Peripheral Chemoreceptor Hypersensitivity

An Ominous Sign in Patients With Chronic Heart Failure

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Background—Peripheral chemoreceptor hypersensitivity is a feature of abnormal cardiorespiratory reflex control in chronic heart failure (CHF) and may contribute to sympathetic overactivity, attenuated baroreflex sensitivity (BRS), and excessive ventilation during exercise. We studied whether augmented peripheral chemosensitivity carries independent prognostic significance.

Methods and Results—We assessed peripheral chemosensitivity (ventilatory response to hypoxia using transient inhalation of pure nitrogen) and BRS (phenylephrine and spectral methods) in 80 consecutive CHF patients (age 58±9 years; left ventricular ejection fraction [LVEF] 24±12%; peak oxygen consumption [peak VO₂] 18±7 mL·min⁻¹·min⁻¹). CHF patients demonstrated augmented peripheral chemosensitivity and decreased BRS (all P<0.01 versus reference values). During follow-up (median 41 months, >3 years in all survivors), 37 patients died. High peripheral chemosensitivity (>0.72 L·min⁻¹·%SaO₂⁻¹) predicted impaired survival (hazard ratio 3.2, 95% CI 1.6 to 6.0, P=0.0006). In the 27 patients (34%) with high peripheral chemosensitivity, 3-year survival was 41% (95% CI 22% to 60%) compared with 77% (66% to 89%) in 53 patients with normal chemosensitivity (P=0.0002). In multivariate analyses, augmented chemosensitivity independently predicted death (hazard ratio 2.8, 95% CI 1.5 to 5.5, adjusted for age, peak VO₂, and VE/VCO₂ [P=0.002]; hazard ratio 2.6, 95% CI 1.3 to 5.1, adjusted for age, LVEF, and peak VO₂ [P=0.008]). Depressed BRS was related to unfavorable prognosis in univariate analysis (P<0.05) but not in multivariate analyses.

Conclusions—Hypersensitivity of the peripheral chemoreceptors independently predicts adverse prognosis in ambulatory patients with CHF. This hyperactive excitatory reflex, through its inhibitory effect on the baroreflex, may be the reason for the previously observed prognostic association of the latter. (Circulation. 2001;104:544-549.)

Key Words: peripheral chemoreceptors ■ heart failure ■ baroreceptors ■ prognosis

In chronic heart failure (CHF), reflex control within the cardiovascular system is severely impaired and associated with sympathetic overactivation, which may contribute to long-term deterioration of cardiac function.1–2 Investigation of baroreflex responses in CHF is well developed3,4 and has shown that in advanced CHF, attenuated baroreflex sensitivity (BRS) predicts poor outcome.5,6 The response being assessed by BRS is, however, an inhibitory input from the periphery into the sympathetic nervous system. Excitatory reflexes in CHF, in contrast, have been less well investigated.2,7 One of the major excitatory reflex inputs originates from peripheral chemoreceptors, which are overactive in CHF.7–9 This reflex may contribute importantly to the generalized sympathetic overactivity of CHF both directly and indirectly via suppression of the baroreflex.10,11 In previous studies,1,12 we have characterized CHF patients with augmented peripheral chemosensitivity as having excessive ventilation, severe autonomic imbalance, and a higher prevalence of ventricular arrhythmias; these factors may unfavorably influence prognosis.

Methods

To test the hypothesis that peripheral chemoreceptor hypersensitivity would be a marker of poor outcome in CHF, we designed a prospective study protocol. All consecutive patients who attended the outpatient CHF clinic in our institution between April 1994 and December 1996 and met the following prespecified criteria were considered for the study: ≥6-month history of CHF due to idiopathic dilated cardiomyopathy or ischemic heart disease, left ventricular ejection fraction (LVEF) <45%, clinical stability, unchanged medication for ≥1 month preceding the study, absence of signs of fluid retention at baseline assessment with currently used treatment, and no acute coronary events within the 6 months preceding the study. Exclusion criteria included age >75 years; seriously limiting musculoskeletal, peripheral vascular, or pulmonary disease; significant renal dysfunction; and treatment with β-blockers. The local Ethics Committee approved the study protocol.
All patients underwent routine clinical assessment, including symptom-limited exercise testing with respiratory gas exchange analysis (Amis 2000, Innovision), for determination of peak oxygen consumption (peak $\dot{V}O_2$) and the regression slope relating minute ventilation to carbon dioxide output ($V_{E}/\dot{V}CO_2$ slope). All patients also underwent evaluation of chemosensitivity and where possible, BRS, as described below.

### Peripheral Chemosensitivity Evaluation

Peripheral chemosensitivity was assessed by the transient hypoxic method as described and validated previously. The test was performed while subjects were seated, after a period of quiet breathing. Minute ventilation was measured breath-by-breath with a heated pneumotachograph, and $O_2$ and $CO_2$ concentrations were monitored continuously by mass spectrometer (Amis 2000, Innovision), calibrated before each test. Patients, unaware of the timing of the test, breathed pure nitrogen for 2 to 8 breaths. This was repeated 10 to 15 times to provide a wide range of $O_2$ saturations (75% to 100%). Tests were performed every 2 minutes with room air inspired between exposures, so that $O_2$ saturation, end-tidal $CO_2$, and ventilation returned to baseline. Arterial $O_2$ saturation was measured with the pulse oximeter (model N-200E, Nellcor) set at fast mode with a response time of 2 to 3 seconds with a lightweight ear probe attached to the subject’s right earlobe. The average of the 2 largest consecutive breaths, which gave the highest ventilation after the hypoxic stimulus, was used to calculate maximal ventilation. The peripheral chemosensitivity was expressed as the slope of the regression line relating ventilation to arterial oxygen saturation in liters per minute per percent $O_2$ saturation ($L \cdot min^{-1} \cdot %SaO_2^{-1}$). On the basis of our previously reported data, we defined an abnormally augmented peripheral chemosensitivity in CHF patients as greater than the mean + 2 SD of age-matched control subjects.

### BRS Assessment

BRS was measured by the 2 major standard techniques: the noninvasive α-index spectral analysis method and the bolus phenylephrine method. These tests were performed between 9 AM and noon, and patients were asked not to smoke or drink caffeine on the study day.

#### Spectral Method

After 20 minutes of supine rest in a quiet room, 20-minute recordings of heart rate (ECG) and noninvasive blood pressure (Finapres, Ohmeda) were obtained. Subjects breathed spontaneously and were asked to relax but not to fall asleep. R-R interval and blood pressure signals were acquired by a computer program at a sampling rate of 1000 Hz. Stationary 10-minute periods of recording were selected, and autoregressive power spectral analysis was applied to the R-R interval and systolic blood pressure time series. The following spectral bands were identified: low-frequency (LF, 0.04 to 0.15 Hz) and high-frequency (HF, 0.15 to 0.40 Hz), and the areas below each peak were calculated in absolute units (ms$^2$ or mm Hg$^2$). The α-index was computed as the square root of the ratio between R-R and systolic blood pressure spectral powers within the LF band, with the condition that coherence was adequate (>0.50) between the R-R interval and systolic blood pressure as assessed by cross-spectral analysis.

#### Phenylephrine Method

Patients received intravenous injections of phenylephrine, with an initial dose of 150 μg, which was subsequently increased by 50 to 100 μg at a time up to a maximum dose of 500 μg, to obtain an increase in systolic blood pressure of >15 mm Hg. BRS was calculated as the slope of the regression line relating changes in R-R interval to changes in systolic blood pressure, with the condition that the correlation coefficient for this relationship exceeded 0.80. BRS measured by either method was expressed in milliseconds per mm Hg (ms/mm Hg). The reference values in our laboratory for an abnormally low BRS (ie, less than the mean–2 SD of normal controls) are <1.7 ms/mm Hg for the spectral method and <2.0 ms/mm Hg for the phenylephrine method.

### Follow-Up

Follow-up duration was ≥3 years in all who survived. Survival at January 31, 2000, was ascertained from the hospital information system and from the United Kingdom’s Office of National Statistics. No patient was lost to follow-up. The end point of the study was all-cause mortality.

### Statistical Analyses

Data are given as mean±SD. Unpaired Student’s t test and the Mann-Whitney U test were used to compare mean values between groups. Regression analysis was applied to assess correlations between chemosensitivity and other parameters. A value of $P<0.05$ was considered significant. The relationship of baseline variables with survival was assessed by Cox proportional-hazards analysis (univariate and multivariate). To estimate the influence of risk factors on 1-year and 3-year survival, Kaplan-Meier cumulative survival curves were constructed and compared by the Mantel-Haenszel log-rank test (Statview 4.5, Abacus Concepts). There was no evidence of violation of the proportional hazards assumption. In addition, we tested for interaction between chemosensitivity, peak $\dot{V}O_2$, and BRS in predicting survival (SAS software, SAS Institute).

#### Results

During the study period, 170 patients attended our CHF clinic: 95 met the entry criteria and were asked to participate, and 80 (84%) agreed. The patients’ clinical characteristics are included in a study on the prognostic value of $V_{E}/\dot{V}CO_2$ slope in CHF.

### Peripheral Chemosensitivity and BRS in CHF Patients

Assessment of peripheral chemoreceptor sensitivity was successful in all 80 patients. Overall, the mean peripheral chemosensitivity was abnormally high at 0.69±0.50 L · min$^{-1}$ · %SaO$^{-1}$ ($P<0.001$) compared with our laboratory’s...
reference values. Twenty-seven of the 80 patients (34%) demonstrated an abnormally augmented peripheral chemosensitivity (ie, >0.72 L · min⁻¹ · %Sao₂⁻¹; mean 1.20±0.53 L · min⁻¹ · %Sao₂⁻¹). These patients showed a trend toward more impaired functional capacity and lower LVEF (P = 0.007) than patients with normal chemosensitivity (Table 2). Chemosensitivity did not correlate with peak VO₂ (r = −0.15, P > 0.2) and correlated only modestly with LVEF (r = 0.23, P = 0.05) and V̇ E /V̇ CO₂ slope (r = 0.27, P = 0.015).

Of the 80 patients in the study, both protocols for BRS assessment were performed in all patients who were suitable (n = 61, 76%): 12 patients were unsuitable because of atrial fibrillation, 3 because of paced rhythm, and 4 because of diabetes mellitus. Of the 61 patients tested, 6 had to be excluded because of frequent ectopic beats, and thus BRS was measurable in 55 patients (69% of the total study population). BRS was decreased in these patients, whether measured by the phenylephrine method (mean 3.4±3.1 ms/mm Hg, n = 37) or by the spectral method (mean 4.3±3.9 ms/mm Hg, n = 36), both P < 0.001 versus reference values.

Nineteen patients (35%) had abnormally low BRS (<1.7 ms/mm Hg for spectral method and <2.0 ms/mm Hg for phenylephrine method; see Methods). These individuals demonstrated severely compromised functional capacity compared with the patients with normal BRS (with 0/6/11/2 versus 2/21/13/0 in NYHA classes I/II/III/IV, respectively, P < 0.001), lower peak VO₂ (15.1±4.9 versus 21.5±7.5 mL · min⁻¹ · kg⁻¹, P < 0.01), and elevated V̇ E /V̇ CO₂ slope (41.6±9.1 versus 32.7±6.8, P < 0.001).

### Predictors of Mortality

During follow-up (median 41 months, >3 years in all survivors), 37 deaths were observed (median time to death 23 months). The cumulative survival of all patients was 81% at 1 year and 65% at 3 years.

### Univariate Analyses

In univariate Cox proportional-hazards analysis, we found the following clinical variables related to impaired overall prognosis: NYHA class (risk ratio [RR] 2.1, 95% CI 1.1 to 4.1, P = 0.034 for NYHA III/IV versus I/II), low peak VO₂ (RR 0.9, 95% CI 0.8 to 0.98, P = 0.008 as a continuous variable; RR 2.5, 95% CI 1.3 to 4.8, P = 0.007 when dichotomized at 14.0 mL · min⁻¹ · kg⁻¹), elevated V̇ E /V̇ CO₂ slope (RR 1.04, 95% CI 1.01 to 1.1, P = 0.02), and augmented peripheral chemosensitivity (RR 3.2, 95% CI 1.6 to 6.0, P = 0.0006). There were trends for age (RR 1.04, 95% CI 1.0 to 1.1, P = 0.054), LVEF (RR 0.97, 95% CI 0.94 to 1.0, P = 0.07), and decreased BRS (RR 2.2, 95% CI 0.99 to 5.06, P = 0.053) to predict poor prognosis.

### Multivariate Analyses

In bivariate analyses, we confirmed that augmented chemosensitivity was a marker of poor prognosis independently of each of the factors with univariate prognostic power (chemosensitivity plus one of these factors; data presented in Table 3). Subsequently, in analyses with 4 covariates, we found chemosensitivity to be an independent predictor of death, first, when adjusted for age, peak VO₂, and V̇ E /V̇ CO₂ slope (hazard ratio 2.8, 95% CI 1.5 to 5.5, P = 0.002), and second, when adjusted for age, peak VO₂, and LVEF (hazard ratio 2.6, 95% CI 1.3 to 5.1, P = 0.008) (Table 3).

To investigate further whether evaluation of chemosensitivity might provide additional prognostic information, we dichotomized our population, considering conventional prognostic indicators, into the following subgroups: according to age (≥60 years, >60 years), LVEF (<25%, ≥25%), and peak VO₂ (<14 mL/min, ≥14 mL/min). In each of these subgroups, augmented chemosensitivity was related to poor outcome (in 5 of 6 subgroups, P < 0.05) (Table 4).

Low BRS was not related to unfavorable prognosis when adjusted for the other factors in the bivariate analyses. In the

### TABLE 2. Comparison of Clinical Data Between CHF Patients With Augmented Chemosensitivity (>0.72 L · min⁻¹ · %Sao₂⁻¹) and Normal Chemosensitivity (=0.72 L · min⁻¹ · %Sao₂⁻¹)

<table>
<thead>
<tr>
<th></th>
<th>CHF Patients With Augmented Chemosensitivity (n=27)</th>
<th>CHF Patients With Normal Chemosensitivity (n=53)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±7</td>
<td>58±8</td>
<td>NS</td>
</tr>
<tr>
<td>Cause of heart failure, n (%)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>20 (74)</td>
<td>35 (66)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>7 (26)</td>
<td>18 (34)</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II/III/IV</td>
<td>1/10/13/3</td>
<td>2/28/23/0</td>
<td>0.1</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>20±10</td>
<td>27±12</td>
<td>0.007</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>71±9</td>
<td>68±11</td>
<td>NS</td>
</tr>
<tr>
<td>Peak VO₂, mL · kg⁻¹ · min⁻¹</td>
<td>16.4±5.5</td>
<td>19.3±7.1</td>
<td>0.07</td>
</tr>
<tr>
<td>V̇ E /V̇ CO₂ slope</td>
<td>38.7±8.9</td>
<td>34.7±8.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Low BRS, n (%)</td>
<td>13 (62)</td>
<td>6 (18)</td>
<td>0.01</td>
</tr>
<tr>
<td>Treatment, n</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>26</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>27</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>11</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end-diastolic diameter. Values are n or mean±SD. NS = P > 0.2.
multivariate analysis with 3 covariates (chemosensitivity, BRS, and peak VO₂), only augmented chemosensitivity independently predicted poor survival (RR 2.55, 95% CI 1.04 to 6.29, P=0.04). There was no evidence of statistically significant interaction between chemosensitivity and peak VO₂ in predicting survival (Wald χ² 0.1864, P=0.67). There was also no evidence of interaction between chemosensitivity and BRS (Wald χ² 0.0574, P=0.81).

Patients with augmented chemoreflex sensitivity had a worse survival than patients with normal values of chemosensitivity at 1 year (63% [95% CI 45% to 81%] versus 91% [83% to 98%], P=0.001) and at 3 years (Figure).

**Discussion**

The primary new finding of this study is that augmented peripheral chemosensitivity is a strong and independent predictor of poor outcome in ambulant CHF patients. The assessment of peripheral chemoreceptors appears to be more useful than the evaluation of BRS for prognostic purposes in CHF.

There are numerous studies on cardiorespiratory reflex control in patients with CHF, but the majority of them focus on inhibitory reflex responses from arterial baroreceptors. Baroreceptor function is markedly deranged in CHF. The loss of this restraining influence on the sympathetic nervous system has been postulated to be responsible for the sympathoexcitation seen in CHF.1–4 Impaired capacity of baroreceptors to increase vagal activity has been linked to impaired survival in CHF and after myocardial infarction.5,6,17,19 There are, however, some shortcomings of the assessment of the baroreflex in patients with CHF that may hinder its general applicability. BRS cannot be measured in all CHF patients, such as those with atrial fibrillation, pacemaker rhythms, and frequent ectopic beats, all of which occur frequently in advanced CHF. Because of these limitations, valid BRS evaluation was possible in only 69% of our study population. A similar proportion (65%) was achieved by Mortara et al6 in
the largest study of BRS in CHF to date. Furthermore, even the developers of the technique have reported that repeated measurements of the baroreflex show in the short term "considerable variation in sensitivity... the reasons for [which] are not entirely clear,"20 which limits the accuracy with which it can be described. This problem is greater in patients with CHF,21 because measurement of the smaller signal is more disturbed by the background noise of heart rate variation.

The sympathetic nervous system is only partially controlled by inhibitory inputs from baroreceptors; it also receives excitatory inputs. There is growing evidence that these excitatory reflexes are overactive in CHF and may be no less important than the baroreflex in their contribution to sympathetic overactivity in CHF.2,7

The grim prognostic significance of augmented peripheral chemosensitivity may result from its excitatory effects on the sympathetic nervous system, which have been demonstrated in experimental and clinical settings of CHF.8,9 The peripheral chemoreflex may contribute to the sympathetic overactivity of CHF either by an increased direct excitatory input to the sympathetic nervous system or by enhanced suppression of the baroreflex.10,11 We recently documented the role of augmented peripheral chemosensitivity in the generation of periodic oscillations in respiration, with concomitant slow rhythms in heart rate and blood pressure in CHF.22 CHF patients with such rhythms were seen to be deficient in protective baroreflex effects (because of marked baroreceptor downregulation) and demonstrated severely overactive sympathetic drive with an increased prevalence of nonsustained ventricular tachycardia.22 We also reported that depressed heart rate variability23 and general body wasting24 (both are strong predictors of death in CHF25,26) are linked to augmented peripheral chemosensitivity. Furthermore, augmented peripheral chemosensitivity may be one of the mechanisms responsible for the increased ventilatory response to exercise,8 which in turn is an independent marker of poor prognosis in CHF.18,27

In this study, we confirmed a significant correlation between ventilatory response to exercise and chemosensitivity and that $\frac{V_{E}}{V_{CO_2}}$ slope predicted death independently of other clinical factors (age, peak $V_O_2$, LVEF; data not shown). If chemosensitivity was added to this multivariate analysis, however, it became the strongest independent predictor of death ($P=0.009$). Therefore, despite a mutual relationship between chemosensitivity and $\frac{V_{E}}{V_{CO_2}}$ slope, the prognostic value of augmented chemosensitivity is independent and potentially higher than that of the ventilatory response to exercise. In contrast, depressed BRS was predictive of higher mortality only in univariate analysis, but not when the clinical variables were also considered. This finding is in agreement with that of Mortara et al,6 who demonstrated that BRS lost its predictive power when adjusted for hemodynamic indices. In addition, there was no interaction between chemosensitivity, peak $V_O_2$, and BRS in predicting mortality. All these considerations suggest that enhanced peripheral chemosensitivity may be the fundamental adverse reflex abnormality underlying these observed disturbances and therefore may itself provide stronger prognostic information.

Peripheral chemoreceptors may be involved early in the natural course of CHF because of their anatomic location and because their reflex affects tissue oxygen tension, which may be important to homeostasis, as is maximizing blood pressure.28 Peripheral chemoreceptors may integrate autonomic nervous system changes in the cardiorespiratory system to prevent tissue hypoxia. Over time, these initially favorable responses from upregulated chemoreceptors create a vicious circle of autonomic imbalance and contribute further to patients’ symptoms of dyspnea.

Some drugs, such as opiates, and oxygen have been shown to suppress peripheral chemosensitivity.29,30 Treatment strategies targeted at peripheral chemoreceptors may be a promising option for further evaluation.

The main limitation of this study was its relatively small size (80 patients, 37 events). Our study was, by necessity, a single-center study, because of our desire to measure in all patients not only chemoreflex sensitivity and standard prognostic clinical variables (including peak $V_O_2$) but also the other principal reflex measure, BRS; centers with experience in both are few. Because of these limitations, we regard our

### Table 4. Prognostic Value of Augmented Chemosensitivity

<table>
<thead>
<tr>
<th>Variable</th>
<th>$P$ (Likelihood Ratio Test)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq60$ (n=43)</td>
<td>0.02</td>
<td>3.1 (1.2–8.4)</td>
</tr>
<tr>
<td>$&gt;60$ (n=37)</td>
<td>0.006</td>
<td>3.4 (1.4–8.4)</td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq25%$ (n=41)</td>
<td>0.07</td>
<td>2.7 (0.9–8.3)</td>
</tr>
<tr>
<td>$&lt;25%$ (n=39)</td>
<td>0.03</td>
<td>2.6 (1.1–6.3)</td>
</tr>
<tr>
<td>Peak $V_O_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq14,mL\cdot kg^{-1}\cdot min^{-1}$ (n=56)</td>
<td>0.04</td>
<td>2.5 (1.1–6.0)</td>
</tr>
<tr>
<td>$&lt;14,mL\cdot kg^{-1}\cdot min^{-1}$ (n=24)</td>
<td>0.02</td>
<td>3.3 (1.2–9.2)</td>
</tr>
</tbody>
</table>

Kaplan-Meier survival plot for 3-year survival in CHF patients with normal peripheral chemosensitivity compared with patients with augmented peripheral chemosensitivity.
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study mainly as a hypothesis-generating study. Our results need to be confirmed.

In summary, we found that increased sensitivity of the peripheral chemoreceptors is a powerful and independent predictor of mortality in CHF. The previously reported prognostic association of depressed BRS may reflect its suppression by augmented chemosensitivity. Moreover, because peripheral chemoreceptor sensitivity is enhanced in CHF, it becomes more readily measurable, whereas BRS is depressed in CHF and therefore difficult to measure.

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