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 sympathoexcitation 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

Microneurographic recording of efferent postganglionic sympathetic nerve traffic to the skeletal muscle district (MSNA) has shown that in healthy humans, premature ventricular contractions (PVCs) induced by programmed ventricular stimulation evoke profound modifications in neural adrenergic discharge.1 These modifications include (1) an enhancement in the amplitude and duration of the sympathetic burst immediately after the PVC and (2) a subsequent period of sympathetic silence, followed by the restoration of the normal pattern of adrenergic discharge.1 With the exception of 2 studies2-3 (in which the early sympathoexcitatory responses to spontaneous PVCs were evaluated in 9 patients affected by congestive heart failure [CHF]), no information exists as to whether the MSNA behavior characterizing provoked PVCs is also shared by the spontaneous ones. Furthermore, it is unknown whether the sympathetic responses to PVCs seen in healthy subjects differ from those observed in essential hypertension (EH) and CHF, ie, 2 cardiovascular diseases in which sympathetic neural activity is markedly increased4-11 and its role in the arrhythmogenesis has been documented.12-16

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
diastolic BP between 90 and 109 mm Hg at repeated sphygmomanometric measurements. The remaining 20 subjects were affected by CHF in New York Heart Association class II (n = 14) and III (n = 6), had a cardiothoracic ratio >0.55 at a chest X-ray, and an echocardiographic evidence of a left ventricular end diastolic diameter >55 mm and a left ventricular ejection fraction <40%.

The subjects were included in the study if their ECG-Holter monitoring displayed isolated PVCs with coupling intervals between 50% and 80% of baseline R-R intervals. Exclusion criteria were (1) historical, physical, or laboratory evidence of valvular heart disease; (2) history of smoking and/or excessive alcohol consumption; (3) history of a recent (≤12 months) myocardial infarction; and (4) evidence during Holter monitoring of tachyarrhythmias, plurifocal PVCs with a rate >30 per hour (Lown class ≥II). Control subjects were physically untrained and under no drug treatment. This was the case also for EH patients, in which antihypertensive drugs (ACE inhibitors and/or calcium antagonists) were withdrawn 7 to 10 days before the study. The CHF patients were treated with furosemide, ACE inhibitor, or vasodilators but not with β-blockers and/or antiarrhythmic drugs. Treatment was withdrawn 5 to 7 days before the study, except for furosemide, which was maintained in the 6 patients with CHF belonging to New York Heart Association class III. In control, EH, and CHF subjects, all laboratory tests were normal. All subjects gave written informed consent to the study, the protocol of which was approved by the ethics committee of our institution.

### Measurements

The methodological details of the procedures we used to assess sphygmomanometric and beat-to-beat (Finapres 2300, Ohmeda) BP, heart rate (ECG), respiration rate (pneumotachograph), and MSNA (microneurography) have been described in previous reports.\(^1,7-9,11,18\)

With the exception of the sphygmomanometric BP, all variables were displayed on a thermic paper on a ink polygraph (Gould 3800) and on a frequency-modulated magnetic tape, thus allowing the various signals to be replayed at high speed and accurately evaluated.

### Protocol and Data Analysis

All subjects came to the laboratory in the morning. They were put in a supine position and fitted with the microelectrodes for MSNA recording and the other measuring devices. Sphygmomanometric BP was then measured 3 times, and after 30 minutes, all variables were continuously measured during a recording period that lasted between 60 and 90 minutes to obtain data that would satisfy the analysis criteria described below.

Data were analyzed by a single investigator unaware of the experimental design. In each individual subject, baseline BP, heart rate, respiration rate, and MSNA were collected in 4 different periods that lasted at least 4 minutes, each period being characterized by the presence of sinus rhythm preceding the occurrence of a spontaneous PVC. Only periods in which PVCs had a coupling interval stable over time were considered. In these periods, MSNA was quantified as bursts per minute and as bursts per 100 heart beats. The 2-minute period after any given PVC was not taken into account in the assessment of baseline values. The diastolic BP changes induced by a PVC were quantified by calculating the magnitude of the (1) diastolic BP fall at the time of the PVC, taking as reference the pre-PVC values, and (2) diastolic BP overshoot (average of 4 consecutive peak values) after the PVC, taking as reference the diastolic BP fall induced by the PVC. The concomitant MSNA responses were quantified by calculating (1) the percentage changes in the amplitude of the sympathetic burst occurring immediately after each PVC, in comparison with the mean amplitude of the sympathetic bursts occurring over the baseline period in sinus rhythm preceding the PVC, and (2) the time interval (milliseconds) between the end of this postextrasystolic burst and the appearance of a second burst, ie, the duration of the period of sympathetic silence concomitant with the diastolic BP overshoot.

Both baseline values and responses to the 4 PVCs were averaged in each subject to obtain individual data, which were then averaged for each group and expressed as mean ± SEM. The differences in mean values between groups were assessed by 2-way ANOVA. The 2-tailed t test for unpaired observations was used to locate between-group differences. The Bonferroni correction for multiple comparisons was used. The relationships between the diastolic BP changes induced by the PVC and the coupling interval, as well as the percentage changes in the MSNA amplitude of the postextrasystolic burst and the duration of the MSNA inhibition post-PVC were assessed via univariate and multivariate regression analysis. A value of P<0.05 was considered statistically significant.

### 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 heart 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 sympathetic silence 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 MSNA burst amplitude immediately after the PVC and a strikingly smaller duration of the subsequent sympathetic silence 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.
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, in healthy subjects a spontaneous PVC triggered, 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. 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

### 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>
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<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>
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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.6,23 It is also because, in contrast, CHF is characterized by a marked and generalized impairment of the baroreceptor-sympathetic control.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.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.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.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,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.28,29 Third, given that in CHF sympathetic activity is markedly increased8,10,11 and that this increase has prognostic implications,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.

References


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