Sympathetic and reflex abnormalities in heart failure secondary to ischaemic or idiopathic dilated cardiomyopathy

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ABSTRACT

Congestive heart failure (CHF) is characterized by a sympathetic activation and a baroreflex impairment whose degree is directly related to the clinical severity of the disease. However, whether these abnormalities vary according to the ischaemic or idiopathic dilated nature of the CHF state has not been conclusively documented. In patients with a clinically stable, chronic CHF state in New York Heart Association functional class II and III, due either to ischaemic heart disease (IHD; n = 22, age 60.3 ± 2.4 years, means ± S.E.M.) or to idiopathic dilated cardiomyopathy (IDC; n = 20, age 58.9 ± 2.8 years), and in 30 age-matched controls, we measured arterial blood pressure (using a Finapres device), heart rate (by electrocardiogram) and postganglionic muscle sympathetic nerve traffic (by microneurography) at rest and during baroreceptor manipulation induced by the vasoactive drug-infusion technique. Blood pressure values were not significantly different in CHF patients and controls. Compared with controls, heart rate was similarly increased and left ventricular ejection fraction (by echocardiography) similarly reduced in CHF patients with IHD or IDC. Muscle sympathetic nerve traffic was significantly greater in CHF patients than in controls, and did not differ between patients with IHD or IDC (67.3 ± 4.2 and 67.8 ± 3.8 bursts/100 heart beats respectively). This was also the case for the degree of baroreflex impairment. These data show that CHF states due to IHD or to IDC are characterized by a similar degree of peripheral sympathetic activation and by a similar impairment of the baroreflex function. Thus the neuroadrenergic and reflex abnormalities characterizing CHF are independent of its aetiology.

INTRODUCTION

Congestive heart failure (CHF) is characterized by a sympathetic activation that has been shown to have a prognostic significance, i.e. to be directly related to the CHF severity and inversely related to patients’ survival [1–6]. Whether the adrenergic overactivity typical of CHF is different in CHF conditions of different aetiologies has not been conclusively documented. This is because two methods to quantify cardiac sympathetic influences (the noradrenaline spillover into the coronary circulation and the [123I]metaiodobenzylguanidine-imaging technique), have shown them to be similarly increased in CHF due to

Key words: arterial baroreceptors, autonomic nervous system, heart failure, sympathetic activity.

Abbreviations: CHF, congestive heart failure; IDC, idiopathic dilated cardiomyopathy; IHD, ischaemic heart disease.

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METHODS

Study population

The present study was performed on 42 patients of both sexes ranging from 32 to 69 years who had: (i) a body mass index (body weight in kilograms divided by the square of the height in metres) < 27; (ii) no history or objective evidence of hypertension; (iii) no clinical or laboratory evidence of valvular heart disease, diabetes mellitus or renal insufficiency; (iv) no physical or laboratory evidence of valvular heart disease, diabetes mellitus or renal insufficiency; (v) no history of coronary artery bypass surgery; and (vi) a clinically stable CHF belonging to the New York Heart Association class II or III, and due either to IHD (n = 22) or to IDC (n = 20).

The diagnosis of the IHD aetiology was based on: (i) the history of a previous (≥ 6 months) myocardial infarction and/or the electrocardiographic evidence of myocardial infarction or ischaemia; (ii) the echocardiographic evidence of regional alterations in left ventricular wall motion; (iii) the positive result of an echostress test performed by dipyridamole or dobutamine; and (iv) the angiographic evidence of one or more haemodynamically significant (≥ 70% of the lumen) coronary artery stenoses. The diagnosis of IDC was made by: (i) the lack of history of chest pain; (ii) the absence of signs of ischaemia or myocardial infarction at the electrocardiogram; (iii) the uniform dilatation of the left ventricle at the echocardiogram, with no regional left ventricular dyskinesia at the echostress test; and (iv) the presence of a normal coronary angiogram. IDC diseases due to cardioxic drugs and/or substances (including alcohol abuse) were excluded. All patients were hospitalized for at least 7 days. Pharmacological treatment based on angiotensin-converting-enzyme inhibitors, diuretics or digitalis was withdrawn at least 6 days before the study, whereas aspirin administration was not discontinued. Nitrates were given according to clinical needs, but withdrawn if administered during the 48 h preceding the study. Hospital inpatients (n = 30) recovering from non-cardiovascular disorders (pneumonia, gastrointestinal diseases, urinary infections etc.) were selected as controls. Control patients did not have hypertension, heart disease, diabetes or other conditions known to affect neural cardiovascular control, and were matched to CHF patients for gender, age and body mass index. All patients included in the study were in sinus rhythm. In both controls and congestive CHF patients, blood counts, serum electrolytes and renal laboratory function tests were normal. There were 12 smokers in the CHF group and seven in the control group. Patients were not allowed to smoke for the whole period of hospitalization, during which they were not confined to bed, but were allowed to engage in the recreational activities of inpatients (television watching, walking in the hospital ward, visit of relatives etc.). The study protocol was approved by the Ethics Committee of Ospedale Policlinico, Milan and the University of Milan-Bicocca. All patients gave written consent to participate in the study after being informed of its nature and purpose.

Measurements

Blood pressure was measured three times by a mercury sphygmomanometer, the first and fifth Korotkoff sounds being taken as markers of systolic and diastolic values respectively. In addition, arterial blood pressure was continuously monitored by a finger photoplethysmographic device (Finapres 2300; Ohmeda, Englewood, CO, U.S.A.) capable of providing accurate and reproducible beat-to-beat systolic and diastolic values [13, 20]. Heart rate was continuously monitored by a cardiotachometer triggered by the R wave of an electrocardiographic lead. The respiration rate was monitored by a strain-gauge pneumograph positioned at the mid-chest level. Measurements included an echocardiogram performed in M- and in B-mode. This allowed us to assess left ventricular end-diastolic and end-systolic diameters and volumes and to calculate left ventricular ejection fraction [21]. Echocardiographic data were collected by a single operator unaware of the experimental design. The within-operator coefficient of variation of left-ventricular end-diastolic diameter measurements (i.e. the within-operator reproducibility) was 6%.
Multineurite recording of efferent postganglionic muscle sympathetic nerve traffic was obtained through a tungsten microelectrode inserted into the right or left peroneal nerve, as previously described [13,20,22]. The nerve signal was amplified ×70,000, fed through a bandpass filter (700–2000 Hz), and integrated with a custom nerve traffic analysis system (Bioengineering Department, University of Iowa, Iowa City, IA, U.S.A.). Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A; Tektronix, Heereneveen, The Netherlands), and recorded with blood pressure, heart rate and respiratory movements on thermic paper by an ink polygraph (Gould 3800; Gould Instruments, Cleveland, OH, U.S.A.). The muscle nature of sympathetic nerve traffic was assessed according to the criteria outlined in previous studies [13,20,22], and the recording was accepted only if the signal-to-noise ratio exceeded the value of 3. Under baseline resting conditions, postganglionic muscle sympathetic nerve traffic was quantified as bursts/min and bursts/100 heart beats. This quantification was shown to be highly reproducible, i.e. to differ by only 4.3% when assessed on two separate occasions by a single investigator [20].

Plasma noradrenaline was assayed by HPLC [23], and plasma renin activity by RIA [24]. All measurements were obtained from a blood sample drawn from a cannula placed in an antecubital vein of the arm contralateral to that used for sphygmomanometric and finger blood pressure measurements.

Baroreceptor modulation of muscle sympathetic nerve traffic and heart rate was assessed by intravenous infusion of vasoactive drugs [20]. Briefly, phenylephrine was incrementally infused through the cannula placed in an antecubital vein at doses of 0.3, 0.6 and 0.9 µg · kg⁻¹ · min⁻¹. Nitroprusside was also infused incrementally in an antecubital vein at doses of 0.4, 0.8 and 1.2 µg · kg⁻¹ · min⁻¹. Each infusion was maintained for 5 min, and the drug initially infused was randomly selected. The end of the first infusion was spaced from the beginning of the second infusion by a recovery time of 45 min. Mean blood pressure (diastolic pressure plus 1/3 of pulse pressure), muscle sympathetic nerve traffic and heart rate were averaged for 5 min before infusion and for 5 min of each step infusion. Baroreceptor modulation of muscle sympathetic nerve traffic and heart rate was estimated by calculating: (i) the change in the number of bursts/min; (ii) the % change in the integrated activity, i.e. mean bursts amplitude times the number of bursts over time; and (iii) the absolute change in heart rate in relation to the change in mean blood pressure induced by each dose of phenylephrine and nitroprusside.

**Protocol**

CHF patients and control subjects came to the laboratory in the morning after a light breakfast. They were put in the supine position and fitted with the intravenous cannulas, microelectrodes for the muscle sympathetic nerve traffic recording and the other measuring devices. A blood sample was then drawn, and the three sphygmomanometric blood pressure measurements were obtained. After a 30 min interval, blood pressure, heart rate, respiration rate and muscle sympathetic nerve traffic were continuously measured during: (i) an initial 10 min baseline resting condition; (ii) the intravenous infusion of one vasoactive drug; (iii) a 45 min recovery period followed by a second 10 min baseline resting condition; and (iv) the intravenous infusion of the second vasoactive drug.

**Data analysis**

Data were calculated by a single investigator unaware of the patients’ classification. Values from individual subjects were averaged for the different groups and expressed as means ± S.E.M. All statistical analyses were carried out using the SPSS software package [25]. The statistical significance of the difference in mean values was assessed by two-way ANOVA. The two-tailed t test for unpaired observations was used to locate the difference between groups. The two-tailed t test for paired observations was used to locate the difference between resting conditions and baroreceptor stimulation and deactivation. Bonferroni’s correction for multiple comparisons was used. A value of P < 0.05 was taken as the level of statistical significance.

**RESULTS**

**Baseline values**

Table 1 shows that CHF patients with IHD or IDC had a similar age, gender distribution and New York Heart Association functional class distribution. Blood pressure (measured by sphygmomanometry or beat-to-beat at the finger level), heart rate and left ventricular ejection fraction were also similar between the two groups; however, a difference in left ventricular end-diastolic diameter that was significantly greater in patients with IDC was measured. This, however, was not accompanied by any significant between-group difference in plasma renin activity and noradrenaline values (Figure 1, upper graphs). More importantly, muscle sympathetic nerve traffic was not significantly different in CHF patients with IHD and IDC, both when expressed as bursts/min and when the number of sympathetic bursts was corrected for heart rate (Figure 1, lower graphs).

**Baroreflex responses**

As shown in Figure 2, the stepwise baroreceptor stimulation caused a progressively greater bradycardia and
Table 1  Baseline demographic, anthropometric, haemodynamic and echocardiographic characteristics of control subjects and patients with CHF secondary to IHD or IDC

Values shown are means ± S.E.M. LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MBP, mean blood pressure; NYHA, New York Heart Association. Sphygmomanometric MBP was the average of three measurements.

* P < 0.01 versus control subjects; † P < 0.05 versus CHF patients due to IHD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control subjects (n = 30)</th>
<th>CHF patients due to IHD (n = 22)</th>
<th>CHF patients due to IDC (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.0 ± 1.9</td>
<td>60.3 ± 2.4</td>
<td>58.9 ± 2.8</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>25/5</td>
<td>20/2</td>
<td>18/2</td>
</tr>
<tr>
<td>NYHA functional class (II/III)</td>
<td>10/12</td>
<td>9/11</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.9 ± 0.8</td>
<td>25.0 ± 0.6</td>
<td>25.2 ± 0.5</td>
</tr>
<tr>
<td>Sphygmomanometric MBP (mmHg)</td>
<td>95.7 ± 1.9</td>
<td>92.6 ± 1.8</td>
<td>93.7 ± 1.4</td>
</tr>
<tr>
<td>Finger MBP (mmHg)</td>
<td>94.4 ± 1.4</td>
<td>89.4 ± 2.2</td>
<td>90.7 ± 2.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67.2 ± 1.6</td>
<td>79.0 ± 3.0*</td>
<td>77.2 ± 2.5*</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67.4 ± 1.1</td>
<td>34.3 ± 1.1*</td>
<td>33.1 ± 1.6*</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>49.8 ± 0.7</td>
<td>64.5 ± 1.8*</td>
<td>68.2 ± 1.6*†</td>
</tr>
<tr>
<td>Respiration rate (breaths/min)</td>
<td>17.1 ± 1.2</td>
<td>18.0 ± 0.9</td>
<td>18.1 ± 0.9</td>
</tr>
</tbody>
</table>

Figure 1  Sympathetic and renin–angiotensin activation in IHD and IDC

Baseline individual and mean values of plasma noradrenaline (NA), plasma renin activity (PRA) and muscle sympathetic nerve traffic (MSNA; expressed as bursts incidence over time (bursts/min) and corrected for heart rate values (bursts/100 heart beats)) in control subjects (○) and in patients with IHD (E) or IDC (D). NA and MSNA values were always significantly different (* P < 0.05, ** P < 0.01) between patients with CHF and control subjects, but not between patients with IHD and IDC. hb, heart beat.

Sympatho-inhibition, whereas the stepwise baroreflex deactivation caused a progressively greater tachycardia and sympathoexcitation. The magnitude of the reflex heart rate and sympathetic nerve traffic changes was similar in the two CHF groups.

Comparison with controls

In both CHF groups plasma renin activity, plasma noradrenaline and muscle sympathetic nerve traffic were markedly greater than in controls, whereas baroreflex modulation of heart rate and sympathetic nerve traffic was markedly less (Figures 1 and 2). As expected, compared with CHF patients, controls showed markedly lower heart rate and left ventricular end-diastolic diameter values and markedly greater left ventricular ejection fraction values (Table 1).
DISCUSSION

Confirming previous findings of our group and others [1,20,26,27], in our CHF patients plasma noradrenaline and muscle sympathetic nerve traffic were markedly increased compared with controls who were similar to the CHF patients in age, gender, body mass index and blood pressure values. The new finding of the present study, however, is that muscle sympathetic nerve activity is similarly increased in patients where CHF was due to IDC and where a CHF of a similar clinical severity was due to IHD. We can thus conclude that a typical phenomenon of CHF, such as peripheral sympathetic activation, is not influenced by the aetiology of this condition. Interestingly, in CHF states due to IHD and IDC plasma renin activity was also similarly increased compared with controls. This suggests that not only sympathetic activation but also activation of the renin–angiotensin system (and thus possibly the neurohumoral activation at large) which occurs in CHF is unrelated to its aetiology.

Confirming previous data obtained by several investigators [14,17,20,28,29], baroreflex control of heart rate and muscle sympathetic nerve traffic was much less effective in CHF than in control subjects. Again, however, the loss of baroreflex control of peripheral sympathetic activity was similar in CHF states due to IHD or to IDC. Thus a major mechanism regulating autonomic functions is similarly impaired in CHF states that originate from coronary heart disease and in those that do not, presumably accounting for the similarity in their sympathetic activation. It should be outlined that muscle sympathetic nerve traffic was similar in patients with IDC and IHD, although in the former group there was a greater dilatation of the left ventricle, and thus a more pronounced stimulation of cardiac volume receptors, which powerfully inhibit sympathetic tone [30]. However, cardiac volume receptors have been reported to undergo both functional impairment and structural damage when exposed to persistent stimulation, such as during chronic experimental CHF [30,31]. Furthermore, the cardiopulmonary reflex has been found to be so impaired in CHF patients as to lose most of its sympathetic inhibitory influence [32–34]. This can explain why, compared with CHF patients with IHD, sympathetic activity was no less in patients with IDC, despite the fact that the latter had a greater cardiac volume and, in principle, more cardiac receptor stimulation.

Our study has both a limitation and a clinical implication. The limitation is that the microneurographic approach only allows us to assess sympathetic nerve traffic to skeletal muscle, leaving the question of whether, in CHF patients with IHD and IDC, sympathetic activation is similar in visceral and other regional beds unanswered. However, in the present study plasma noradrenaline values were also similar between the two groups, suggesting that this may indeed be the case, since noradrenaline derives from secretion into neuroeffector junctions of multiple districts, rather than only the skeletal muscle [8,10,12].

The clinical implication refers to the hypothesis that the different effects of treatment on survival in patients with CHF secondary to IHD or IDC, reported in some interventional trials [18,19], were dependent on a different degree of sympathetic activation in the two conditions. By showing that in our patients sympathetic nerve traffic and plasma noradrenaline values were similar in these two aetologically different CHF states, the present study demonstrates that this is not the case.
REFERENCES


