Tonic Chemoreflex Activation Contributes to Increased Sympathetic Nerve Activity in Heart Failure–Related Anemia

Nicolas Franchitto, Fabien Despas, Marc Labrunée, Jérôme Roncalli, Serge Boveda, Michel Galinier, Jean-Michel Senard, Atul Pathak

Abstract—Sympathetic activation contributes to both the initiation and progression of heart failure. The role of anemia in determining sympathetic overactivity in chronic heart failure (CHF) patients is unknown. We tested the hypothesis that, in CHF patients, anemia could lead to increased sympathetic activity through tonic activation of excitatory chemoreceptor afferents. We conducted a double-blind, randomized, vehicle-controlled study to examine the effect of chemoreflex deactivation on muscle sympathetic nerve activity in CHF patients with and without anemia. We compared the effect of breathing 100% oxygen for 15 minutes in 18 stable CHF patients with anemia and 18 control CHF patients matched for age, sex, blood pressure, and body mass index. Baseline muscle sympathetic nerve activity was significantly elevated in CHF patients with anemia compared with patients with CHF alone (56.0±3.2 versus 45.5±3.1 bursts per minute; P<0.0237). Administration of 100% oxygen led to a significant decrease in muscle sympathetic nerve activity in CHF patients with anemia (from 56.0±3.4 to 50.9±3.2 bursts per minute; P<0.0019). In contrast, neither room air nor 100% oxygen changed muscle sympathetic nerve activity or hemodynamics in patients with CHF alone. We report for the first time direct evidence of increased sympathetic nerve traffic in patients with CHF-related anemia. Sympathetic hyperactivity in patients with CHF and anemia is partially chemoreflex mediated and could explain how anemia contributes to the progression of CHF and increases morbidity and mortality in these patients. (Hypertension. 2010;55:00-00.)

Key Words: chemoreflex ■ chronic heart failure ■ anemia ■ microneurography ■ sympathetic nerve activity

Sympathetic activation is a hallmark of chronic heart failure (HF; CHF) involved in both initiation and progression of this syndrome.1,2 Pathologically elevated sympathetic tone worsens survival in CHF and can induce lethal arrhythmias. In recent years, the role of HF comorbidities has been emphasized, and most of these are implicated in the increase of sympathetic tone. Hence, obesity, hypertension,3 and renal failure4 have all been associated with an increase in sympathetic activity, and they partly explain the poor prognosis and outcome of patients with both HF and comorbidities. Among these associations, HF-related anemia is often described in patients with HF and chronic renal failure but also in patients with CHF alone.5 Increasing epidemiological evidence demonstrates the frequent association of anemia and CHF, whatever the etiology of HF, its severity, and mode of presentation. Depending on the type of study and on the cutoff decided for the diagnosis of anemia, the prevalence of CHF ranges widely from 4% to 61% (median: 18%).6 Anemia leads to more rapid progression of CHF and also predicts cardiovascular events and poor outcome.7,8 Low hemoglobin level is an independent prognostic factor for cardiovascular mortality in patients hospitalized for HF9 and also in ambulatory patients.10 In a recent systematic review and meta-analysis of HF patients (n=153 180), 37.2% were anemic, and anemia was independently associated with an increased risk of mortality in both systolic and diastolic HF.3

The relevance of sympathetic activation has been described in various individual conditions, but how anemia increases sympathetic tone is unknown in CHF patients. This question is clinically relevant because anemia and CHF frequently coexist in the same patient, and in CHF the degree of sympathetic activation is related to patient mortality, whereas anemia increases the risk of mortality and morbidity partly through adrenergic stimulation. These mechanisms may also lead to progression of HF and may accelerate adverse ventricular remodeling.11

Received October 30, 2009; first decision November 21, 2009; revision accepted January 26, 2010.

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Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.109.146779
The present study was undertaken to determine the impact of CHF complicated by anemia on sympathetic function as assessed by microneurographic nerve traffic recording. We tested the hypothesis that tonic activation of excitatory chemoreceptor afferents contributes to elevated sympathetic activity in patients with anemia and CHF and that chemo-
flex deactivation with 100% oxygen would, therefore, cause a reduction in sympathetic nerve traffic in these patients. Using a double-blind, randomized, placebo-controlled design, we examined the effects of chemoreflex deactivation on sympathetic activity in patients with both anemia and CHF and in CHF patients matched for age, sex, blood pressure (BP), and body mass index.

Methods

Study Population

We studied 18 patients (15 men and 3 women) with both CHF and anemia (age: 63.4 ± 2.6 years; mean body mass index: 26.7 ± 1.1 kg/m²) and 18 patients with CHF only (15 men and 3 women) matched for age, sex distribution, type of cardiomyopathy, left ventricular ejection fraction, and body mass index. In anemic patients, we used the World Health Organization definition of anemia (hemoglobin concentration <13.0 g/dL in men and 12.0 g/dL in women), which takes into account known sex differences in the distribution of hemoglobin values, and we enrolled patients in whom other causes of potential pathophysiological mechanisms for anemia in HF8,12 (hemodilution, renal dysfunction, patent inflammation, iron deficiency, cachexia, or malnutrition) had been excluded. None of the participants were receiving erythropoi-
etin, and none had diabetes mellitus. No individual had any pre-existing lung disease history. All of the patients were free of any symptoms or signs of respiratory dysfunction on clinical examination. Furthermore, there was no suggestion of sleep apnea, as assessed by a sleep questionnaire (Epworth test) and polysomnography. Informed, written consent was obtained from all of the partici-
pants. The study was approved by the Institutional Human Subjects Review Committee.

Measurements

Heart rate was measured continuously by ECG (AD Instruments). BP was measured continuously by the Finapres system (Finapres Medical System BV). Oxygen saturation was monitored with a pulse oximeter (AD Instruments). Multifunctional sympathetic nerve activity was recorded as described previously. Briefly, a tungsten microelectrode, with an insulated tip of 1 to 5 mm, was inserted selectively into muscle or skin fascicles of the peroneal nerve. A subcutaneous reference electrode was first inserted 2 to 3 cm away from the recording electrode, which was itself inserted into the nerve fascicle. The neural signals were amplified, filtered, rectified, and integrated to obtain a voltage display of sympathetic nerve activity. The intral-
batory reproducibility of microneurography has been assessed previously. In stable HF patients, muscle sympathetic nerve activity (MSNA) was measured twice at a 2-week interval. We observed a high and significant correlation between sessions (r = 0.88; P < 0.001).

All of the patients underwent standard transthoracic echocardiogra-
phy with measurement of conventional parameters, including left ventricular end-diastolic and systolic diameters, septum and poste-
rrior wall thicknesses during both systole and diastole, and calculation of left ventricular mass index with the Penn method. Standard laboratory tests were performed to determine hemoglobin levels, red blood cell volume, serum creatinine, plasmatic sodium, levels of brain natriuretic peptide (ADVIA Centaur B-type natriuretic peptide reagent and Bayer Diagnostic). Samples were not frozen, and the time between blood sampling and analysis was <20 minutes. Laboratory tests (plasma iron and ferritin, C-reactive protein, serum creatinine, and albumin) were also performed to exclude known causes of anemia. In 10 patients, 5 in each group, we performed arterial blood gas analysis during normoxia and hyperoxia (to assess in both groups and during both conditions pH, PaO₂, PaCO₂, HCO₃⁻, and arterial oxygen saturation).

Protocol and Procedures

Participants were studied in the supine position under carefully standardized conditions. Baseline recording of all of the parameters was done for 15 minutes. To study the effect of chemoreflex deactivation with 100% oxygen, we used a randomized, double-
blind, placebo-controlled crossover design. Placebo consisted of breathing room air. In random order, 100% oxygen or room air was administered via a nonrebreathing mask for 15 minutes. After a 30-minute recovery period, the other gas (room air or 100% oxygen) was administered via a nonrebreathing mask for 15 minutes.

Analyses

The amplitude of each burst was determined, and sympathetic activity was calculated as bursts per minute, bursts for 100 heartbeats (which allows comparison of sympathetic discharge between indi-
viduals), and bursts per minute multiplied by mean burst amplitude (in arbitrary units). MSNA-related data were collected by N.F., F.D., and M.L.; sampled by a research assistant; and analyzed blindly by investigators. The baseline data of the 36 patients included were analyzed. Demographic data and baseline characteristics of the 2 groups (CHF and anemia, as well as CHF) were compared by use of an unpaired Student t test. The responses to administration of 100% oxygen and room air were assessed as comparisons between measure-
ments taken during the last 5 minutes of each period of hyperoxia or room air administration. Data were analyzed by repeated-measures ANOVA within gas (100% oxygen versus room air). The P values for differences within a session were obtained by post hoc tests. Measurements of nerve activity during each period were compared between the 2 groups using the unpaired Student t test. Data are presented as the mean ± SEM. A P value <0.05 was considered significant.

Results

Clinical Characteristics

The demographic characteristics of the 2 populations did not significantly differ (Table 1). According to the definition we used, hemoglobin value was the only characteristic that differed significantly between the 2 groups (P < 0.0001). There were no differences in drugs received, including neurohormonal blockers in particular. Patients in both groups had significant dilation of the left ventricle. These parameters did not differ between the 2 groups.

Assessment of Sympathetic Nerve Activity

Baseline characteristics of the patients with CHF and the patients with CHF and anemia are presented in Table 2. BP and heart rate in patients with CHF and anemia did not significantly differ from those observed in patients with only CHF. Baseline MSNA was elevated (expressed in bursts per minute, in bursts per 100 heartbeats, and in MSNA mean amplitude) in patients with CHF and anemia compared with patients with CHF alone (Table 2).

MSNA was strongly correlated with severity of anemia (P = 0.0084; r = 0.433; Figure 1). In patients with HF alone, BP, heart rate, and MSNA when breathing 100% oxygen were similar to those observed when breathing room air (Table 3 and Figure 2A). Chemoreflex deactivation with 100% oxygen decreased MSNA significantly in patients with CHF and anemia (Table 3 and Figure 2B). The frequency of
MSNA typical of this condition. This confirms the results of previous studies that, in the absence of any concomitant disease, anemia is associated with sympathetic activation. However, these observations refer to anemia not associated with CHF, and this link has been extrapolated to CHF-related anemia without any pathophysiological evidence, until our study. Our findings, on the basis of direct recording of sympathetic nervous system (SNS) activity in patients with CHF-related anemia, are the first evidence that such a link exists. We also document for the first time that this sympathostimulating influence is retained even under conditions in which sympathetic activity is already elevated.

This study also provides information on the mechanisms that may be responsible for the greater sympathetic activation characterizing a CHF state complicated by anemia. Hence, chemoreflex deactivation decreases MSNA in patients with CHF and anemia. Additional sympathoactivation could, thus, be mediated by anemia-related tonic activation of chemoreflex.

This, in turn, contributes to elevated MSNA, BP, or heart rate and conceivably increases the cardiovascular risk profile of CHF patients.

Discussion

The novel and important findings of this study are that anemia increases sympathetic activity in patients with CHF and that chemoreflex deactivation decreases MSNA in patients with CHF and anemia. Tonic chemoreflex activation may, therefore, partly contribute to elevated MSNA and, thus, to increased cardiovascular risk in patients with anemia and CHF. This study provides for the first time a possible explanation for the high incidence of sudden death, mortality, or morbidity observed in patients with CHF and comorbid anemia, namely, chemoreflex-related sympathetic activation.

Our data provide evidence that CHF associated with anemia considerably enhances the already elevated levels of MSNA bursts/min with increasing hemoglobin concentration (P=0.0084, r=0.433).

Table 1. Main Demographic, Clinical, and Biochemical Data in the Study Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CHF Patients (n=18)</th>
<th>CHF-A Patients (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>15/3</td>
<td>15/3</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.8±2.3</td>
<td>63.4±2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.1±0.8</td>
<td>26.7±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic cardiopathy cause, n (%)</td>
<td>11 (61)</td>
<td>14 (77)</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA distribution (n)</td>
<td>II (9); III (9)</td>
<td>II (12); III (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Radionuclide LVEF, %</td>
<td>28.7±1.8</td>
<td>29.9±2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter, mm</td>
<td>69.1±2.6</td>
<td>66.4±3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Natremia, mmol/L</td>
<td>136±1.1</td>
<td>134±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Kalemia, mmol/L</td>
<td>4.1±0.1</td>
<td>4.1±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>10.1±2.9</td>
<td>19±5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma brain natriuretic peptide, pg/mL</td>
<td>415±79</td>
<td>573±134</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.6±0.2</td>
<td>11.2±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Red blood cell volume, fl</td>
<td>93.8±1.8</td>
<td>87.6±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>102.1±4.1</td>
<td>102.1±3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>82.1±4.0</td>
<td>75.5±4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>13 (72)</td>
<td>16 (89)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitors + AT₁ receptor blockers</td>
<td>16 (89)</td>
<td>12 (66)</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>16 (89)</td>
<td>13 (72)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are the mean±SEM; CHF-A indicates CHF associated with anemia; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; AT₁, angiotensin II type 1; NS, not significant; CRP, C-reactive protein.

Figure 1. Regression of baseline MSNA (bursts per minute)/hemoglobin (grams per deciliter; n=36).
We can exclude the possibility that the greater sympathetic activity seen in patients with CHF and anemia was attributed to greater CHF severity, because patients were matched according to New York Heart Association class, left ventricular ejection fraction, and telediastolic diameter. It is also known that respiratory rate is an important parameter that can interfere with autonomic tone. Comparison between groups at baseline and during hyperoxia showed no differences despite peripheral chemoreflex activation (Table 3). This could be related to experimental and clinical observations showing that peripheral chemoreceptors are not the main mediator of increased ventilation and that there are other nonperipheral chemoreceptor-mediated mechanisms involved.\textsuperscript{17} Furthermore, hemoglobin level was strongly correlated with MSNA, pointing out a possible link between anemia and sympathetic tone in CHF (Figure 1).

We emphasize the role of the chemoreflex in the increased sympathetic activity of patients with CHF and anemia. Sympathetic activation has been increasingly implicated in both CHF and anemia. This feature is mainly related to a blunted effect of inhibitory reflexes.\textsuperscript{18,19} Regarding excitatory reflexes, data are conflicting. In HF animal models, the augmented sympathetic drive during hypoxia is largely influenced by the tonic excitatory influence of peripheral chemoreflex activity.\textsuperscript{20,21} In humans, van de Borne et al\textsuperscript{22} showed that tonic chemoreflex activation does not contribute to elevated MSNA in HF patients, whereas Ponikowski et al\textsuperscript{23} observed that HF patients with peripheral chemoreceptor hypersensitivity were those with a poor outcome. Our study suggests that anemia, in combination with CHF, could lead to chemoreflex-related sympathetic overactivity. The strength of this study lies, first, in the randomized vehicle-controlled study design and, second, in the inclusion of anemia and CHF patients and control CHF patients with similar age, BP, body mass index, left ventricular ejection fraction, and sex distribution. This minimized any potential effects of confounding factors on our data. Finally, we excluded all of the other causes of anemia to include only “true” HF-related anemia.\textsuperscript{9,10}

Hyperoxia does not result in normalization of sympathetic traffic, despite a significant decrease in the amplitude of SNS

### Table 3. Effects of Room Air (Placebo) and 100% Oxygen

<table>
<thead>
<tr>
<th>Measurement</th>
<th>CHF Patients (n=18)</th>
<th>CHF-A Patients (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>100% Oxygen</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg</td>
<td>108.9±3.9</td>
<td>109.6±4.4</td>
</tr>
<tr>
<td>Mean diastolic blood pressure, mm Hg</td>
<td>66.9±2.6</td>
<td>66.9±2.7</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>42.0±2.6</td>
<td>42.7±3.2</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67.7±3.4</td>
<td>67.1±3.4</td>
</tr>
<tr>
<td>Respiratory rate, cycles per min</td>
<td>17.6±1.2</td>
<td>17.1±1.2</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>95.3±0.4</td>
<td>99.2±0.1*</td>
</tr>
<tr>
<td>MSNA, bursts per min</td>
<td>45.9±3.2</td>
<td>47.3±3.4</td>
</tr>
</tbody>
</table>

Values are mean±SEM. CHF+A indicates CHF associated with anemia.

*P<0.05 vs normoxia.
†P<0.05 vs patients with heart failure only.

We can exclude the possibility that the greater sympathetic activity seen in patients with CHF and anemia was attributed to greater CHF severity, because patients were matched according to New York Heart Association class, left ventricular ejection fraction, and telediastolic diameter. It is also known that respiratory rate is an important parameter that can interfere with autonomic tone. Comparison between groups at baseline and during hyperoxia showed no differences despite peripheral chemoreflex activation (Table 3). This could be related to experimental and clinical observations showing that peripheral chemoreceptors are not the main mediator of increased ventilation and that there are other nonperipheral chemoreceptor-mediated mechanisms involved.\textsuperscript{17} Furthermore, hemoglobin level was strongly correlated with MSNA, pointing out a possible link between anemia and sympathetic tone in CHF (Figure 1).

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Hyperoxia does not result in normalization of sympathetic traffic, despite a significant decrease in the amplitude of SNS

![Figure 2](https://hyper.ahajournals.org/)

**Figure 2.** A, Individual SNS activity during hyperoxia in patients with CHF. B, Individual SNS activity during hyperoxia in patients with CHF associated with anemia.
activity when patients with anemia were exposed to hyperoxia. Although differences were not statistically significant, MSNA after hyperoxia in CHF patients with anemia tended to be higher than MSNA in patients with CHF alone. These observations suggest that anemia is able to increase sympathetic activity through various mechanisms other than tonic activation of chemoreflexes. Most of these mechanisms can directly increase SNS activity. Hence, hemodilution is a key factor for “pseudoanemia” in HF. In our study, sodium and B-type natriuretic peptide level did not differ between the 2 groups, but transient increase in natriuretic peptide could have contributed to partial sympathetic activation. We excluded patients with renal dysfunction, which is a known factor able directly or indirectly to increase SNS tone. Through C-reactive protein screening, we excluded patients with subclinical inflammation; however, all of the cytokines were not measured, and some are known to increase SNS tone during anemia. Chronic disease and/or cachexia are also associated with anemia and are known to increase SNS, but the patients in our study did not present these states. Finally, we excluded iron deficiency and drug adverse effects. Renin angiotensin system blockers and β-blockers are known to be associated with anemia, but their distribution was similar in both groups.

A limitation in our study is the lack of difference in baseline oxygen saturation between the groups. However, it is well established that oxygen saturation only partly reflects arterial oxygen level and extraction capacity. Hence, for an oxygen saturation value between 90% and 100%, the partial pressure in oxygen can range from 60 to 100 mm Hg. We performed arterial blood-gas analysis in a subset of patients, and none of collected parameters were different between the groups. Thus, we propose that chemoreflex activation in CHF patients with anemia could be mediated through tissular hypoxemia at the level of carotid bodies by a lack of oxygen extraction. This local tissular hypoxemia is not detectable and incompletely reflected by noninvasive and invasive measurement realized in our study. This also underlines that the diagnosis of anemia should be sought even in CHF patients without clinical signs of hypoxemia and that normal oxygen saturation falsely reassures but is in fact associated with an increased SNS drive to the cardiovascular system. We performed extensive red blood cell and white blood cell counts but we cannot rule out the possibility that CHF patients may have partly impaired bone marrow function or erythropoietin resistance. Another limitation in our study is the effect of treatment. For ethical reasons, treatment was not withdrawn in patients. Nevertheless, prescription of β-blockers and renin-angiotensin-aldosterone system blockers was similar in both groups. These drugs are likely to improve baroreflex control and, thus, diminish the effect of chemoreflex deactivation, and they should rather decrease the chemoreflex-mediated effect on MSNA. Furthermore, we did not investigate other reflexes, such as metaboreflexes, mechanoreflexes, central chemoreflexes, or baroreflexes.

In our study, patients had normal creatinine values as assessed by standard laboratory tests. Studies have shown that chronic renal failure in CHF patients is associated with elevated MSNA, but by laboratory tests for chronic renal failure we excluded all of the patients with potential chronic kidney disease. Our findings do not indicate whether the excessive sympathetic activation occurring in CHF complicated by anemia is limited to the muscular vascular district only or whether it is generalized to the whole cardiovascular system. However, evidence is available that, in both congestive HF and anemia, sympathetic outflow is increased not only at the level of skeletal muscle but also in the coronary and renal circulation, suggesting that a generalized extrapolantion of sympathetic activity by anemia in CHF is a likely possibility. Finally, in CHF and anemia, adrenergic activity is closely related to cardiovascular mortality. Thus, the present demonstration of greater sympathoactivation by anemia in CHF may offer information of prognostic significance and help proper assessment of the overall risk in a number of patients.

Perspectives
The results of the present study demonstrate that anemia potentiates the sympathetic activation characterizing CHF. Despite a significant number of publications, to the best of our knowledge this is the first study investigating specific pathophysiological mechanisms leading to CHF-related anemia. Chemoreflexes appear to be important modulators of neural circulatory control in CHF patients with anemia. The potential role of chemoreflexes in inducing tonic sympathetic activation may be of potential relevance to devising future treatment strategies for anemia in HF and its cardiovascular consequences. They further show the involvement of chemoreflex activation in this setting, and it would be interesting to determine whether the above-mentioned alterations can be reversed by therapeutic interventions.

Sources of Funding
This work was supported by Centre National de Gestion des Essais de Produits de Santé (F.D.), Programme Hospitalier de Recherche Clinique (equipment and technical staff), and Centre d’Etudes du Système Nerveux Autonome (equipment).

Disclosures
None.

References


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Hypertension. published online March 1, 2010;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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