91%, 34%, 35%, and 17% of patients had plasma level of NT-proBNP, norepinephrine, direct renin, and aldosterone above the upper reference limit (>157 ng/L, >500 ng/L, >39.9 mU/L, and >190 ng/L), respectively.

CARDIORESPIRATORY MONITORING AND BAROREFLEX AND CHEMOREFLEX ASSESSMENTS. The results of the 24-hour ECG recording and cardiorespiratory recording are shown in Supplemental Table 2.

At 24-hour ECG recording, 50% and 20% of patients had reduced and severely reduced HRV (SD of the normal-normal RR intervals <100 ms and <70 ms), respectively, whereas 50% of patients showed nonsustained ventricular tachycardia.

By using an apnea-hypopnea index (AHI) ≥15 events/h cutpoint (apneas of moderate to severe entity), obstructive sleep apneas (>50% of events being obstructive) were found in 15% of patients at nighttime, whereas central apneas (CAs, >50% of events being central) were observed in 49% at nighttime and in 27% at daytime.

BRS was calculated in 267 patients (76 were excluded for atrial fibrillation, 53 for ventricular pacing, 23 for frequent ectopic beats, and 6 for suboptimal quality of either the ECG or blood pressure signals). CRS was calculated in 369 patients (56 excluded for either intolerance or suboptimal quality of the maneuver). BRS and CRS were both available in 211 patients.

BRS was reduced (<5.5 ms/mm Hg) in 96 of 267 patients (36%).[21] Seventy-four of 369 patients (20%) had a combined increase in CRS to both hypoxia (HVR >0.77 L/min/%SaO_2) and to hypercapnia (HCVR >0.79 L/min/mm Hg), whereas an isolated increase in either CRS to hypoxia or hypercapnia was found in 32 and 158 patients (9% and 43%), respectively.[23]

The characteristics of the population according to BRS are shown in Tables 1 and 2. Patients with BRS <5.5 ms/mm Hg showed a higher body mass index, an increased right ventricular dimension, a reduced tricuspid annular plane systolic excursion, a worse functional capacity at CPET, and a reduced HRV (Figure 1A), as well as a trend toward a higher prevalence of CA.

TABLE 2 24-Hour ECG and Cardiorespiratory Recording and CRS of Patients According to BRS

	All Patients (N = 267)	BRS ≥5.5 ms/mm Hg (n = 171, 64%)	BRS <5.5 ms/mm Hg (n = 96, 36%)
24-h ECG			
Mean heart rate, beats/min	68 ± 6	68 ± 8	68 ± 5
SDNN, ms	96 (78-122)	100 (83-125)	89 (72-117)[a]
SDANN, ms	77 (60-96)	77 (63-99)	72 (56-91)[a]
pNN50, %	4 (2-14)	6 (2-15)	3 (2-10)
rMSSd, ms	34 (25-54)	37 (25-56)	33 (25-49)
NSVT	122 (46)	84 (49)	38 (39)
24-h cardiorespiratory			
Daytime AHI, events/h	8 (2-15)	6 (2-15)	10 (4-16)
Nighttime AHI, events/h	19 (8-33)	18 (6-33)	21 (13-37)
24-h AHI, events/h	12 (5-22)	12 (4-22)	14 (9-22)
Daytime CAI ≥15 events/h	33 (13)	22 (13)	11 (12)
Nighttime CAI ≥15 events/h	67 (25)	44 (26)	23 (24)
Nighttime OAI ≥15 events/h	20 (7)	12 (7)	8 (8)
T-90, min	4 (1-11)	4 (1-10)	5 (1-15)
Chemoreflex sensitivity			
Baseline $etCO_2$, mm Hg	32 (28-35)	32 (28-35)	32 (28-37)
Baseline VE, L/min	12 (10-15)	12 (11-15)	12 (10-15)
HVR-slope, L/min/%SaO_2	0.5 (0.3-0.9)	0.5 (0.3-0.8)	0.5 (0.3-0.9)
HCVR-slope, L/min/mm Hg	1.0 (0.7-1.4)	0.9 (0.6-1.4)	1.0 (0.6-1.4)
HVR >0.77 L/min/%SaO_2	23 (9)	17 (10)	6 (6)
HCVR >0.79 L/min/mm Hg	94 (35)	61 (36)	33 (34)
HVR >0.77 L/min/%SaO_2 + HCVR >0.79 L/min/mm Hg	38 (14)	21 (12)	17 (18)

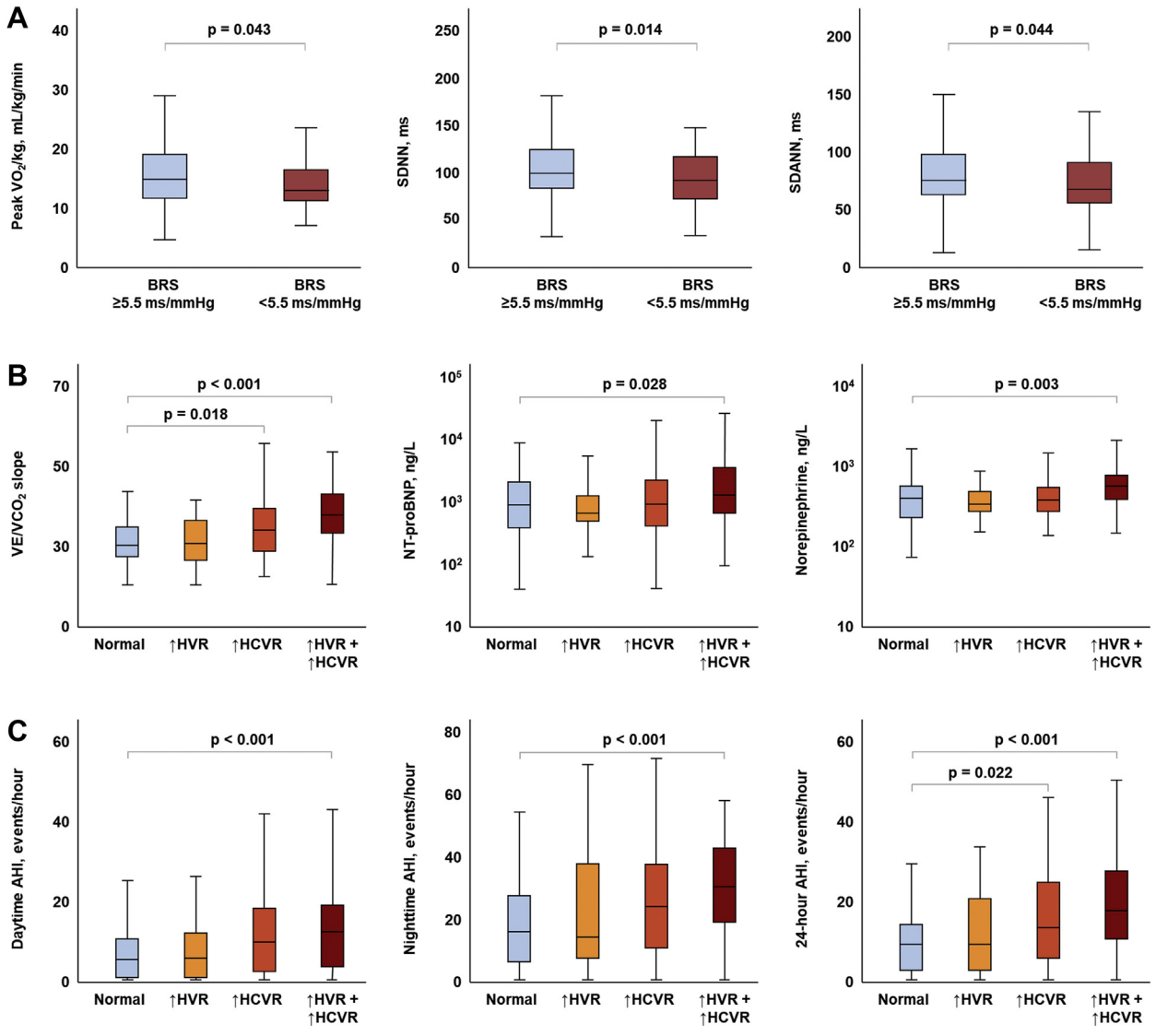
Values are mean ± SD, median (IQR), or n (%). [a]$P < 0.05$ vs BRS ≥5.5 ms/mm Hg.

AHI = apnea-hypopnea index; CAI = central apnea index; CRS = chemoreflex sensitivity; ECG = electrocardiogram; $etCO_2$ = end-tidal carbon dioxide; HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response; NSVT = nonsustained ventricular tachycardia; OAI = obstructive sleep apnea index; pNN50 = the number of pairs of successive normal-to-normal intervals that differ more than 50 ms divided by the total number of normal-to-normal intervals; rMSSd = root mean square of the successive difference between normal heartbeats; SaO_2 = saturated oxygen; SDANN = standard deviation of the average normal-to-normal intervals for each of the 5-minute segments; SDNN = standard deviation of normal-to-normal intervals; T-90 = percentage of time asleep with SaO_2 <90%; VE = minute ventilation; other abbreviation as in Table 1.

The characteristics of the population according to CRS are shown in Tables 3 and 4. Patients with a combined increase in HVR and HCVR were more frequently male and showed a worse renal function and LV diastolic function, a higher systolic pulmonary pressure, a reduced ventilatory efficiency on effort (higher VE/VCO_2 slope), higher plasma levels of NT-proBNP and norepinephrine (Figure 1B), and higher prevalence of CA, as expressed by the AHI (Figure 1C) and the CA index (CAI), both at daytime and at nighttime.

Patients were then stratified depending on the status of both BRS and CRS in: 1) patients with both normal (higher) BRS and (lower) CRS (n = 112 of 211, 53%); 2) patients with either abnormal BRS or CRS (n = 82 of 211, 39%); and 3) patients with both

FIGURE 1 Comparison of Clinical and Instrumental Parameters According to Baroreflex and Chemoreflex Sensitivity



(A) Patients with BRS (ie, <5.5 ms/mm Hg) showed lower exercise tolerance and heart rate variability. Patients with increased HVR (ie, >0.77 L/min/%SaO_2) and increased HVCR (ie, >0.79 L/min/mm Hg) showed lower ventilatory efficiency on effort, higher neurohormonal activation **(B),** and ventilatory instability across the 24 hours **(C).** AHI = apnea-hypopnea index; BRS = baroreflex sensitivity; HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SaO_2 = oxygen saturation; SDANN = standard deviation of the average normal-to-normal intervals for each of the 5 minutes segments; SDNN = standard deviation of normal-to-normal intervals; VE/VCO_2 = ventilation-to-carbon dioxide output; VO_2 = oxygen consumption.

abnormal BRS and CRS (n = 17 of 211, 8%) (Supplemental Tables 3 and 4). Compared to patients with normal BRS and CRS, patients with both abnormal reflexes had worse LV and right ventricular systolic function, lower exercise tolerance and ventilatory efficiency, higher plasma norepinephrine level (Supplemental Figure 1A), and higher AHI (Supplemental Figure 1B) and CAI (Supplemental Figure 1C) across the 24-hour period.

BRS and CRS did not differ between patients with HFrEF and HF with mildly reduced ejection fraction (Supplemental Table 5) (all $P > 0.05$).

SURVIVAL ANALYSIS. Over a 50-month median follow-up (24 to 94 months), 119 patients died: 69 patients for cardiovascular causes (59 from HF progression, 7 from sudden cardiac death, and 3 from acute myocardial infarction), and 50 patients for noncardiovascular causes. There were 29

TABLE 3 Clinical Features of Patients According to CRS

	All Patients (N = 369)	Normal CRS (n = 105, 28%)	Isolated Increased HVR[a] (n = 32, 9%)	Isolated Increased HCVR[a] (n = 158, 43%)	Increased HVR + Increased HCVR (n = 74, 20%)
Clinical					
Age, y	65 ± 12	63 ± 14	62 ± 12	65 ± 10	67 ± 12
Males	303 (82)	75 (71)	29 (91)[b]	128 (81)	71 (96)[c]
BMI, kg/m^2	27 ± 5	27 ± 4	28 ± 5	27 ± 5	27 ± 4
Ischemic etiology	157 (43)	34 (32)	14 (44)	74 (47)[b]	35 (47)
NYHA functional class III-IV	64 (17)	17 (16)	2 (6)	30 (19)	15 (20)
Atrial fibrillation	76 (21)	25 (24)	5 (16)	28 (18)	18 (24)
Heart rate, beats/min	68 ± 10	69 ± 11	68 ± 9	68 ± 10	68 ± 10
Systolic blood pressure, mm Hg	118 ± 25	116 ± 25	120 ± 23	117 ± 26	121 ± 21
Comorbidities					
Hypertension	191 (52)	56 (53)	13 (41)	85 (54)	37 (50)
Dyslipidemia	178 (48)	44 (42)	17 (54)	79 (50)	38 (52)
Diabetes	56 (15)	19 (18)	6 (18)	17 (11)	14 (19)
COPD	196 (53)	56 (53)	17 (53)	84 (53)	39 (53)
Hb, g/dL	13.4 ± 1.7	13.2 ± 1.7	13.5 ± 1.7	13.3 ± 1.7	13.9 ± 1.7
eGFR, mL/min/1.73 m^2	77 ± 27	84 ± 30	82 ± 27	74 ± 26[b]	70 ± 24[b]
Echocardiography					
LAD, mm	46 ± 7	44 ± 7	46 ± 7	46 ± 7	47 ± 7
Severe MR	60 (16)	17 (16)	5 (16)	20 (13)	18 (24)
Diastolic dysfunction III	110 (30)	19 (18)	9 (27)	46 (29)	36 (48)[c]
LVEDD, mm	62 (57-67)	62 (56-66)	61 (56-67)	62 (57-67)	64 (58-68)
LVESD, mm	52 (45-58)	51 (45-56)	50 (45-58)	52 (46-58)	53 (46-59)
LVEF, %	31 (25-38)	33 (27-39)	33 (25-38)	31 (25-38)	30 (25-35)
RVD, mm	27 (25-30)	27 (25-30)	28 (25-30)	27 (25-30)	28 (26-32)
TAPSE, mm	18 (15-22)	19 (15-23)	20 (16-24)	18 (16-21)	17 (13-20)
sPAP, mm Hg	39 (30-48)	33 (29-45)	40 (28-47)	38 (31-47)	46 (35-55)[b]
CPET parameters					
Workload, W	80 (60-108)	85 (60-119)	101 (70-123)	80 (62-99)	80 (60-95)
Peak VO_2/kg, mL/kg/min	14 (11-17)	14 (12-18)	14 (11-17)	14 (11-16)	13 (11-16)
VE/VCO_2 slope	34 (29-40)	31 (28-35)	31 (27-38)	34 (29-40)[b]	38 (34-45)[c]
EOV	102 (28)	25 (24)	2 (5)[b]	47 (30)	28 (38)
Neurohormonal activation					
NT-proBNP, ng/L	1,029 (482-2,367)	1,022 (408-2,159)	676 (511-1,350)	1,021 (422-2,244)	1,298 (674-3,625)[b]
Norepinephrine, ng/L	396 (272-571)	390 (226-530)	348 (257-468)	365 (269-525)	511 (358-743)[c]
Aldosterone, ng/L	99 (61-165)	100 (61-179)	117 (56-157)	95 (59-156)	99 (64-156)
Treatment					
Beta-blockers	350 (95)	100 (95)	29 (91)	150 (95)	71 (96)
ACEI/ARBs	329 (89)	93 (89)	32 (100)	139 (88)	65 (88)
ARNI	16 (4)	2 (2)	0 (0)	10 (6)	4 (5)
MRA	284 (77)	80 (76)	24 (75)	124 (79)	56 (76)
Furosemide	263 (71)	73 (70)	24 (75)	108 (68)	58 (78)
ICD/CRT	76/69 (21/19)	15/16 (14/15)	5/4 (16/13)	35/34 (22/22)	21/15 (28/20)

Values are mean ± SD, n (%), or median (IQR). [a]Increased HVR and Increased HCVR refer to values >0.77 L/min/%SaO_2 and >0.79 L/min/mm Hg, respectively. [b]$P < 0.05$ vs "normal" CRS. [c]$P < 0.01$ vs "normal" CRS.

Abbreviations as in Tables 1 and 2.

appropriate ICD shocks, and 130 patients were hospitalized for HF.

The calculated optimal prognostic cutoff of BRS was 4.9 ms/mm Hg, which improved the prediction of cardiac death or ICD shock when compared to the previous cutoff of 3.0 ms/mm Hg (Δ in C-statistic 0.05; $P = 0.033$). The optimal prognostic cutoffs of HVR and HCVR were 0.72 L/min/%SaO_2 and 0.74 L/min/mm Hg.

At Kaplan-Meier analysis, patients with BRS ≤4.9 ms/mm Hg were at higher risk considering both the primary endpoint ($P = 0.001$) (Figure 2A) and the secondary endpoints of cardiac death plus appropriate ICD shock ($P < 0.001$) (Figure 2B), cardiac death

TABLE 4 24-Hour ECG and Cardiorespiratory Recording and BRS of Patients According to CRS

	All Patients (N = 369)	Normal CRS (n = 105, 28%)	Isolated Increased HVR[a] (n = 32, 9%)	Isolated Increased HCVR[a] (n = 158, 43%)	Increased HVR + Increased HCVR (n = 74, 20%)
24-h ECG					
Mean heart rate, beats/min	68 ± 6	69 ± 7	68 ± 6	67 ± 7	67 ± 65
SDNN, ms	100 (76-137)	115 (80-171)	100 (77-192)	95 (71-126)[b]	103 (72-156)
SDANN, ms	72 (53-96)	82 (58-100)	72 (60-98)	72 (47-94)	65 (53-91)
pNN50, %	7 (2-25)	11 (2-43)	6 (2-37)	5 (2-15)[b]	8 (3-34)
rMSSd, ms	42 (27-91)	49 (30-132)	35 (21-115)	41 (26-63)	46 (29-121)
NSVT, n	182 (49)	54 (51)	16 (50)	75 (48)	37 (52)
24-h cardiorespiratory					
Daytime AHI, events/h	8 (2-17)	6 (1-11)	7 (1-13)	10 (3-19)	13 (4-20)[b]
Nighttime AHI, events/h	20 (8-33)	15 (6-25)	17 (7-35)	22 (10-34)	28 (17-39)[c]
24-h AHI, events/h	13 (5-23)	10 (3-15)	10 (3-21)	14 (6-25)[b]	18 (11-30)[c]
Daytime CAI ≥15 events/h	45 (12)	6 (6)	2 (7)	21 (13)	16 (22)[b]
Nighttime CAI ≥15 events/h	103 (28)	14 (13)	9 (29)	40 (25)	40 (54)[c]
Nighttime OAI ≥15 events/h	21 (6)	5 (5)	1 (4)	13 (8)	2 (3)
Maximum apnea length, s	40 (26-55)	38 (26-54)	41 (17-47)	39 (26-52)	45 (33-61)
Maximum desaturation, %	9 (6-14)	9 (6-13)	9 (7-18)	9 (7-13)	10 (7-14)
T-90, min	5 (1-12)	4 (1-10)	7 (2-13)	5 (1-12)	6 (0-16)
BRS					
BRS, ms/mm Hg	7 (4-11)	7 (4-13)	7 (5-14)	6 (4-9)	7 (4-11)
BRS <5.5 ms/mm Hg	137 (37)	41 (39)	8 (26)	55 (35)	33 (45)

Values are mean ± SD, median (IQR), or n (%). [a]Increased HVR and increased HCVR refer to values >0.77 L/min/%SaO_2 and >0.79 L/min/mm Hg, respectively. [b]$P < 0.05$ vs "normal" CRS. [c]$P < 0.01$ vs "normal" CRS.

Abbreviations as in Tables 1 and 2.

($P < 0.001$) (Figure 2C), and HF hospitalization ($P = 0.043$) (Figure 2D).

Compared to patients with normal CRS and with an isolated increase in CRS, patients with a HVR >0.72 L/min/%SaO2 and HCVR >0.74 L/min/mm Hg were at higher risk both for the primary endpoint ($P < 0.001$) (Figure 3A) and for the secondary endpoints of cardiac death plus appropriate ICD shock ($P < 0.001$) (Figure 3B), cardiac death ($P < 0.001$) (Figure 3C), and HF hospitalization ($P < 0.001$) (Figure 3D).

The presence of a concomitant alteration of BRS/CRS held a negative prognostic significance compared to normal BRS/CRS or the condition of only one dysfunctional reflex, both for the primary endpoint ($P < 0.001$) (Figure 4A) and for each secondary endpoint (cardiac death plus appropriate ICD shock; $P < 0.001$; cardiac death; $P < 0.001$; and HF hospitalization; $P = 0.001$) (Figures 4B to 4D).

Finally, similar effects for decreased BRS, combined increased in CRS, and abnormal BRS/CRS were observed when considering all-cause mortality as endpoint (Figure 5).

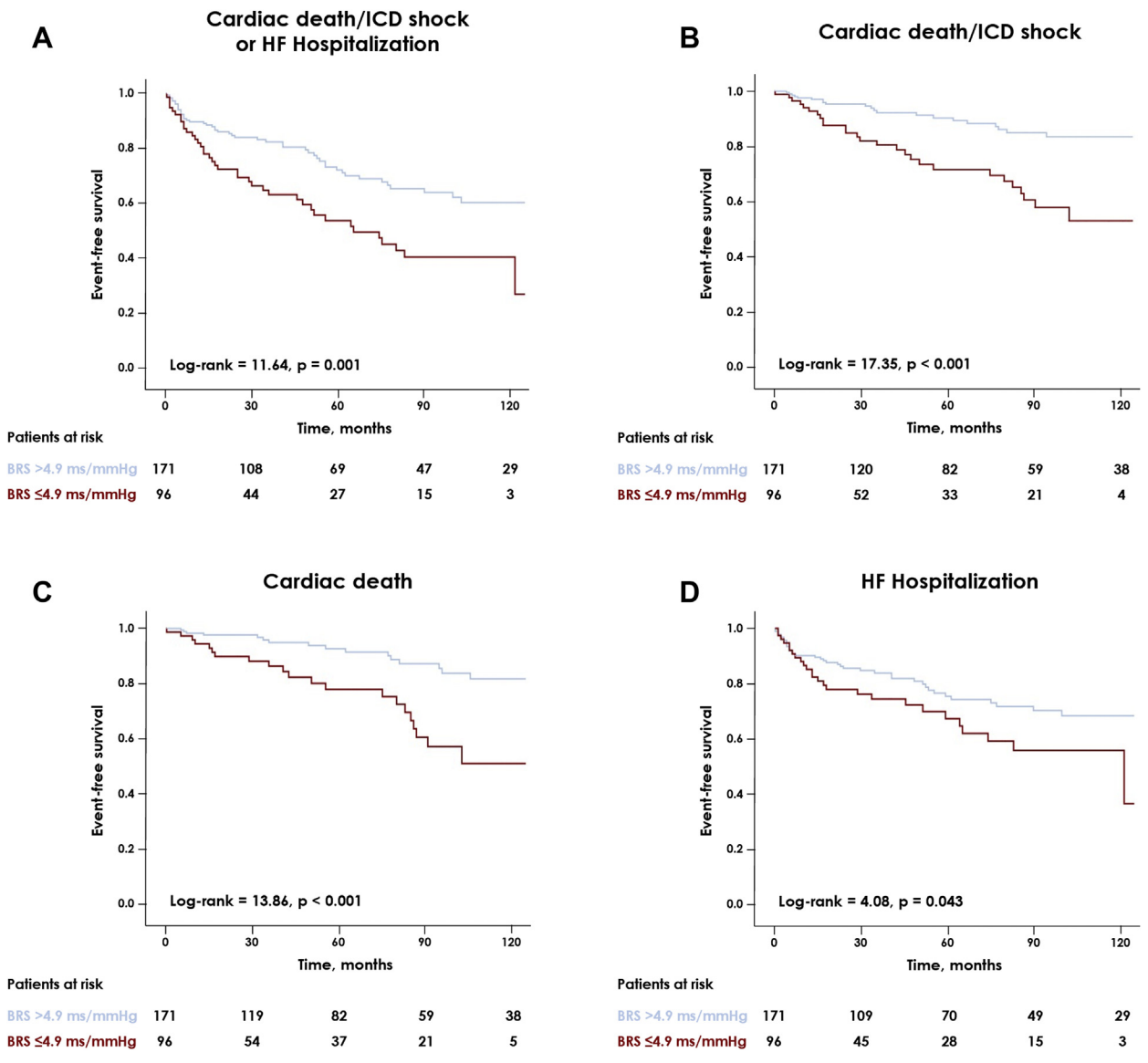
At the competing-risk regression analysis (Table 5), only reduced BRS ($P = 0.005$) and combined increased CRS ($P = 0.007$) were independent predictors of the primary endpoint. As for the secondary endpoints, combined increase in CRS was the only independent predictor of HF hospitalization ($P = 0.027$), whereas reduced BRS was the only independent predictor of cardiac death ($P = 0.009$). Abnormal BRS ($P = 0.001$) and CRS ($P = 0.019$), together with reduced LVEF ($P = 0.013$) and eGFR ($P = 0.022$) were predictors of the combined endpoint of cardiac death plus appropriate ICD shock.

Adding both abnormal BRS and abnormal CRS to the multivariate model including patients' age, ischemic HF etiology, LVEF, values of peak VO_2/kg and of VE/VCO_2 slope, eGFR, and plasma NT-proBNP significantly improved event prediction for the primary endpoint (Δ in C-statistics 0.08; $P = 0.03$) and for the secondary endpoint of cardiac death plus ICD shock (Δ in C-statistics 0.13; $P = 0.004$). Abnormal BRS improved the prediction of cardiac death (Δ in C-statistics 0.08; $P = 0.05$), and abnormal CRS improved the prediction of HF hospitalization (Δ in C-statistics 0.09; $P = 0.01$).

DISCUSSION

This is the first study in which both BRS and CRS have been simultaneously evaluated in a large cohort of patients with chronic HF (novel findings of the study are summarized in Table 6). Despite modern treatment, 36% of patients showed a

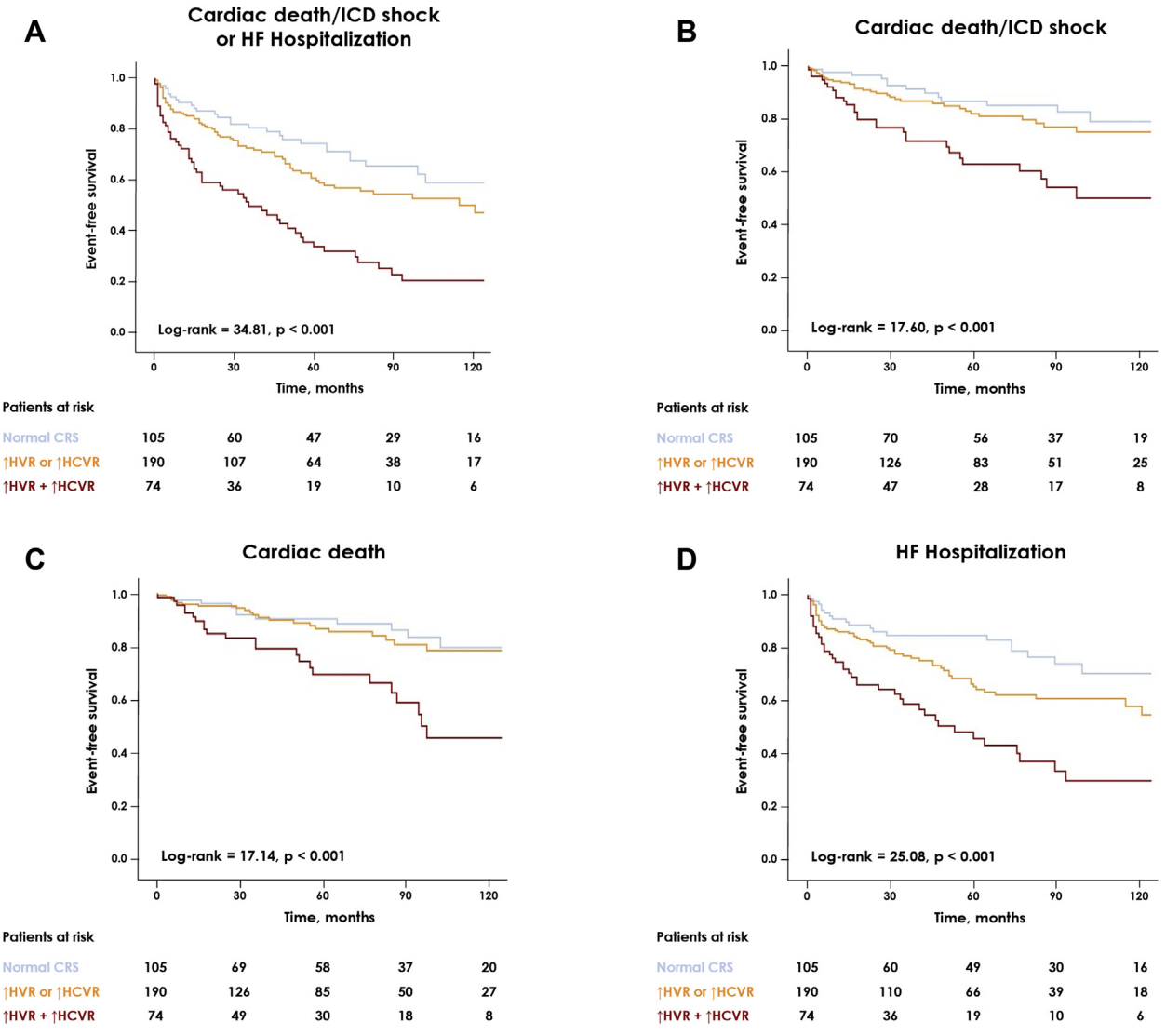
FIGURE 2 Kaplan-Meier Curves for the Primary and Secondary Endpoints According to BRS



Patients with baroreflex sensitivity (BRS) ≤4.9 ms/mm Hg were at higher risk for the primary endpoint **(A)** and for each of the secondary endpoints **(B to D).** HF = heart failure; ICD = implantable cardioverter-defibrillator.

decreased BRS and 20% had an increased CRS to both hypoxia and hypercapnia. Patients with decreased BRS had a lower HRV and functional capacity, whereas those with a combined increase in CRS (hypoxia and hypercapnia) showed higher adrenergic activation and CA across the 24-hour period. Both abnormal BRS and CRS resulted independent predictors of the primary endpoint (cardiac death, appropriate ICD shocks, and HF hospitalization), and abnormalities of both BRS and CRS, present in 8% of patients, were associated with the worst outcome (5-year event-free survival <10%) (**Central Illustration**). Focusing on secondary outcomes, reduced BRS was the only independent predictor of cardiac death and increased CRS of HF hospitalization, whereas reduced BRS and increased CRS both predicted the endpoint of cardiac death or ICD shock. Notably, by adding BRS and CRS assessment to standard prognostic markers in HF, the precision of the model improved for each endpoint.

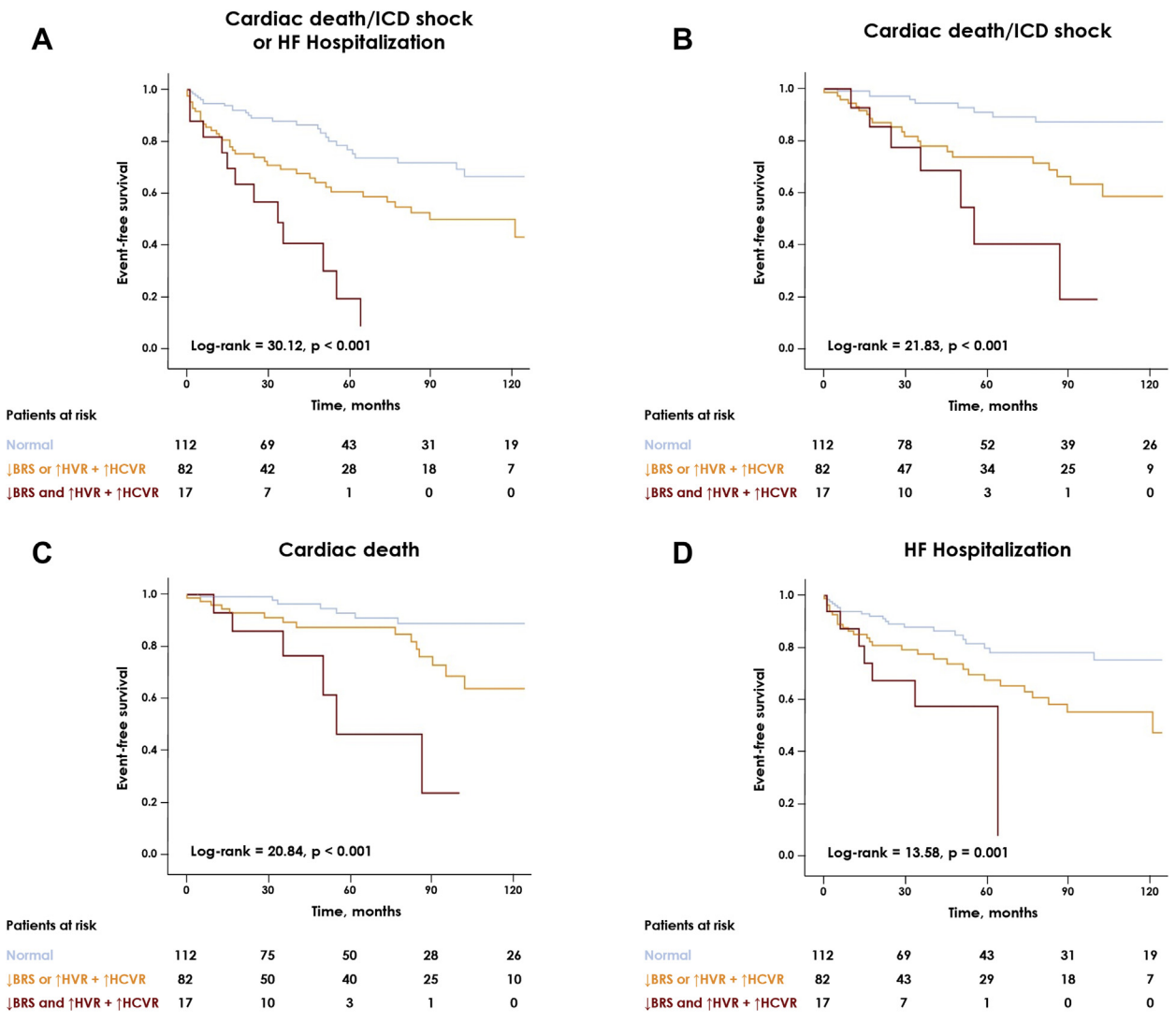
FIGURE 3 Kaplan-Meier Curves for the Primary and Secondary Endpoints According to CRS



Patients with increased HVR (ie, >0.72 L/min/%SaO_2) and increased HVCR (ie, >0.74 L/min/mm Hg) were at higher risk for the primary endpoint **(A)** and for each of the secondary endpoints **(B to D)** compared to both patients with normal chemoreflex sensitivity (CRS) and with isolated increased HVR or increased HCVR. Abbreviations as in Figures 1 and 2.

The study findings support the various lines of research in the field of feedback modulation.[6-10,25,26] Indeed, feedback resetting is usually considered a cornerstone of the neurohormonal model and the pathophysiology of HF, especially of HFrEF.[26-28] Nonetheless, the incorporation of abnormal BRS and CRS are mainly based on animal studies, in which the neurohormonal treatment is usually not administered, or on small studies, partly performed before the use of beta blockers or CRT.[5,11,13] A few studies have shown beneficial effects of beta blockers on BRS, and carvedilol on CRS.[27,29,30] ACEI/ARBs seem to improve BRS.[31] Although the effect of sacubitril-valsartan on BRS/CRS is unknown, its action on CRS may be inferred considering the beneficial effect on CA in HF.[32] Finally, CRT seems to decrease CRS.[33] Some recent studies have challenged the clinical significance of BRS and CRS in patients with HF and modern treatment.[15,16] The smaller population recruited, the shorter follow-up (<5 years), and the lower number of events (<35 events) in those studies may justify the discrepancy with our findings.[15,16]

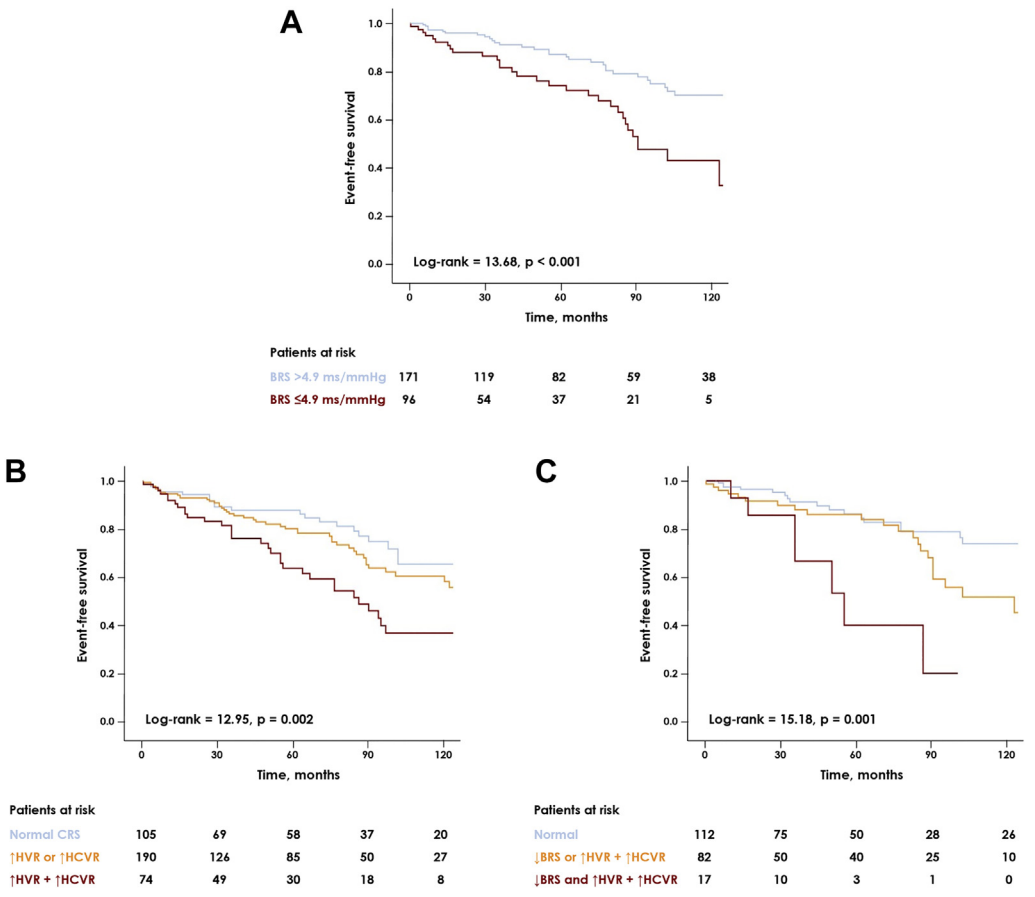
FIGURE 4 Kaplan-Meier Curves for the Primary and Secondary Endpoints According to BRS and CRS



Patients with decreased BRS (ie, ≤4.9 ms/mm Hg), increased HVR (ie, >0.72 L/min/%SaO_2), and increased HVCR (ie, >0.74 L/min/mm Hg) were at higher risk for the primary endpoint **(A)** and for each of the secondary endpoints **(B to D)** compared to both patients with "normal" BRS/CRS and with isolated abnormal reflex. Abbreviations as in Figures 1 and 2.

Likewise, the choice of studying CRS in hyperoxia, thus abolishing peripheral chemoreceptors, may have provided unphysiological measures considering that peripheral and central chemoreceptor are intertwined and interdependent.[15,34] Indeed, a combined increase of CRS to both hypoxia and hypercapnia identified the subset at higher risk of events in our study, confirming previous reports.[23] The mechanisms behind sensitization of either peripheral or central chemoreceptors in HF are only partly known thanks to animal models.[35] However, if the 2 groups of receptors are overactive, the likelihood of developing CA was higher in both animals and humans with HF.[23,36] CRS seems unrelated to apnea duration and desaturation severity, which might be influenced by other factors than CRS, such as the plant gain and circulatory delay.[22] Chemoreceptors are known to have also an adrenergic output;[27,37] thus, in case of combined increased of CRS and unstable breathing, the human body may be challenged by sympathetic surges during phases of hypoxia/hypercapnia. This seems of particular interest after the evidence that the surgically or pharmacological modulation of the chemoreflex system may have

FIGURE 5 Kaplan-Meier Curves for All-Cause Mortality According to BRS and CRS



(A) Patients with decreased BRS (ie, ≤4.9 ms/mm Hg) were at higher risk of all-cause mortality. **(B)** Patients with increased HVR (ie, >0.72 L/min/%SaO_2), and increased HVCR (ie, >0.74 L/min/mm Hg) were at higher risk of all-cause mortality than patients with either normal CRS or isolated increased HVR or increased HCVR. **(C)** Patients with decreased BRS, increased HVR, and increased HCVR were at higher risk of all-cause mortality compared to both patients with normal BRS/CRS and those with isolated abnormal reflex. Abbreviations as in Figures 1 and 2.

TABLE 5 Multivariable Competing Risk Regression Analysis for the Primary and Secondary Endpoints in the Study Population

	Cardiac Death/ICD Shock or HF Hospitalization			Cardiac Death/ICD Shock			Cardiac Death			HF Hospitalization		
	SHR	95% CI	*P* Value	SHR	95% CI	*P* Value	SHR	95% CI	*P* Value	SHR	95% CI	*P* Value
Age, y	0.99	0.96-1.01	0.610	1.01	0.97-1.07	0.460	1.03	0.96-1.10	0.458	0.99	0.95-1.02	0.377
Ischemic etiology	0.92	0.45-1.86	0.431	0.35	0.12-1.07	0.064	0.26	0.06-1.18	0.080	1.27	0.58-2.81	0.547
LVEF, %	0.98	0.94-1.01	0.172	0.94	0.89-0.98	0.013	0.96	0.90-1.02	0.172	0.98	0.94-1.02	0.302
Peak VO_2/kg, mL/kg/min	0.91	0.83-1.01	0.164	0.99	0.88-1.08	0.684	0.89	0.76-1.05	0.159	0.92	0.83-1.01	0.080
VE/VCO_2 slope	0.98	0.92-1.02	0.609	0.99	0.92-1.05	0.719	1.02	0.95-1.12	0.479	0.94	0.92-1.08	0.072
eGFR, mL/min/1.73 m^2	0.72	0.31-1.73	0.635	0.31	0.12-0.85	0.022	0.28	0.10-1.02	0.055	0.72	0.24-2.22	0.571
NT-proBNP, ng/L	1.07	0.82-1.42	0.529	0.93	0.65-1.32	0.681	0.77	0.49-1.20	0.261	1.13	0.81-1.56	0.470
BRS <4.9 ms/mm Hg	2.76	1.36-5.63	0.005	5.54	2.03-14.9	0.001	6.12	1.58-23.6	0.009	1.45	0.64-3.26	0.374
HVR >0.72 L/min/%SaO_2 and HCVR >0.74 L/min/mm Hg	2.91	1.34-6.31	0.007	4.39	1.29-15.1	0.019	6.79	0.92-47.0	0.052	2.53	1.01-5.85	0.027

HF = heart failure; SHR = subdistribution hazard ratio; other abbreviations as in Tables 1 and 2.

positive effects CA and sympathetic overactivity in HF.[9,10,37]

The assessment of BRS and CRS provides complementary and only partially overlapping information. BRS evaluation, assessed in the current study using an easy and time-saving technique, returns information about HRV, functional capacity, and risk of cardiac mortality, as observed in patients after myocardial infarction, and in HF patients, both in the pre- and the post-beta-blockade era.[12,14,20,21,38] Unfortunately, BRS is not feasible in patients in atrial fibrillation, a subset of HF patients per se at higher risk.[39] However, the evaluation of CRS, feasible also for patients in atrial fibrillation, seems to provide information about the risk of ventilation instability (CA) throughout the 24-hour period, and ventilatory inefficiency during exercise.[19,22,23] Considering that worsening dyspnea is one of the leading symptoms causing HF-related hospitalizations and that ascending pathways from the chemoreflex network are activating subcortical and cortical areas controlling aversive reaction to breathlessness, the strong link between HF hospitalization and altered CRS seems biologically plausible.[40]

The main effort to translate our findings in a real clinical scenario should be directed toward the development of easy tests for visceral reflex assessment (as the ones used in our study), with a high degree of automation and good reproducibility. Furthermore, considering that each reflex has an afferent arm, an integrative center and an efferent arm (with pre and postganglionic neurons), a stronger effort should be made in the future to identify which component is impaired, and focus our therapeutic efforts on the right target to maximize impact and minimize risk.[41]

STUDY LIMITATIONS. The monocentric design of the study and the lack of standardized procedure to assess BRS and CRS worldwide may limit the external applicability of the results. However, the clinical significance of BRS and CRS documented in this study, together with the low cost and relatively technical easiness of the test we used (no need of drug and gas mixtures), should encourage a wider availability and application of these tests in the clinical arena.

Although we recruited a larger population compared with prior studies, some patient categories may have been underrepresented (BRS was unmeasurable in ~30% of patients with atrial fibrillation or atrial paced rhythm; and was CRS unmeasurable in <10% of patients due to intolerance to the maneuver). Similar to other studies conducted in our geographic area, women represented a minority of the HF population, and all patients recruited were Caucasian; thus, the possible influence of sex and ethnicity on BRS and CRS remains to be clarified.

Some imprecisions in HVR assessment (relationship between ventilation and SaO_2) may derive from potential influences of pH on the oxygen desaturation curve, and some underestimation of obstructive sleep apnea may have occurred in our study based on a type-3 home-portable system; but this risk was minimized by the manual scoring of events by board-certified sleep technicians and the use of obstructive sleep apnea index rather than AHI to correct for misclassification of hypopneas.[42,43]

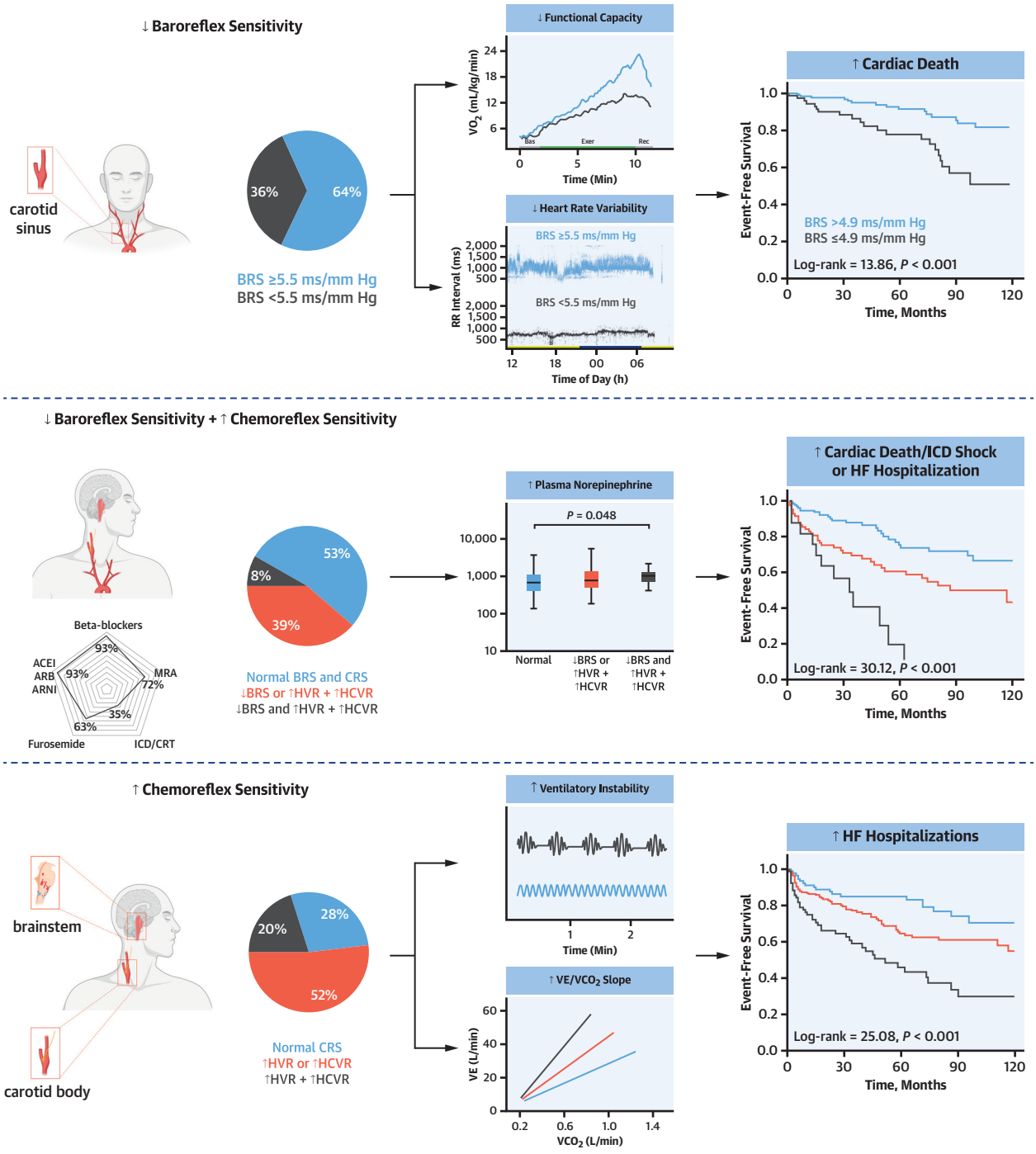
Although most of the patients were on optimal anti-neurohormonal treatment at the time of enrollment (Supplemental Table 1), with no significant differences across BRS and CRS subgroups (**Tables 1 and 3,** Supplemental Table 3), as well as between patients who met vs those who did not meet the study endpoints (Supplemental Table 6), details about the specific prescribed molecules and dosages were not retrieved. Moreover, similar to nearly all studies of this kind, the possible therapeutic changes secondary to clinical variations or guidelines' updates were not accounted for during follow-up. Therefore, the potential effects of a novel class of HF drugs (eg, sodium-glucose cotransporter-2 inhibitors) on BRS and CRS remain to be evaluated. Although no data on patients' adherence (including medication, lifestyle, diet, and physical activity) have been collected during the study course, this has been periodically reassessed in our outpatient clinics for most patients (>80%) every 6 months to 1 year according to clinical severity, and drugs were up titrated to the maximum tolerated dose according to guidelines.

TABLE 6 Novel Findings

	BRS	CRS
Methodological novelties	• A novel and simple method, BRS-SD has been clinically validated in large cohort of HF patients • BRS-SD shows moderate consistency at repeated measures	• CRS assessment by rebreathing technique shows good consistency at repeated measures
Clinical novelties	• BRS as assessed by BRS-SD was an independent predictor of cardiac mortality and arrhythmias in HF	• CRS beyond predicting cardiac mortality and arrhythmias also independently provide information on HF hospitalization
Therapeutic implications	• BRS and CRS assessment with simple and unexpensive methods should be used to select patients undergoing targeted approaches on visceral reflexes to maximize efficacy and reduce the risk of harm in patients with HF	

Abbreviations as in Tables 1, 2, and 5.

CENTRAL ILLUSTRATION Abnormal Baroreflex and Chemoreflex Sensitivities in Patients With Chronic Heart Failure



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Abnormal baroreflex (BRS) and chemoreflex sensitivity (CRS) may be frequently observed in patients with chronic heart failure (HF) on modern therapies and both contribute to autonomic dysfunction. Abnormal BRS is also associated with functional impairment and a significant increase in the risk of cardiac death, whereas abnormal CRS with ventilatory instability and a significant increase in the risk of HF hospitalization. When both reflexes are abnormal, the risk of adverse events is very high with less than 10% of patients being free of events over 60 months of follow-up. ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; Bas = baseline; CRT = cardiac resynchronization therapy; Exer = exercise; HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; Rec = recovery; RR = time elapsed between two successive R-waves of the QRS signal on the electrocardiogram; VE/VCO_2 = ventilation-to-carbon dioxide output; VO_2 = oxygen consumption.

BRS and CRS, as well as other variables, were evaluated only at enrollment in most patients; thus, some individuals might have crossed over from "normal" to "altered" BRS/CRS during follow-up. However, in the sample (10% of the population) of patients in whom the tests were repeated, a moderate consistency of BRS and fairly high consistency of CRS were observed over time (Supplemental Methods).

CONCLUSIONS

Abnormal baroreflex and/or chemoreflex may be frequently observed in patients with HF despite modern drug and device treatment. These 2 visceral reflexes likely contribute in a different, complementary way to the hemodynamic (BRS) and ventilatory (CRS) impairment observed in chronic HF, eliciting autonomic dysfunction, characterized by sympathetic predominance and vagal withdrawal. Decreased BRS has a stronger effect on cardiac mortality, whereas increased CRS has a stronger effect on hospitalizations for worsening HF. When both BRS and CRS are abnormal, short-term outcome is exceedingly poor. The current study supports the search for novel therapies targeting BRS/CRS resetting in HF, either based on drugs, surgery, or bioelectronic medicine devices.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with HF often have baroreflex and chemoreflex derangement despite modern medical and device treatment, 2 important drivers of neurohormonal activation and disease progression.

COMPETENCY IN PATIENT CARE: HF specialists should know that baroreflex and chemoreflex may be easily evaluated in patients with HF, identifying patients at risk of hospitalization/mortality (refractory and difficult to treat HF) and potential candidates for reflex modulation strategies (advanced HF therapies).

TRANSLATIONAL OUTLOOK 1: Although this is a monocentric study, the methods used are technically easy and have low cost. A wider application of baroreflex and chemoreflex assessment is advisable, especially considering the important clinical and prognostic information provided.

TRANSLATIONAL OUTLOOK 2: The systematic study of the baroreflex and chemoreflex in patients with HF (and potentially with neurogenic hypertension) will maximize the impact of novel treatment approaches, such as baroreflex activation therapy, phrenic nerve stimulation, chemoreflex denervation, or chemoreflex pharmacologic modulation.

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KEY WORDS autonomic nervous system, baroreflex, mortality, chemoreflex, heart failure, hospitalization

APPENDIX For an expanded Methods section as well as a supplemental figure and tables, please see the online version of this paper.