Sympathetic Response to Ventricular Extrasystolic Beats in Hypertension and Heart Failure

Guido Grassi, Gino Seravalle, Giovanni Bertinieri, Maria Luisa Stella, Carlo Turri, Giuseppe Mancia

Abstract—Provoked premature ventricular contractions (PVCs) evoke, in concomitance with an early and late blood pressure fall and overshoot, an early sympathoexcitatory and a later period of sympathoinhibition, respectively. The present study was designed to examine whether in healthy subjects this is the case for spontaneous PVCs. Because of their pathophysiological relevance for arrhythmogenesis, it was also designed to determine whether the sympathetic responses are different from those seen in essential hypertension and congestive heart failure. In 14 untreated mild essential hypertensives (EH; age, 53.8±2.6 years; mean±SEM), 20 untreated congestive heart failure patients (CHF; age, 56.7±2.5 years; New York Heart Association class, II or III), and 16 age-matched healthy subjects (control) in Lown class <II, we evaluated the blood pressure (Finapres), heart rate (ECG), and muscle sympathetic nerve traffic (MSNA; by microneurography) responses to isolated monofocal PVCs. MSNA, quantified as bursts/100 heart beats, was significantly increased in EH (57.8±3.8, P<0.05) and CHF patients (77.7±4.0, P<0.01) compared with controls (44.6±4.4). In controls, the PVC-induced blood pressure fall and overshoot were accompanied by a sympathoexcitation (144.2±14%), followed by a period of sympathoinhibition (average duration, 1204±985 ms). The responses were similar in EH but not in CHF, in whom the magnitude of the sympathoexcitation and particularly the duration of the subsequent sympathoinhibition were strikingly reduced (average reduction, −46.1 and −72.8%, respectively). The most important factor accounting for this reduction appeared to be an altered baroreflex response to the PVC-induced BP changes. These data demonstrate that the MSNA responses to spontaneous PVCs are similar in controls and EH but markedly impaired in CHF, presumably because of the baroreflex alteration. This may represent an important factor for the genesis of the life-threatening ventricular arrhythmias that characterize CHF. (Hypertension. 2002;39:886-891.)

Key Words: arrhythmia ■ heart failure ■ sympathetic nervous system ■ baroreflex

In the present study, we investigated the behavior of the changes in MSNA, as directly quantified by microneurography, that follow spontaneous unprovoked PVCs in healthy subjects and in patients with EH or CHF. Because evidence in animals and man1,17,18 suggests that the sympathetic changes after provoked PVCs are related to (1) the blood pressure (BP) changes induced by PVCs, (2) their degree of prematurity (expressed by the coupling interval time), and (3) the level of the resting sympathetic tone, we further investigated in the 3 groups the relationships between the MSNA adjustments to spontaneous PVCs and the above-mentioned variables.

Methods

Study Population
The study population consisted of 50 hospitalized patients of both genders (39 men, 11 women), ranging in age from 45 to 65 years, who had a body mass index ≤25 kg/m². Sixteen subjects recovering from noncardiovascular diseases (pneumonia, gastrointestinal diseases, urinary infections, etc) and in good clinical conditions served as controls. Fourteen subjects had mild essential hypertension, ie, a
TABLE 1. Anthropometric, Hemodynamic, Echocardiographic, and Microneurographic Characteristics of Control Subjects and EH and CHF Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Subjects (n=16)</th>
<th>EH Patients (n=14)</th>
<th>CHF Patients (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.9±2.4</td>
<td>53.8±2.6</td>
<td>56.7±2.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.4±0.4</td>
<td>23.9±0.4</td>
<td>23.8±0.4</td>
</tr>
<tr>
<td>Sphygmo BP (systolic/diastolic), mm Hg</td>
<td>138.2±2.5/84.3±2.4</td>
<td>149.3±2.6/98.0±2.5</td>
<td>134.0±2.9/82.1±2.8†</td>
</tr>
<tr>
<td>Finger BP (systolic/diastolic), mm Hg</td>
<td>135.9±2.4/82.2±2.5</td>
<td>147.1±2.5/96.4±2.6</td>
<td>131.6±3.0/80.4±2.5†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72.4±1.9</td>
<td>71.8±2.1</td>
<td>83.9±2.6†</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>68.8±2.1</td>
<td>66.4±2.4</td>
<td>36.5±1.9†</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>50.1±2.7</td>
<td>50.8±2.6</td>
<td>72.1±2.9†</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>18.8±0.6</td>
<td>18.4±0.8</td>
<td>19.1±0.7</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>31.8±3.1</td>
<td>42.0±2.9†</td>
<td>64.7±3.5#</td>
</tr>
<tr>
<td>MSNA, bursts/100 heart beats</td>
<td>44.6±4.4</td>
<td>57.8±3.8‡</td>
<td>77.4±4.0‡#</td>
</tr>
<tr>
<td>Mean burst amplitude</td>
<td>10.1±0.5</td>
<td>10.8±0.5</td>
<td>13.3±0.6‡</td>
</tr>
<tr>
<td>PVCs rate, n/h</td>
<td>9.2±0.7</td>
<td>9.8±0.5</td>
<td>12.9±0.9‡</td>
</tr>
</tbody>
</table>

Data are shown as mean±SEM. Sphygmo (sphygmomanometric) BP was the average of 3 measurements. LVEF indicates left ventricle ejection fraction; LVEDD, left ventricle end diastolic diameter.

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Results

Table 1 shows the anthropometric, hemodynamic, echocardiographic, and MSNA data in control subjects and in EH and CHF patients. Compared with controls, EH patients displayed significantly greater sphygmomanometric and finger systolic
and diastolic BP values, whereas CHF patients had significantly lower left ventricular ejection fraction and significantly greater left ventricular end diastolic diameter. Both heat rate and the incidence of PVCs were significantly more elevated in CHF patients than in controls and EH patients. Compared with controls, MSNA values were significantly greater in patients with EH and more so in patients with CHF.

As shown in the example of Figure 1 (left panel) and in the average data of Figure 2, in control subjects spontaneous PVCs were characterized by an average coupling interval time of 56.5 ± 2% (range, 50% to 72%). As expected, these PVCs evoked a marked and significant (P < 0.01) decrease in diastolic BP, followed by a transient and significant (P < 0.01) diastolic BP rise (overshoot) at the spontaneous restoration of the sinus rhythm. Immediately after the PVC, MSNA displayed a postextrasystolic burst with an amplitude that was significantly greater than the average amplitude of the sympathetic bursts occurring in sinus rhythm. This was followed by a period of complete absence of sympathetic neural bursts (sympathetic silence) and then by the restoration of the normal pattern of MSNA discharge. In EH patients, the coupling interval time of the PVCs was similar to that in normotensive controls (58.8 ± 1.8%; range, 50% to 74%), and so were the diastolic BP and MSNA changes (Figure 1, central panel, and Figure 2). In contrast, in CHF patients the coupling interval time of the PVCs was significantly greater (67.2 ± 1.9%; range, 51% to 79%; P < 0.01), and the BP and MSNA changes were qualitatively similar but quantitatively different from those seen in controls and EH patients. In these patients, the PVCs evoked a smaller diastolic BP fall and subsequent overshoot. It also evoked a lesser increase in MSNA burst amplitude immediately after the PVC and a strikingly smaller duration of the subsequent sympathoinhibition phase (Figure 1, right panel, and Figure 2). In a subgroup of CHF patients (n = 6) who were matched with controls (n = 6) for PVC coupling, interval time values (57.3 ± 1.5 versus 57.1 ± 1.9%, P = NS) and PVC-induced diastolic BP changes (diastolic BP fall, −12.8 ± 1.8 versus −13.1 ± 1.6 mm Hg; diastolic BP overshoot, 13.9 ± 1.5 versus 14.3 ± 2.5 mm Hg; P = NS for both), a similar attenuation of the increase in MSNA burst amplitude after PVC (77.2 ± 9.3 versus 116.5 ± 11.2%, P < 0.05), and duration of the post-PVC sympathoinhibitory phase (4375.1 ± 658 versus 8609.6 ± 775 ms, P < 0.05) was seen.

As shown in Table 2, in control subjects the increase in MSNA immediately after the PVC was directly related to the diastolic BP fall, inversely related to the coupling interval of the PVC, and inversely related to resting MSNA values. A larger BP fall, a more premature PVC, and a lower basal sympathetic traffic were accompanied by a greater increase in

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Original recordings of ECG, beat-to-beat BP, and MSNA tracings before, during, and after a spontaneous PVC in a healthy subject (control), in a patient with EH, and in a patient with CHF. PVC triggered a diastolic BP reduction coupled with a MSNA burst of amplitude greater than the average amplitude of MSNA bursts occurring in sinus rhythm. These changes were followed by a BP overshoot and a transient period of sympathoinhibition. Compared with healthy subjects and EH patients, in CHF patients both the amplitude of the postextrasystolic MSNA burst and the temporal duration of MSNA inhibition were strikingly reduced.

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

**Figure 2.** Upper panels refer to the diastolic BP reduction (ΔDBP) and the subsequent DBP overshoot induced by spontaneous PVCs in healthy subjects (○) and in EH (○) and CHF patients (●). Lower panels refer to the amplitude of the postextrasystolic MSNA burst (Δ burst amplitude, expressed as percentage values of integrated activity) and to the subsequent duration of MSNA inhibition. Individual and average data are shown. In each individual, data refer to the average responses calculated during 4 different PVCs. Symbols refer to the statistical significance between responses observed in CHF patients vs controls (**P < 0.05**, ***P < 0.01) or vs EH (†P < 0.05, ††P < 0.01). For symbols, see Tables and text.
sympathetic burst amplitude after the PVC, the BP fall being the most important contributor on multivariate analysis. The duration of the postextrasystolic MSNA inhibition was directly related to the magnitude of the BP overshoot, inversely related to the coupling interval of the PVC and inversely related to resting MSNA values. A more pronounced rebound increase in BP, a more premature PVC, and a lower basal sympathetic traffic were accompanied by a longer sympathetic silence, the BP increase being the most important contributor on multivariate analysis. Similar relationships were seen in EH and CHF patients.

**Discussion**

Our study provides the first detailed comparison of the effects of spontaneous PVCs on efferent postganglionic MSNA in healthy subjects and in patients with EH or CHF. It also provides information on the possible determinants of the sympathetic neural responses to spontaneous extrasystolic ventricular beats in conditions characterized by normal or elevated BP values, normal or impaired left ventricular function, and normal or elevated resting sympathetic nerve activity. These issues will be separately discussed.

Similar to what has been recently reported in CHF patients, the sympathoexcitatory response to a provoked PVC elicited, along with a diastolic BP reduction, a postextrasystolic MSNA burst characterized by an amplitude markedly and significantly greater than the average amplitude of the MSNA bursts occurring in sinus rhythm. Furthermore, in these subjects the above-mentioned changes were followed by a transient diastolic BP increase and a concomitant transient suppression of spontaneous MSNA bursts. These findings are in line with the results of previous studies performed in both experimental animals and humans, in which a provoked PVC elicited, along with a diastolic BP reduction, a marked increase in cardiac, renal, and skeletal muscle sympathetic outflow, which was followed by a BP overshoot and a concomitant period of sympathetic silence. We can thus conclude that in healthy subjects, the sympathetic responses to provoked and unprovoked PVCs are qualitatively similar to each other, and thus, artificially induced PVCs represent a valid model for studying the hemodynamic and neural adjustments to spontaneously occurring arrhythmias of this type.

Our study, however, provides new important information on the sympathetic responses to spontaneous PVCs in EH and CHF patients, 2 conditions in which both PVC prevalence and sympathetic tone can be altered sometimes to an even dramatic degree. Also in these patients, an extrasystolic ventricular beat caused an increase in MSNA, indicating no substantial disruption of its mechanisms of production. However, although in EH patients the magnitude of the early increase in MSNA and the duration of the subsequent period of sympathetic silence were almost superimposable to those seen in control subjects, in CHF patients they were both much less pronounced. The sympathetic silence following the PVC, in particular, was so strikingly less in CHF patients as to make its duration on average only one fourth of that observed in controls. If the behavior of MSNA after a spontaneous PVC reflects the behavior of cardiac sympathetic nerve traffic (an assumption justified by the evidence that in animals, an evoked PVC alters in a similar fashion peripheral and cardiac sympathetic nerve activity), then these results have an obvious clinical implication: that in CHF, the reduced duration of the sympathoinhibition after a PVC may allow to resume sympathetic activity at a time when there is a postextrasystolic augmentation of electrical instability and a reduced arrhythmogenic threshold of myocardial tissue. This may favor the occurrence of the life-threatening ventricular arrhythmias that characterize CHF and explain why in this condition the occurrence of PVCs increases the cardiovascular risk as compared with healthy subjects.

In experimental animals, the sympathoexcitatory response to a provoked PVC was abolished by sino-aortic denervation or bilateral carotid artery occlusion, suggesting an important involvement of the arterial baroreflex in its determination. This is supported by our finding, because in multivariate analysis the post-PVC increase in sympathetic activity and the subsequent duration of the sympathetic silence following the PVC were seen in EH and CHF patients.

**TABLE 2. Correlation Coefficients (r) Between Electrophysiologic, Hemodynamic, Neural Variables, and MSNA Changes Accompanying PVCs in Control Subjects and EH and CHF Patients**

<table>
<thead>
<tr>
<th>Relationships</th>
<th>Control Subjects</th>
<th>EH Patients</th>
<th>CHF Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Coupling interval (%) vs DBP ↓ (mm Hg) at PVC</td>
<td>-0.35</td>
<td>&lt;0.006</td>
<td>-0.32</td>
</tr>
<tr>
<td>Coupling interval (%) vs MSNA ↑ (burst amplitude, %) at PVC</td>
<td>-0.27</td>
<td>&lt;0.03</td>
<td>-0.26</td>
</tr>
<tr>
<td>DBP ↓ vs MSNA ↑ (burst amplitude, %) at PVC</td>
<td>0.44</td>
<td>&lt;0.002</td>
<td>0.40</td>
</tr>
<tr>
<td>Resting MSNA (bursts/min) vs MSNA ↑ (burst amplitude, %) at PVC</td>
<td>-0.25</td>
<td>&lt;0.04</td>
<td>-0.23</td>
</tr>
<tr>
<td>Coupling interval (%) vs duration of MSNA inhibition (ms) post-PVC</td>
<td>-0.23</td>
<td>&lt;0.05</td>
<td>-0.26</td>
</tr>
<tr>
<td>ΔDBP overshoot (mm Hg) at PVC vs duration of MSNA inhibition (ms) post-PVC</td>
<td>0.38</td>
<td>&lt;0.004</td>
<td>0.33</td>
</tr>
<tr>
<td>Resting MSNA (bursts/min) vs duration of MSNA inhibition (ms) post-PVC</td>
<td>-0.30</td>
<td>&lt;0.01</td>
<td>0.28</td>
</tr>
</tbody>
</table>

DBP indicates diastolic blood pressure.
silence were much closely related to the concomitant BP fall and rise, respectively, than to other variables such as resting MSNA and coupling interval time. A baroreflex origin of the sympathetic changes after a spontaneous PVC is also not incompatible with the unchanged and reduced MSNA responses to a spontaneous PVC observed in EH and CHF patients, respectively. This is because we have shown that in EH, the baroreceptor ability to modulate sympathetic nerve activity is largely preserved at variance from the baroreceptor ability to modulate heart rate, which undergoes an early impairment.\textsuperscript{6,23} It is also because, in contrast, CHF is characterized by a marked and generalized impairment of the baroreceptor-sympathetic control.\textsuperscript{10,24} This was clearly the case in our CHF patients, in whom calculation of the baroreflex gain—ie, of the ratio between the increase in MSNA and diastolic BP fall or between the duration of the sympathetic silence and the diastolic BP rise—resulted in values 34.1% and 52.0%, respectively, less than in those in controls. Considering that in these patients there was also less change in BP and thus in baroreceptor stimuli, this is compatible with an overall reduced participation of the baroreflex as being the major factor in the attenuation of the sympathetic responses to spontaneous PVCs in conditions characterized by an impaired left ventricular function. Our study was not designed to clarify the mechanisms by which baroreflex-mediated sympathetic adjustments to PVCs are altered in CHF, a goal inevitably difficult to achieve in clinical setting. The following (not mutually exclusive) possibilities should be considered, however. First, the baroreflex impairment may originate from a baroreceptor inability to properly signal blood pressure changes, possibly because of the marked reduction in arterial distensibility occurring in heart failure.\textsuperscript{25} Second, the central integration of the reflex input may be altered inherently or because of the influence of a variety of humoral factors modified by heart failure. One of them could be angiotensin II, which is increased in heart failure and can centrally affect the baroreflex.\textsuperscript{26} Third, sympathetic afferents responsible for spinal reflexes and for a reduction in a baroreflex gain may, when activated by volume overload, cause baroreflex impairment.\textsuperscript{27}

Three final points should be made. First, in our study the sympathetic responses to PVCs were also related to resting MSNA and the PVC coupling interval. This suggests that factors other than the baroreflex may also play a role. It is likely that this role may be somehow related to the baroreflex one, however, because (1) resting MSNA may in turn be dependent on the baroreflex,\textsuperscript{10} (2) the PVC coupling interval may act just by varying the BP changes in response to PVCs, and (3) in CHF patients a marked alteration of the sympathetic responses to spontaneous PVCs was seen also when the coupling interval times and the BP changes were matched with those of controls. Second, we did not measure central venous pressure and thus cannot offer any evidence on whether it changed in the same or opposite direction to the BP changes after spontaneous PVCs. This makes it impossible to exclude that the MSNA responses to these arrhythmic events also depend on reflexes originating from the heart, which are known to importantly modulate MSNA in man.\textsuperscript{28,29} Third, given that in CHF sympathetic activity is markedly increased\textsuperscript{8–11} and that this increase has prognostic implications,\textsuperscript{6,30} it should also be mentioned that in this condition a blunted sympathoexcitatory response to PVC might also be seen as objectively protecting the patient from an additional adrenergic activation triggered by an arrhythmic event.

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10. Grassi G, Seravalle G, Cattaneo BM, Lanfranchi A, Vailati S, Giannattasio C, Del Bo A, Sala C, Bolla GB, Pozzi M, Mancia G. Baroreflex-mediated sympathetic adjustments to PVCs are altered in CHF, a goal inevitably difficult to achieve in clinical setting. The following (not mutually exclusive) possibilities should be considered, however. First, the baroreflex impairment may originate from a baroreceptor inability to properly signal blood pressure changes, possibly because of the marked reduction in arterial distensibility occurring in heart failure.\textsuperscript{25} Second, the central integration of the reflex input may be altered inherently or because of the influence of a variety of humoral factors modified by heart failure. One of them could be angiotensin II, which is increased in heart failure and can centrally affect the baroreflex.\textsuperscript{26} Third, sympathetic afferents responsible for spinal reflexes and for a reduction in a baroreflex gain may, when activated by volume overload, cause baroreflex impairment.\textsuperscript{27}

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