Excessive Sympathetic Activation in Heart Failure With Obesity and Metabolic Syndrome
Characteristics and Mechanisms

Guido Grassi, Gino Seravalle, Fosca Quart-Trevano, Francesco Scopelliti, Raffaella Dell’Oro, Gianbattista Bolla, Giuseppe Mancia

Abstract—Congestive heart failure is characterized by sympathetic activation, which has also been described in the metabolic syndrome. No information exists, however, as to whether the sympathostimulating effects of these 2 conditions summate when heart failure is complicated by the metabolic syndrome, leading to an exceedingly high adrenergic drive. This is clinically relevant, because in heart failure sympathetic activation is closely related to mortality. We studied 48 control subjects (age: 58.4 ± 1.6 years, mean ± SEM) and 89 age-matched heart failure patients (New York Heart Association class II), of whom 47 were without and 42 were with metabolic syndrome. Measurements included blood pressure (Finapres), heart rate (ECG), and sympathetic nerve traffic (microneurography) at rest and during baroreceptor manipulation. Waist circumference, blood pressure, and metabolic variables were greater in heart failure with metabolic syndrome than in heart failure without metabolic syndrome and in control subjects. Left ventricular ejection fraction and end-diastolic diameter were similarly altered in the 2 heart failure groups. Compared with control subjects, sympathetic nerve activity was greater in heart failure patients without metabolic syndrome (64.7 ± 3.2 versus 45.9 ± 2.9 bursts/100 heartbeats; P < 0.01), a further pronounced increase being detected in those with metabolic syndrome (80.9 ± 3.2 bursts/100 heartbeats; P < 0.01). In the multivariate analysis, waist circumference and body mass index were the variables most closely related to sympathetic activation. Compared with control subjects, baroreflex responses were significantly attenuated in the 2 heart failure groups, the impairment being more marked in the group with than without metabolic syndrome. Thus, obesity and metabolic syndrome potentiate the sympathetic activation characterizing heart failure. This potentiation is likely to mainly depend on metabolic and baroreflex mechanisms. (Hypertension. 2007; 49:535-541.)

Key Words: baroreflex □ metabolic syndrome □ heart failure □ sympathetic nervous system

Indirect and direct indices of sympathetic activity, such as venous plasma norepinephrine, plasma norepinephrine spillover from adrenergic nerve terminals, and muscle sympathetic nerve firing rate, have shown that sympathetic cardiovascular influences are increased in a high-risk condition such as congestive heart failure (CHF).1–4 They have also shown that this neuroadrenergic alteration is directly related to the severity of the CHF state1,4 and similar in magnitude in CHF of ischemic or idiopathic dilated etiology.1,5 Evidence has also been provided that a hyperadrenergic state characterizes the clustering of risk factors known as metabolic syndrome (MS),6–8 which also represents a high-risk condition for the development of CHF.9 Several studies have shown that some components of MS (eg, obesity and hypertension) have sympathostimulating effects,10–13 which can, to some extent, also be seen in CHF patients.14 Whether and to what extent the clustering of blood pressure, body weight, and metabolic alterations known as MS leads to a further increase in sympathetic drive is unknown, however. This is a question of clinical relevance, because CHF and MS frequently coexist in the same patient15,16 and, in CHF, the degree of sympathetic activation is related to patient’s mortality.17,18

The present study has been undertaken to determine the impact of CHF complicated by MS on sympathetic function, as assessed by either microneurographic nerve traffic recording or venous plasma norepinephrine assay. The study was also aimed at assessing whether and to what extent reflex mechanisms are involved in the sympathetic overactivity possibly occurring in CHF combined with MS. This was done by examining in the study population baroreceptor influences on sinus node activity, as well as on muscle sympathetic nerve traffic.

Methods

Study Population
The study population consisted of 137 subjects of both genders (85 men and 52 women, with age ranging from 49 to 66 years).

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From the Clinica Medica, Dipartimento di Medicina Clinica (G.G., F.Q.-T., F.S., R.D., G.M.), Prevenzione e Biotecnologie Sanitarie, Università Milano-Bicocca, Ospedale San Gerardo, Milan, Italy; Istituto Auxologico Italiano (G.G., G.S., G.M.), Milan, Italy; and Centro Interuniversitario di Fisiologia Clinica e Ipertensione (G.G., G.B., G.M.), Milan, Italy.
Correspondence to Guido Grassi, Clinica Medica, Ospedale San Gerardo dei Tintori, Via Pergolesi 33, 20052 Milan, Italy. E-mail guido.grassi@unimib.it
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Eighty-nine subjects had a CHF, whereas the remaining subjects were age-matched healthy controls. Subjects with CHF were recruited if belonging to New York Heart Association class II, with only a modest reduction in echocardiographic ejection fraction (35% to 45%) and with or without the concomitant presence of MS, as defined at a routine control visit a few days before the study. MS was diagnosed based on the presence of ≥3 of the 5 diagnostic criteria proposed by the National Cholesterol Educational Program Adult Treatment Panel in the 2005 revised version,\(^9\) that is, abdominal obesity (waist circumference >102 cm in men and >88 cm in women), fasting hypertriglyceridemia (plasma triglycerides ≥150 mg/dL), low high-density lipoprotein cholesterol (plasma high-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women), a blood pressure elevation (blood pressure values ≥130/85 mm Hg or treatment with antihypertensive drugs), and fasting hyperglycemia (plasma glucose >100 mg/dL).\(^1\)

Subjects were excluded from the study if they had secondary hypertension, atrial fibrillation or other major cardiac arrhythmias, history of myocardial infarction in the 12 months preceding the study, clinical or laboratory evidence of valvular heart disease, history of smoking and/or excessive alcohol consumption, presence of renal insufficiency or other conditions known to affect autonomic cardiovascular control, history of regular exercise habit or involvement in physical training programs, and history of symptoms suggestive of obstructive sleep apnea syndrome. Each subject underwent sphygmomanometric blood pressure measurements, as well as assessment of body weight, body mass index, and waist circumference. Total serum cholesterol, plasma triglycerides, high-density lipoprotein plasma cholesterol (enzymatic method), and glucose (standard glucose oxidase method) were measured in the fasting state from a venous blood sample. Subjects were classified as one of the following: (1) healthy control subjects (n = 48), (2) patients with CHF (n = 47) of either ischemic (n = 30) or idiopathic (n = 17) nature without MS, or (3) patients with congestive CHF (n = 42) of either ischemic (n = 26) or idiopathic (n = 16) nature who met the definition of MS. Control subjects were under no drug treatment, and they were studied on an outpatient basis. No patient with CHF was under antiadrenergic drugs. All of the CHF patients were under treatment with furosemide, angiotensin-converting enzyme inhibitors, \(\beta\)-blockers, or angiotensin II receptor blockers. With the exception of loop diuretics, cardiovascular drugs were withdrawn 4 to 6 days before the study, which was performed after a 2- to 3-day hospitalization.

The study protocol was approved by the ethics committee of 1 of the institutions involved. All of the subjects gave written consent to participate at the study after being informed of its nature and purpose.

**Measurements**

The details of the procedures used to assess sphygmomonanometric and beat-to-beat (Finapres 2300, Ohmeda) systolic (S) and diastolic (D) blood pressure (BP) values, heart rate (HR) ECG, respiration rate (pneumotachograph), echocardiographic variables (left ventricular end-diastolic diameter and left ventricular ejection fraction), multi-unit recording of efferent muscle sympathetic nerve activity ([MSNA] microneurography), plasma norepinephrine (high-performance liquid chromatography), and plasma renin activity (radioimmunoassay) have been described previously.\(^3,5,7,11,14,20–22\)

Mean BP was calculated by adding one third of pulse pressure to diastolic BP. Beat-to-beat BP, HR, respiration rate, and MSNA were displayed on a thermic paper of an ink polygraph (Gould 3800). Under baseline conditions, MSNA was quantified either as number of bursts per minute or as number of bursts per 100 heart beats. Either quantification has been shown to be highly reproducible, that is, to differ by only 3.8% when assessed on the same tracing on 2 separate occasions by a single investigator.\(^23\) Baroreceptor modulation of MSNA and HR was assessed by the vasoactive drug technique.\(^5,7,11,14\)

Briefly, phenylephrine was incrementally infused in an antecubital vein at doses of 0.3, 0.6, and 0.9 \(\mu\)g/kg per minute, each step being maintained for 5 minutes. Nitroprusside was also incrementally infused in an antecubital vein at doses of 0.4, 0.8, and 1.2 \(\mu\)g/kg per minute, each step being maintained for 5 minutes. In all of the subjects, the drug initially infused was selected randomly, and the end of the first infusion was separated from the beginning of the second one by a suitable recovery period. Systolic BP, diastolic BP, mean BP, MSNA, and HR were averaged for the 5 minutes before infusion and for the 5 minutes of each step infusion. Baroreceptor modulation of MSNA and HR was estimated by calculating the absolute and percentage changes in integrated activity (ie, mean burst amplitude multiplied by bursts number over time) and the changes in HR in relation to the BP changes induced by each dose of phenylephrine and nitroprusside. In each patient, the ratio between MSNA and HR changes was analyzed separately for the 3-step infusions of phenylephrine and nitroprusside. The data were then further averaged to obtain MSNA- or HR-baroreflex sensitivity.

**Protocol and Data Analysis**

All of the subjects were brought to the laboratory in the morning after an overnight fasting. They were put in the supine position and fitted with intravenous canulas, microelectrodes for MSNA recording, and other measuring devices. Blood samples for norepinephrine and renin assay were then taken, and BP was measured 3 times with a mercury sphygmomanometer. After a 30-minute interval, BP, HR, respiration rate, and MSNA were continuously measured during an initial 10-minute basal state, the intravenous infusion of 1 vasoactive drug, a 45-minute recovery period followed by a second 10-minute basal state, and the intravenous infusion of the second vasoactive drug.

Data were collected in a quiet room at a constant temperature of 20°C to 21°C and analyzed by a single investigator unaware of the belonging of the patients to different groups. Baseline individual values were averaged for each group and expressed as mean ± SEM. This procedure was also followed for the changes in mean BP, MSNA, and HR induced by each dose of vasoactive drugs. Comparisons between data obtained in different groups were made by 2-way ANOVA. The 2-tailed \(t\) test for unpaired observations was used to locate between-group differences. The Bonferroni correction was used to account for multiple comparisons. A multivariate analysis was also performed with age, gender, BP, left ventricular ejection fraction, body mass index, waist circumference, plasma triglycerides, blood glucose, and high-density lipoprotein cholesterol as independent variables and MSNA as the dependent one. A value of \(P<0.05\) was considered statistically significant.

**Results**

**Baseline Values**

As shown in the Table, CHF patients with MS, CHF patients without MS, and control subjects were matched for age. Compared with control subjects, patients with CHF displayed a significant reduction in left ventricular ejection fraction, as well as a significant increase in left ventricular end-diastolic diameter, HR, plasma renin activity, and plasma norepinephrine. The average values were superimposable in the groups without and with MS, which also showed similar ranges of left ventricular ejection fraction and end-diastolic diameter.

As expected, sphygmomonanometric and finger BP, body mass index, waist circumference, and biochemical variables related to glucose and lipid metabolism were all altered in CHF patients with MS when compared both with control subjects and CHF patients without MS (Table).

**Sympathetic Activity**

The individual and the average MSNA data for the 3 groups are shown in Figure 1. MSNA showed an interindividual variability within each group. Compared with control subjects, CHF patients without MS displayed greater MSNA values (+41.2%), which showed, however, a further increase...
MSNA values in Control Subjects and in Heart Failure Patients Without and With MS

<table>
<thead>
<tr>
<th>Variable</th>
<th>C (n=48)</th>
<th>CHFMS− (n=47)</th>
<th>CHFMS+ (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male/female</td>
<td>28/20</td>
<td>30/17</td>
<td>27/15</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.4±1.6</td>
<td>59.2±1.4</td>
<td>60.1±1.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2±0.4</td>
<td>23.8±0.4</td>
<td>30.3±0.6†</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>94.7±1.3</td>
<td>94.0±0.9</td>
<td>103.5±1.7†</td>
</tr>
<tr>
<td>Sphygmo BP, S/D, mm Hg</td>
<td>129.4±1.4/79.5±1.1</td>
<td>125.6±1.5/78.2±0.9</td>
<td>144.5±1.9*/88.7±1.7†</td>
</tr>
<tr>
<td>Finger BP, S/D, mm Hg</td>
<td>127.6±1.3/77.8±1.2</td>
<td>123.8±1.4/77.1±0.8</td>
<td>142.3±2.0*/87.2±1.7†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67.5±1.5</td>
<td>74.7±1.8‡</td>
<td>78.2±2.0*</td>
</tr>
<tr>
<td>LVEF %, mean</td>
<td>62.1±0.8</td>
<td>38.9±1.1*</td>
<td>38.1±0.9*</td>
</tr>
<tr>
<td>LVEF %, range</td>
<td>58 to 66</td>
<td>36 to 45</td>
<td>35 to 45</td>
</tr>
<tr>
<td>LVEDD mm, mean</td>
<td>52.7±0.7</td>
<td>63.9±1.0*</td>
<td>64.3±0.9*</td>
</tr>
<tr>
<td>LVEDD mm, range</td>
<td>49 to 54</td>
<td>58 to 64</td>
<td>58 to 65</td>
</tr>
<tr>
<td>PRA, ng/mL per hour</td>
<td>1.2±0.2</td>
<td>2.9±0.4*</td>
<td>3.0±0.5*</td>
</tr>
<tr>
<td>Plasma NE, pg/mL</td>
<td>217.4±18.0</td>
<td>340.5±26.0‡</td>
<td>359.6±29.0‡</td>
</tr>
</tbody>
</table>

Data are shown as mean±SEM. C indicates control subjects; CHFMS−, heart failure patients without and with MS; BMI, body mass index; Sphygmo, sphygmomanometric; S, systolic; D, diastolic; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; PRA, plasma renin activity; NE, norepinephrine.

Symbols refer to the statistical significance between groups (*P<0.05, †P<0.01 vs controls; ‡P<0.01 vs congestive heart failure without MS).

(±38.4%) in CHF patients with MS. The between-group average differences were statistically significant, and the results were similar both when MSNA was quantified as burst incidence per unit of time and as burst incidence corrected for HR. This was the case also when we excluded from the analysis individuals in which sphygmomanometric BP was ≥130 mm Hg systolic and/or >85 mm Hg diastolic, that is, when MS included the BP elevation as a component (Figure 2). In the multivariate analysis performed on the whole study sample, MSNA was directly related to waist circumference and body mass index (β-coefficient 0.64±0.08 and 0.60±0.09, respectively; P<0.01 for both) while showing no significant relationship with other hemodynamic and metabolic variables.

Baroreflex Responses

Figure 3 (top) shows that, in control subjects and in CHF patients, HR and MSNA decreased linearly as mean BP increased progressively from the lowest value observed with the greatest nitroprusside dose to the highest value observed with the greatest phentolamine dose, the overall range of HR and MSNA changes being markedly less than that observed in controls. Figure 3 (top) also shows that, in CHF patients, because of their higher baseline MSNA and HR values, the set point of the baroreflex was displaced to the right and more so when MS was present. Furthermore, as shown in the bottom of Figure 3, the sensitivity of baroreceptor HR and baroreceptor MSNA was markedly reduced in CHF patients without MS as compared with control subjects, a further
Figure 2. MSNA values, expressed as bursts incidence over time (bs/min) and as bursts number corrected for HR (bs/100 hb), in CHFMS− and in CHF with MS not complicated (CHFMS+HT−) or complicated (CHFMS+HT+) by hypertension. Data referring to baseline mean BP, body mass index (BMI), and waist circumference (WC) in each group are shown below each panel. Data are shown as mean±SEM. For symbols and explanations see Figure 1. **P<0.01 refers to the statistical significance between groups.

Figure 3. Top, Absolute values of HR and MSNA before and during graded increases and reductions in mean BP induced by vasoactive drugs in the 3 groups of subjects of Figure 1. Bottom, baroreceptor HR and MSNA sensitivities, expressed as average ratios between changes in HR (ΔHR) or MSNA (ΔMSNA) over changes in mean BP, in the 3 groups of subjects. Data are shown as mean±SEM. For symbols and explanations see Figure 1. **P<0.01 refers to the statistical significance between groups.
significant reduction occurring in patients in which CHF was combined with MS. This is shown also in Figure 4, which illustrates the HR and MSNA changes in response to stepwise doses of phenylephrine and nitroprusside. Baseline MSNA was significantly and inversely related to MSNA-baroreflex sensitivity in all of the study’s sample \( (r = -0.38; P < 0.01) \). No such correlation was found between baseline HR values and HR baroreflex sensitivity \( (r = -0.08; P \text{ value not significant}) \).

Discussion

Our data provide evidence that CHF associated with obesity and MS considerably enhances the already elevated levels of MSNA typical of this condition. This confirms the results of previous studies that, in the absence of any concomitant disease, MS is associated with sympathetic activation.6–8 It documents for the first time, however, that this sympathostimulating influence is retained even under conditions in which sympathetic activity is already elevated.

Our study also provides information on the mechanisms that may be responsible for the greater sympathetic activation characterizing a CHF state complicated by MS. We can rule out that the greater sympathetic activity seen when CHF was associated with MS was because of a greater CHF severity, because patients were selected only if their CHF belonged to New York Heart Association class II and the groups with or without MS had similar average values (as well as similar ranges) of left ventricular ejection fraction and end-diastolic diameter. Furthermore, they had similar plasma renin activity values, suggesting a similar degree of renin–angiotensin system activation. We can also rule out that differences in drug treatment were responsible, because hospitalization allowed drugs used in CHF (and known to affect sympathetic cardiovascular influences24–27) to be withdrawn and to uniformly maintain all of the patients under diuretic treatment only. We can finally rule out that a between-group imbalance of patients with ischemic CHF versus idiopathic cardiomyopathy was involved, because for the same severity these 2 conditions have been shown to be similarly capable of triggering a sympathetic activation.5 This means that the greater sympathetic activation should be ascribed to the components of this condition. In this context, although a BP elevation has been shown to exert sympathostimulating effects,10–11,14 we can rule out that the BP component played a major role, because, in CHF patients with MS, MSNA was greater than in those without MS also when hypertensive subjects were excluded, and, in the multivariate analysis, no significant independent relationship was found between BP and MSNA. We can, on the other hand, suggest that the increase in body weight plays an important role, because, in the multivariate analysis, body mass index did show an independent relationship with MSNA. It is interesting to note that in this analysis MSNA was independently related also to waist circumference, suggesting an independent sympathostimulating effect of visceral adiposity. We can speculate that substances with sympathostimulating effects of which the circulating plasma levels are increased in obesity (leptin, adiponectin, etc28,29) are responsible for the finding. It is also possible that factors such as insulin and sleep apnea play an important role, because insulin is a powerful stimulant of MSNA29 and its plasma levels are already elevated in CHF because of an insulin resistance state,30 and, even in absence of a clinical history, sleep apnea might have been present and promoted a sympathetic activation via chemoreceptor activa-
tion and possibly sleep deprivation.31,32 In this context, however, it should be emphasized that, compared with CHF patients without MS, in our CHF patients with MS the set point of the baroreflex was displayed to the right in relation to the greater baseline HR and MSNA. Furthermore, the baroreflex ability to modulate MSNA was more markedly impaired in these patients. This means that the ability of the baroreflex to tonically and phasically restrain MSNA is more markedly impaired in CHF with than without MS. Our study, thus, indicates baroreflex derangement as a further mechanism behind the excessive sympathetic activation seen when CHF and MS are combined together.

Several other findings deserve to be discussed. First, plasma norepinephrine, although significantly greater in CHF than in control subjects, did not differ in patients with or without MS. This represents a further example that, in humans, plasma levels of the adrenergic neurotransmitter often represent a less than optimal marker of changes in sympathetic drive presumably because short- and long-term reproducibility of plasma norepinephrine assay is limited.23 and plasma norepinephrine levels depend not only on secretion but also on tissue clearance and reuptake.33,34 Second, our data do not clarify whether the excessive sympathetic activation occurring in CHF complicated by MS is limited to the muscle vascular district or whether it is generalized to the whole cardiovascular system. Evidence is available, however, that in both congestive CHF and MS, sympathetic outflow is increased not only at the level of the skeletal muscle but also in the coronary and renal circulation,2,3 suggesting that a generalized extrapolentiation of sympathetic activity by MS in CHF is a likely possibility. Third, in CHF, adrenergic activity is closely related to cardiovascular mortality.17,18 Thus, the present demonstration of a greater sympathoactivation by MS 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 MS potentiatates the sympathetic activation characterizing mild CHF. They further show that the most important determinant of this activation is likely to be visceral obesity with a contribution, however, from a greater baroreflex dysfunction compared with that already characterizing heart failure. Future studies are needed to determine whether and to what extent the above-mentioned alterations can be reversed by the therapeutic intervention.

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Disclosures

None.

References


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