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Combined Increased Chemosensitivity to Hypoxia and Hypercapnia as a Prognosticator in Heart Failure

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Objectives The aim of the present study was to investigate the prognostic significance of chemosensitivity to hypercapnia in chronic heart failure (HF).

Background Increased chemosensitivity to hypoxia and hypercapnia has been observed in HF. The potential value of enhanced chemosensitivity to hypercapnia to risk prediction in systolic HF has not been specifically evaluated.

Methods One hundred ten consecutive systolic HF patients (age 62 ± 15 years, left ventricular ejection fraction [LVEF] 31 ± 7%) underwent assessment of chemosensitivity to hypoxia and hypercapnia (rebreathing technique) and were followed up for a median period of 29 months (range 1 to 54 months). The end point was a composite of cardiac death and aborted cardiac death (ventricular tachyarrhythmia treated by cardioverter-defibrillator).

Results At baseline, 31 patients (28%) had enhanced chemosensitivity to both hypoxia and hypercapnia. Although they had the same LVEF as the 43 patients (39%) with normal chemosensitivity, they were more symptomatic (New York Heart Association functional class), had higher plasma brain natriuretic peptide and norepinephrine, steeper regression slope relating minute ventilation to carbon dioxide output (V_E/V_{CO_2} slope), more Cheyne-Stokes respiration, and more ventricular arrhythmias (all $p < 0.05$). Four-year survival was only 49%, in marked contrast to 100% for patients with normal chemosensitivity ($p < 0.001$). On multivariate analysis, combined elevation in chemosensitivity was the strongest independent prognostic marker, even when adjusted for univariate predictors (V_E/V_{CO_2} slope, Cheyne-Stokes respiration, LVEF, and brain natriuretic peptide, $p < 0.05$).

Conclusions Increased chemosensitivity to both hypoxia and hypercapnia, eliciting neurohormonal derangement, ventilation instability, and ventricular arrhythmias, is a very serious adverse prognostic marker in HF. (J Am Coll Cardiol 2009;53:1975–80) © 2009 by the American College of Cardiology Foundation

Despite advances in treatment, the prognosis of patients with chronic heart failure (HF) is poor (1). Isolated increased chemosensitivity to either hypoxia or hypercapnia is associated with clinical severity in HF, as well as with activation of the adrenergic (2,3) and natriuretic peptide (3) systems, unstable ventilatory control (Cheyne-Stokes respiration [CSR]) (3–5), ventilatory inefficiency during exercise (3,6), and ventricular arrhythmias (3–7). Chemosensitivity to hypoxia and to hypercapnia can be measured separately. We have recently found that when both chemosensitivities are abnormally enhanced (rather than only one), there is worse instability of ventilatory control, more neurohormonal activation, and a greater tendency toward arrhythmia (3).

The independent prognostic significance of increased chemosensitivity in HF has only been reported once before (8), and the report addressed only the hypoxic chemosensitivity. The prognostic significance of increased sensitivity to hypercapnia has never been investigated. The purpose of our study was to evaluate in a cohort of systolic HF patients whether enhanced chemosensitivity to hypercapnia has a prognostic significance.

Methods

Subjects and study design. Between September 2003 and January 2007, we prospectively screened 168 HF patients with impaired left ventricular systolic function (left ventricular ejection fraction [LVEF] <45%). Exclusion criteria were New York Heart Association (NYHA) functional class IV, acute coronary syndrome within 6 months before

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Abbreviations and Acronyms

BNP = brain natriuretic peptide
CI = confidence interval
CSR = Cheyne-Stokes respiration
HCVR = hypercapnic ventilatory response
HF = heart failure
HR = hazard ratio
HVR = hypoxic ventilatory response
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
V_E/V_{CO_2} slope = regression slope relating minute ventilation to carbon dioxide output
V_{O_2} = oxygen uptake

examination, severe renal and pulmonary disease, history of obstructive sleep apnea, and therapy with morphine or derivates, theophylline, oxygen, benzodiazepines, or acetazolamide. One hundred ten patients matched the entry criteria, all on stable optimal pharmacological and device treatment (Table 1) for more than 1 month.

They were evaluated during a period of at most 5 days, including evaluation of chemosensitivity to hypoxia and to hypercapnia by rebreathing technique (9,10), as previously described (3), assay of brain natriuretic peptide (BNP) (Shionoria BNP, Shionogi, Japan) and norepinephrine (HPLC HCL-725 CA, Tosoh Corporation, Tokyo, Japan), symptom-limited maximal cardiopulmonary exercise test (Vmax, Sensormedics, Yorba Linda, California), standard Doppler echocardiography, 24-h electrocardiographic recording (Elamedical, Montrouge, France), 20-min daytime polygraphy (3,10), and standard nocturnal polysomnography (E-series 2, Compumedics, Melbourne, Australia) for CSR assessment. The study protocol was approved by the Institutional Ethics Committee of the G. Monasterio Foundation CNR-Regione Toscana and CNR Institute of Clinical Physiology, Pisa, Italy, and informed consent was obtained from all subjects.

Table 1 Characteristics of Patients

	HF Patients (n = 110)
Age (yrs)	62 ± 15
Male (%)	83
BMI ($kg \cdot m^{-2}$)	27.1 ± 4.2
ECrCl ($ml \cdot min^{-1}$)	77.0 ± 30.8
Ischemic/idiopathic/secondary (%)	47/40/13
Atrial fibrillation (%)	25
NYHA functional class I to II/III (%)	68/32
LVEF (%)	31.1 ± 7.1
HVR ($l \cdot min^{-1} \cdot \%Sa_{O_2}{}^{-1}$)	0.67 ± 0.45
HCVR ($l \cdot min^{-1} \cdot mm\ Hg^{-1}$)	0.80 ± 0.41
Furosemide (%)	80
Beta-blockers (%)	86
ACEI-ARB (%)	78
Spironolactone (%)	42
CRT (%)	27
ICD (%)	17

Unless noted, values are expressed as mean ± SD or median (interquartile range).

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BMI = body mass index; CRT = cardiac resynchronization therapy; ECrCl = estimated creatinine clearance from Cockroft-Gault formula; HCVR = hypercapnic ventilatory response; HF = heart failure; HVR = hypoxic ventilatory response; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Follow-up and documentation of end points. Patients were followed up at the outpatient clinic of our hospital, and their outcome status was determined from the medical records or telephone interviews. The composite end point was death attributable to cardiac cause (sudden death, progressive HF–related death, acute myocardial infarction) or life-threatening ventricular tachyarrhythmia requiring cardioverter-defibrillator shock. Patients who died of non–cardiac-related causes or who underwent heart transplantation were considered censored at the time of the event.

Statistical analysis. Statistical analysis was performed using the SPSS program (version 13.0, 1989 to 2004, SPSS Inc., Chicago, Illinois). Values are presented as mean ± SD, or median and interquartile range (IQR) (for values with non-normal distribution); variables with a skewed distribution were logarithmically transformed before further analysis. A value of $p < 0.05$ was considered significant.

Mean differences among groups were evaluated through the unpaired Student *t* test or analysis of variance 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 candidate independent variables used for univariate Cox proportional analysis were selected on the basis of the strength of association with outcome shown by previous studies in similar populations: age; sex; body mass index; serum creatinine level; HF etiology; atrial fibrillation; NYHA functional class; LVEF; left ventricular dimensions; peak oxygen uptake (V_{O_2})/kg; regression slope relating minute ventilation to carbon dioxide output (V_E/V_{CO_2}); chemosensitivity to: 1) hypoxia, 2) hypercapnia, and 3) both hypoxia and hypercapnia; diurnal and nocturnal CSR; plasma BNP; norepinephrine and renin activity; and 24-h beat-to-beat standard deviation of normal RR intervals. Only chemosensitivity, among the continuous variables, was considered as a dichotomized variable, with cutoff values of 0.77 $l \cdot min^{-1} \cdot \%SaO_2{}^{-1}$ for hypoxic ventilatory response (HVR) and 0.79 $l \cdot min^{-1} \cdot mm\ Hg^{-1}$ for hypercapnic ventilatory response (HCVR), as previously described (3). All variables significantly associated with outcome at univariate analysis were then entered in multivariate analysis, limited to a maximum of 2 covariates because of the number of events. Survival was estimated by the product-limit Kaplan-Meier method and log-rank statistics.

Results

Overall, 43 patients (39%) showed normal chemosensitivity, whereas 67 patients (61%) showed increased hypoxic and/or hypercapnic chemosensitivity. Isolated increased HVR and HCVR was found in 13 (12%) and 23 (21%) patients, and combined increased HVR and HCVR was present in 31 patients (28%). Patients with increased chemosensitivity did not differ from those with normal chemosensitivity with regard to age, sex, left ventricular dimensions or function, renal function (Table 2), pulmonary function, and resting

Table 2 Clinical Characteristics, Neurohormonal Profile, Functional Capacity, Ventilatory Efficiency, and Arrhythmias According to Chemosensitivity

	Normal HVR and HCVR	Increased HVR	Increased HCVR	Increased HVR and HCVR
n (%)	43 (39)	13 (12)	23 (21)	31 (28)
Age (yrs)	60 ± 15	62 ± 14	60 ± 18	68 ± 9
Male, n (%)	31 (72)	12 (92)	19 (82)	29 (94)
BMI ($kg \cdot m^{-2}$)	27.0 ± 4.8	28.4 ± 4.3	26.0 ± 4.3	27.4 ± 2.8
ECrCl ($ml \cdot min^{-1}$)	82.4 ± 36.1	77.1 ± 28.5	80.5 ± 31.1	70.1 ± 20.5
NYHA functional class III (%)	18	31	39	45*
LVEF (%)	32.9 ± 6.8	30.9 ± 9.3	29.8 ± 6.7	29.5 ± 6.4
LV end-diastolic diameter (mm)	60.1 ± 8.1	63.1 ± 10.4	63.7 ± 8.2	63.3 ± 8.9
Norepinephrine ($ng \cdot l^{-1}$)	300 (186–543)	484 (288–562)	459 (309–777)	642 (393–778)†
BNP ($ng \cdot l^{-1}$)	67 (33–212)	96 (39–270)	214 (108–376)*	325 (200–710)†‡
Peak Vo_2/kg ($ml \cdot min^{-1} \cdot kg^{-1}$)	14.2 ± 6.0	14.7 ± 7.4	11.7 ± 5.6	10.5 ± 2.8*
V_E/Vco_2 slope	34.1 ± 5.9	36.7 ± 11.4	39.6 ± 6.7	45.2 ± 8.2†
SDNN (ms)	106.5 ± 41.5	129.6 ± 57.2	85.1 ± 28.4	63.7 ± 39.8§
Atrial fibrillation (%)	7	15	9	45†‡‖
NSVT (%)	26	53	48	60§
Diurnal CSR (%)	0	15	14	58†
Nocturnal AHI (n/h)	3.0 (0.9–5)	13.8 (2.1–14.0)	13.0 (3.1–15.9)	19.0 (10.8–29.3)§

Values are expressed as mean ± SD for continuous normally distributed variables, as median (25th to 75th percentile) for continuous non-normally distributed variables, and as percent for categorical data. *$p < 0.05$, †$p < 0.001$, §$p < 0.01$ versus normal HVR and HCVR. ‡$p < 0.05$ versus increased HVR alone. ‖$p < 0.05$ versus increased HCVR alone.

AHI = apnea-hypopnea index; BNP = brain natriuretic peptide; CSR = Cheyne-Stokes respiration; LV = left ventricular; NSVT = nonsustained ventricular tachycardia; SDNN = standard deviation of all RR intervals; V_E/Vco_2 slope = regression slope relating minute ventilation to carbon dioxide output; Vo_2 = oxygen uptake; other abbreviations as in Table 1.

arterial gas analysis values, but showed higher NYHA functional class (Table 2). A combined HVR and HCVR enhancement was associated with neurohormonal activation (increased plasma norepinephrine concentration and BNP and N-terminal part of the pro–B-type natriuretic peptide levels) (Table 2), despite a similar degree of left ventricular systolic dysfunction.

In addition, compared with patients with normal chemosensitivity, patients with combined HVR and HCVR enhancement showed lower functional capacity (peak Vo_2/kg) and ventilatory efficiency (higher V_E/Vco_2 slope). Those in sinus rhythm (n = 71) also showed lower heart rate variability and a greater prevalence of paroxysmal atrial fibrillation and nonsustained ventricular tachycardia on 24-h electrocardiographic monitoring (Table 2). Finally, all HF patients with normal chemosensitivity had a normal breathing pattern, whereas daytime and nighttime CSR occurrence increased progressively from isolated up to combined enhanced HVR or HCVR (Table 2).

Prognostic value of chemoreflex. No patient was lost to follow-up, which lasted for a median period of 29 months (range 1 to 54 months). Five patients died of noncardiac causes (2 stroke; 3 cancer), 11 of cardiac causes (4 sudden deaths; 4 progressive HF; 3 myocardial infarction), and 4 patients were appropriately treated by the implantable cardioverter-defibrillator for ventricular fibrillation. Thus, 15 patients (14%) had major cardiac events with a median time to an event of 16 months (range 1 to 45 months). Actuarial early (6 months) and late (4 years) event-free survival rates were 94%, and 79%, respectively.

There was no difference in age, sex, pharmacological and device treatment, HF etiology, and peak Vo_2 between patients with events and those without (all $p > 0.1$). Patients who had major cardiac events had a lower LVEF (27.8 ± 5.3% vs. 31.7 ± 7.2%, $p = 0.03$), higher chemosensitivity to hypercapnia (1.03 ± 0.28 $l \cdot min^{-1} \cdot mm\ Hg^{-1}$ vs. 0.77 ± 0.41 $l \cdot min^{-1} \cdot mm\ Hg^{-1}$, $p = 0.02$), higher V_E/Vco_2 slope (44.2 ± 8.5 vs. 37.8 ± 8.6, $p = 0.02$), higher incidence of daytime CSR (65% vs. 8%, $p < 0.001$), and worse neurohormonal status, as expressed by increased plasma levels of BNP (442 [IQR: 246 to 671] $ng \cdot l^{-1}$ vs. 138 [IQR: 47 to 182] $ng \cdot l^{-1}$, $p < 0.001$), norepinephrine (588 [IQR: 481 to 782] $ng \cdot l^{-1}$ vs. 412 [IQR: 268 to 675] $ng \cdot l^{-1}$, $p = 0.004$), and plasma renin activity (3.1 [IQR: 1.1 to 13.5] $ng \cdot l^{-1} \cdot h^{-1}$ vs. 1.2 [IQR: 0.4 to 3.3] $ng \cdot l^{-1} \cdot h^{-1}$, $p = 0.04$). In this subset, we observed nonsignificant trends to worse NYHA functional class (III) (30% vs. 10%, $p = 0.06$), nocturnal CSR, as expressed by the apnea-hypopnea index (18.6 ± 8.7 vs. 11.0 ± 10.7, $p = 0.07$), and chemosensitivity to hypoxia (0.85 ± 0.41 $l \cdot min^{-1} \cdot \%SaO_2^{-1}$ vs. 0.64 ± 0.45 $l \cdot min^{-1} \cdot \%SaO_2^{-1}$, $p = 0.09$).

Survival analysis. A Kaplan-Meier analysis was performed for early (6-month) and late (4-year) survival. Early and late event-free survivals were 87% and 49%, respectively, for patients with higher combined chemosensitivity, compared with 96% and 84% for patients with isolated enhanced hypercapnic sensitivity, and 100% and 88% in patients with isolated hypoxic hypersensitivity. No patient with normal chemosensitivity had cardiac events (overall log-rank among the 4 subgroups: 20.02, $p < 0.001$) (Fig. 1).

Univariate analysis. The following clinical variables were related to the occurrence of major cardiac events: LVEF (hazard ratio [HR]: 0.90, 95% confidence interval [CI]: 0.84 to 0.98, $p = 0.02$), elevated V_E/Vco_2 slope (HR: 1.07,

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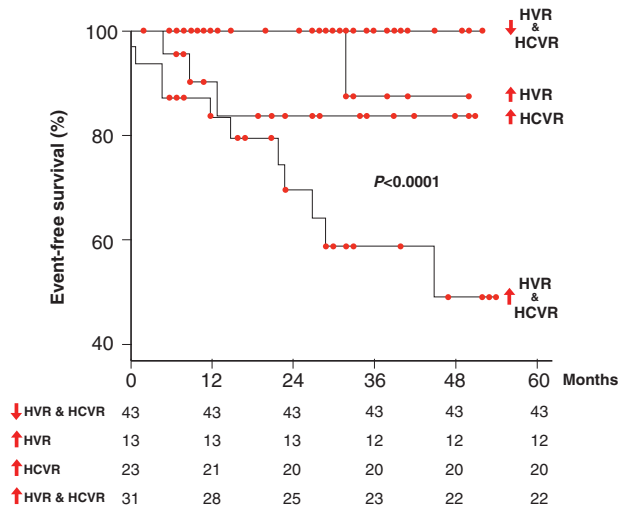

Figure 1 **Chemosensitivity and Survival in Heart Failure**

Kaplan-Meier survival plot in heart failure patients with normal chemosensitivity (norm HVR & HCVR) compared with patients with augmented chemosensitivity to: hypoxia alone (↑ HVR), hypercapnia alone (↑ HCVR), and hypoxia and hypercapnia combined (↑ HVR & HCVR). HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response.

95% CI: 1.01 to 1.13, p = 0.02), chemosensitivity to both hypoxia and hypercapnia (HR: 7.94, 95% CI: 2.52 to 25.01, p = 0.001), occurrence of diurnal CSR (HR: 6.02, 95% CI: 2.15 to 16.87, p = 0.001), and higher BNP plasma level (HR: 2.62, 95% CI: 1.54 to 4.45, p < 0.001).

Multivariate analyses. On bivariate analyses, we found that augmented chemosensitivity to both hypoxia and hypercapnia was a marker of poor prognosis independent of the other univariate predictors (Table 3). Combined enhanced chemosensitivity remained an independent predictor of death, even when adjusted for V_E/V_{CO_2} slope, diurnal CSR, LVEF, and BNP (Table 3).

Discussion

The novel finding of this study is that in patients with systolic HF, enhanced chemosensitivity to hypercapnia, especially when combined with hypersensitivity to hypoxia, is a strong, independent predictor of cardiac death, including aborted death (cardioverted life-threatening tachyarrhythmias). Patients with normal chemosensitivity, despite a similar degree of left ventricular dysfunction, were instead spared from fatal events.

There is growing evidence that the enhancement of chemosensitivity (7) may be important in HF, as well as withdrawal of the inhibitory baroreflex stimulus (11,12), by increasing sympathetic drive (13,14). There is also growing evidence for a key role of central afferent sympathoexcitation in modulating chemoreflex sensitivity and medullary autonomic centers (15,16). Therefore, the association between altered chemosensitivity and increased sympathetic drive might be causal in both directions, and might therefore be able to engender a self-sustaining vicious cycle. We found that the worst clinical status, neurohormonal activation (as expressed by higher norepinephrine, plasma renin activity, and natriuretic peptide levels), and ventilatory derangement (at rest with CSR occurrence, and during exercise with worse ventilatory efficiency) were observed in the subset of patients with combined enhancement of chemosensitivity to hypoxia and hypercapnia, confirming our previous observations in a smaller group (3).

Notably, all of these variables are acknowledged prognostic markers in HF (17–21), and combined chemosensitivity, considered in our study for the first time, was the strongest independent predictor of cardiac death and life-threatening arrhythmias. The grim prognostic significance of augmented chemosensitivity to hypoxia and hypercapnia may result mainly from its excitatory effects on the sympathetic nervous system through a direct excitatory input (2,22), and indirectly by means of the CSR-related hypoxia phases (7,23). In a study conducted before beta-blockade became routine therapy, Ponikowski et al. (8) observed that chemosensitivity to hypoxia was an independent prognostic marker in HF patients. This apparent discrepancy may be explained by the extensive use of beta-blockers in our more recent population with a putative more selective effect on peripheral chemoreceptors. One-half of the events in our population were arrhythmic, suggesting sympathovagal imbalance elicited by activated chemoreceptors. In this respect, we found in patients with combined enhancement of chemosensitivity both reduced heart rate variability and higher occurrence of atrial fibrillation and nonsustained ventricular tachycardia, in agreement with previous findings (24). More importantly, however, the study by Ponikowski et al. (8) did not measure hypercapnic chemosensitivity, and therefore could not distinguish patients with isolated enhanced hypercapnic sensitivity from those with combined chemoreflex enhancement: we will never know whether it was both notional subgroups, or only one, that had the increased risk. We believe our more comprehensive study builds on the

Table 3 **Predictors of Major Cardiac Events in HF Patients (Bivariate Cox Proportional Hazard Analysis)**

Variable	HR (95% CI)	p Value
Augmented HVR and HCVR vs. LVEF		
↑ Chemosensitivity	6.86 (2.16–21.83)	0.001
LVEF	0.92 (0.85–1.00)	0.050
Augmented HVR and HCVR vs. V_E/V_{CO_2} slope		
↑ Chemosensitivity	8.12 (1.84–35.85)	0.005
V_E/V_{CO_2} slope	1.01 (0.94–1.09)	0.749
Augmented HVR and HCVR vs. diurnal CSR		
↑ Chemosensitivity	4.33 (1.09–19.44)	0.038
CSR	2.25 (0.61–8.28)	0.222
Augmented HVR and HCVR vs. BNP		
↑ Chemosensitivity	4.26 (1.26–14.47)	0.02
BNP	2.03 (1.15–3.58)	0.014

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

work of Ponikowski et al. (8) to highlight the importance of the combined enhancement.

Study limitations. A limitation of this study is the number of patients recruited and therefore the relatively small number of events observed. Therefore, although we limited the multivariate analysis to a maximum of 2 covariates, we cannot exclude the possibility of overfitting models. Such limitations are common in real-world, hypothesis-generating, single-center studies. Attempting to run such a study on a multicenter basis might increase numbers but may well be hampered with the likely great difficulty in establishing and maintaining equivalence between centers in methods (neurohormonal, sleep, cardiopulmonary exercise, and chemosensitivity assessment).

Finally, it is a limitation that hypercapnic chemosensitivity is not routinely measured in clinical practice worldwide. However, the rebreathing circuit required is very inexpensive (<$50) and is easy to set up at any site where cardiopulmonary exercise testing is carried out. The tests can be performed by technicians. If our findings are confirmed in other studies, chemosensitivity testing might become a useful, simple, and convenient addition to routine prognostic evaluation in HF patients. Recognition of the powerful adverse significance of combined enhanced chemoreflex sensitivity may stimulate more work into its origin and pathophysiology.

Conclusions

Increased sensitivity of chemoreceptors to both hypoxia and hypercapnia is a powerful and independent predictor of mortality in HF patients. In the early phase of HF syndrome, the chemoreceptors may act in a compensatory way, triggering autonomic nervous system changes in the cardiorespiratory system that prevents tissue hypoxia or hypercapnia. However, over time, chemoreceptor up-regulation might promote a vicious circle eliciting autonomic imbalance, neurohormonal activation, abnormal ventilatory responses, arrhythmias, and favoring adverse events. Chemoreflex overactivation deserves more attention as a potential specific therapeutic target in HF, to be treated by novel pharmacological, device-based, or behavioral approaches (15,16,25–27).

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Key Words: heart failure ■ prognosis ■ chemoreflex ■ arrhythmia ■ brain natriuretic peptide ■ Cheyne-Stokes respiration.