Dysfunctional Baroreflex Regulation of Sympathetic Nerve Activity in Patients With Vasovagal Syncope

Markus Béchir, MD; Christian Binggeli, MD; Roberto Corti, MD; Rémy Chenevard, MD; Lukas Spiker, MD; Frank Ruschitzka, MD; Thomas F. Lüscher, MD; Georg Noll, MD

Background—The interplay of resting muscle sympathetic nerve activity (MSA) and the baroreceptor reflex in patients with vasovagal syncope remains elusive. Hence, the aim of the present study was to investigate MSA, baroreceptor sensitivity, heart rate, and blood pressure under resting conditions and during orthostatic stress in patients with a history of vasovagal syncope.

Methods and Results—MSA was measured using microneurography at rest and during lower body negative pressure (LBNP) to mimic orthostatic stress in patients with a history of vasovagal syncope (n=10) and in age-matched healthy controls (n=8). Heart rate and blood pressure were simultaneously recorded. Cardiac baroreceptor sensitivity was calculated with the spectral technique (α coefficient). Resting MSA in the patients with syncope was significantly increased as compared with controls (42.4±2.3 versus 26.5±3.6 bursts/min, P=0.001), whereas activation of MSA during orthostatic stress in the patient group was significantly blunted (5.1±1.6 versus 15.2±2.1 bursts/min at LBNP −50 mm Hg, P=0.002). In the patients with syncope, cardiac baroreceptor sensitivity was significantly reduced under supine resting conditions (8.5±0.7 versus 13.0±1.1 ms/mm Hg, P=0.001), as well as under orthostatic stress (7.3±0.7 versus 13.4±1.5 ms/mm Hg, P=0.003).

Conclusions—This study shows that in patients with vasovagal syncope, resting MSA is increased and baroreflex regulation during orthostatic stress is blunted, thus leading to impaired MSA adaptation. These results provide new insights into mechanisms of vasovagal syncope and suggest that pharmacological modulation of baroreceptor sensitivity may represent a promising treatment of neuromediated syncope. (Circulation. 2003;107:1620-1625.)

Key Words: syncope ■ baroreceptors ■ nervous system, sympathetic

Vasovagal or neurally mediated syncope is very common, especially in the young. Different pathophysiological mechanisms have been proposed. Vasovagal syncope was defined by Lewis in 1932 as bradycardia and hypotension mediated by a vagal stimulus. Later, Jarisch et al postulated a dysfunction of stretch receptors in the left ventricular wall known as the Bezold-Jarisch reflex as a trigger of vasovagal reactions. An important role of muscle sympathetic activity (MSA) contributing to vasovagal syncope was also suspected. Indeed, immediately before vasovagal fainting, marked reduction of MSA occurs and is thought to cause severe hypotension and loss of consciousness. Thus, the sympathetic nervous system plays a major part in the pathogenesis of vasovagal syncope.

Sympathetic nerve activity represents a fast-acting regulatory system that allows adaptation of the cardiovascular system to different physiological conditions, such as orthostasis and exercise. The activity of the sympathetic nervous system is primarily regulated by mechanoreceptors and, to a smaller degree, by chemoreceptors. The arterial baroreceptors (high pressure receptors) are located in the carotid sinus and the aortic arch, and cardiopulmonary baroreceptors (low pressure receptors) are located in the great veins, atria (A- and B-receptors, Bainbridge reflex), and ventricles (Bezold-Jarisch reflex). These mechanoreceptors are stretch-activated ion channels, which influence sympathetic outflow via an afferent loop to the brain stem and in turn via the efferent loop determine vascular tone. There are other regulatory mechanisms of sympathetic outflow, however, as MSA levels differ in the forearm and calf during mental stress but not during lower body negative pressure (LBNP). LBNP to simulate orthostatic stress is associated with activation of cardiac and arterial baroreceptor mechanisms.

Levels of negative pressure up to −20 mm Hg lead to a decrease of central venous pressure and activation of cardiac low pressure receptors, whereas at higher negative pressure values, a decrease of arterial pressure also activates arterial baroreceptors. A dysfunctional arterial baroreflex has been implicated in the pathophysiology of vasovagal syncope. In principle, alterations of baroreceptor reflex function may occur 2 ways: (1) Baroreceptor reflex control of sympathetic nerve activity and heart rate is shifted to higher or lower...
blood pressure levels (resetting of baroreflex) and (2) baroreceptor sensitivity is reduced leading to an reduced cardiovascular control (alteration of baroslope).

The fact that drugs, which dilate veins, can induce vasovagal syncope suggests a participation of the venous tone in fainting as well.\textsuperscript{13} Some authors described a failure of reflex venoconstriction as part of the origin of vasovagal syncope.\textsuperscript{14} Furthermore, the occurrence of vasovagal reaction in subjects after orthotropic heart transplantation provides strong evidence that mechanisms other than the Bezold-Jarisch reflex are involved in the pathogenesis of vasovagal syncope.\textsuperscript{15,16} Different humoral factors also seem to play a role, including epinephrine and a possible relative lack of norepinephrine,\textsuperscript{17} a decrease of vasopressin and endothelin in plasma,\textsuperscript{18,19} increased endorphin levels,\textsuperscript{20,21} and possibly nitric oxide and serotonin.\textsuperscript{22} However, the contributions of these neurohumoral factors are still controversial.\textsuperscript{23,24} Thus, the underlying pathophysiology of vasovagal syncope remains complex and still incompletely understood.

It was therefore the aim of this study to investigate the role of the sympathetic nervous system activity and baroreceptor function in patients suffering from vasovagal syncope.

**Methods**

**Subjects**

Ten patients with a history of several episodes of vasovagal fainting were recruited in the outpatient clinic of cardiology at the University Hospital Zürich. They had at least 3 episodes of syncpe within the last 12 months (mean 4.1 ± 0.4 episodes) and the diagnosis of vasovagal syncope was confirmed by tilt table testing. None of the patients had a history of coronary or valvular heart disease, hypertension, diabetes mellitus, or impaired renal function. Eight age- and sex-matched healthy volunteers without vasovagal syncope served as controls. None of the subjects was taking any medication. All study participants gave written informed consent before inclusion, and the study was approved by the local ethical research committee.

**Experimental Protocol**

Subjects were positioned in a plexiglas chamber sealed at the iliac crest and tightly fixed by a belt to avoid displacement of the electrodes during the vacuum episodes. Heart rate, blood pressure (conventional [Riva Rocchi] by Dynamap and continuously by Finapress, an oscillometric device) and MSA by means of intraneural electrodes were continuously recorded during a resting period of 20 minutes. Then LBNP of −15 mm Hg and −30 mm Hg were applied for 2 minutes each, then −50 mm Hg was applied and signals were registered for another 20 minutes.

**Microneurographic Measurements**

Subjects were studied in standardized fashion, ie, at 2 pm in a quiet, temperature-controlled room, after micturition to avoid any increase of MSA through bladder distension. The last food intake was in the morning; for lunch, only water was allowed. Multifiber recordings of MSA were obtained from the peroneal nerve as described previously.\textsuperscript{22} For LBNP, negative pressure was applied with a commercial vacuum cleaner (−15, −30, and −50 mm Hg) and was monitored with a manometer connected to the interior of the chamber.

**Lower Body Negative Pressure**

LBNP was used to simulate orthostatic stress as described previously.\textsuperscript{9,10} We used an airtight plexiglas chamber in which the subjects were enclosed up to the waist. Negative pressure was applied with a commercial vacuum cleaner (−15, −30, and −50 mm Hg) and was monitored with a manometer connected to the interior of the chamber.

**Baroreceptor Sensitivity**

Calculation of cardiac baroreceptor sensitivity was based on the spectral analysis technique (\(\alpha\)-coefficient); in brief, subdivisions of the continuous recorded heart rate and blood pressure ranging from 128 to 1024 heartbeats can be used. These segments were then analyzed by fast Fourier transformation (FFT), which provided R-R interval and systolic blood pressure spectral powers. The square root of the ratio of these parameters then was calculated. This method is well established and validated to other methods, ie, sequence method to gain baroreceptor sensitivity.\textsuperscript{26,27} In our study, we used periods of 300 heartbeats. The baseline calculation was done at the end of the baseline measurement and the calculation during LBNP at the beginning of the −50 mm Hg level; therefore, this level of LBNP was longer than the other levels.

**Statistical Analysis**

Results are presented as mean±SEM unless stated otherwise. Single comparisons were made with paired and unpaired Student’s t test (StatView 4.5, Abacus Concepts). Two-way ANOVA for repeated measures (Bonferroni/Dunn post-hoc test) was used to compare responses to LBNP. Statistical significance was accepted at \(P<0.05\).

**Results**

**Patient Characteristics**

The characteristics of the 2 age-matched study groups are shown in Table 1. There were no significant differences in age, weight, height, sex, and heart rate, but there was a trend toward higher resting heart rate in the patients with a history of vasovagal syncope.

**Muscle Sympathetic Activity and Hemodynamics**

Resting MSA in patients with a history of syncope was significantly increased as compared with controls (42.4 ± 2.3 versus 26.5 ± 3.6 bursts/min, \(P=0.001\) [Figure 1], and 60.6 ± 3.7 versus 41.9 ± 6.5 bursts/100 heart beats, \(P=0.018\) [Table 1]). For ranges, see Table 1 and Table 2. At the lower level of LBNP (−15 mm Hg), there was no significant difference in MSA activation between the groups; however, at the higher levels, the activation of MSA in the syncopal group was significantly blunted (3.2 ± 1.4 versus 8.1 ± 1.2 bursts/min at LBNP −30 mm Hg, \(P=0.022\), and 5.1 ± 1.6 versus 15.2 ± 2.1 bursts/min at LBNP −50 mm Hg, \(P=0.002\)) (Figure 2). The patients presented no significant increases versus baseline in these 2 LBNP levels (Table 2). Blood pressure remained stable in both groups. There was no significant difference in heart rate between the groups, except that in the syncopal group at LBNP −50 mm Hg, there was a significant difference within the group compared with the baseline (Table 2).

**Baroreceptor Sensitivity**

Cardiac baroreceptor sensitivity was significantly reduced under supine resting conditions (8.5 ± 0.7 versus 13.0 ± 1.1 ms/mm Hg, \(P=0.001\)) and also under orthostatic stress in the group of the patients (7.3 ± 0.7 versus 13.4 ± 1.5 ms/mm Hg, \(P=0.001\)).
Baroreceptor sensitivity remained stable versus baseline within the groups under LBNP (Figure 3).

**Induction of Syncope by Lower Body Negative Pressure**

Syncope without presyncope occurred in 1 patient after 18 minutes of LBNP −50 mm Hg, but it did not occur in the control group.

**Discussion**

This study for the first time reports that patients with a history of vasovagal syncope exhibit not only an increased peripheral resting sympathetic nerve activity compared with age-matched controls, but also a blunted activation of sympathetic outflow during LBNP-induced orthostatic stress. Furthermore, cardiac baroreceptor sensitivity of patients with syncope was reduced at baseline and during orthostatic stress.

Contrary to previous concepts, our study shows that in patients with a history of vasovagal syncope, resting MSA as assessed directly using microneurography is increased at baseline and not only during events of syncope or presyncope. This suggests that there is a permanent alteration in the regulation of sympathetic outflow in these patients. In line with our findings, healthy subjects who experienced presyncope in response to LBNP (−15 mm Hg) also exhibited a higher baseline MSA at rest. Thus, patients with syncope seem to be more dependent on MSA to maintain preload and less able to increase sympathetic vasoconstrictor outflow in response to orthostatic stimuli.

Blood pressure is determined by heart rate, stroke volume, and peripheral vascular resistance, and its regulation is highly dependent on cardiac and sympathetic baroreceptor reflex. Afferent activity from the high- and low-pressure baroreceptors in turn determines sympathetic outflow and peripheral vascular resistance. The finding of impaired sympathetic baroreflex control in patients with vasovagal syncope must therefore be related to an abnormality in this physiologically important reflex arc. This abnormality may be due to a lack of afferent stimuli from the mechanoreceptors and/or baroreceptors, ie, an afferent dysfunction or to a dysfunction of the efferent limb to the effector organ, ie, the vascular bed. The latter could explain the increased resting MSA in patients with syncope. Indeed, a reduced vascular response to sympathetic nerve activity would generate an increased sympathetic outflow even during resting conditions via negative feedback regulation, thus resulting in a chronic resetting of baroreceptor function. The origin of such a blunted peripheral response might be located in vascular smooth muscle cells or may be related to synaptic dysfunction of neurotransmitter production, release, or reuptake. In line with such an interpretation, a gene mutation leading to a selective norepinephrine reuptake inhibition is associated with increased MSA. Furthermore, an impaired vasoconstriction has been suggested as an underlying cause of vasovagal syncope.

The concept of an afferent dysfunction of the arterial baroreceptor reflex is compatible with our finding of reduced cardiac baroreceptor sensitivity at baseline in patients with vasovagal syncope. Impaired arterial baroreceptor sensitivity is associated with an inappropriate detection of blood pressure changes and in turn decreased baroreceptor afferent discharge. This would increase MSA in an attempt to support vascular resistance and maintain blood pressure. In contrast to

**Table 1. Clinical Characteristics of the Patients With a History of Vasovagal Syncope and the Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=8)</th>
<th>Patients With Syncope (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31±5 (25–39)</td>
<td>30±7 (20–42)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>4/4</td>
<td>5/5</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>75±14 (58–97)</td>
<td>75±16 (58–105)</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>178±4 (173–185)</td>
<td>175±11 (160–193)</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.3±3.9 (19.4–30.6)</td>
<td>24.2±3.9 (20.0–32.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±9 (58–78)</td>
<td>71±11 (56–96)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>116±9 (105–128)</td>
<td>116±13 (99–146)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>69±10 (60–83)</td>
<td>72±9 (58–86)</td>
<td>NS</td>
</tr>
<tr>
<td>MSA, bursts/min</td>
<td>26.5±10.1 (11–40)</td>
<td>42.4±7.3 (31–2)</td>
<td>0.001</td>
</tr>
<tr>
<td>MSA, bursts/100 heart beats</td>
<td>41.9±18.4 (16–67)</td>
<td>60.6±11.8 (37–73)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD (range) or n. NS indicates not significant.
our study, other investigators tested baroreflex sensitivity in patients with vasovagal syncope with stimulus-dependent methods. Commonly, intravenous phenylephrine infusion was used to quantify baroreceptor function. Those studies showed controversial results; some reported reduced baroreceptor sensitivity in patients suffering from neurally mediated syncope, whereas another one could not confirm these findings. The latter study found an impaired cardiopulmonary baroreceptor sensitivity, which was explained by a possible abnormality in the afferent loop of the reflex arch. This particular finding occurred only during LBNP and not under resting conditions. Whether this abnormality is confined to the venous system or includes the arterial part of the circulation as well remains unclear. In any case, assessment of baroreceptor sensitivity by stimulus-dependent methods (ie, intravenous phenylephrine) has poorer reproducibility than spontaneous analyzing methods like spectral analysis. Indeed, interactions between the drug used and baroreceptor function might occur. The present study, which used a more reliable methodology, reveals permanently impaired baroreceptor function, ie, a chronic resetting of the sympathetic baroreceptor function and an impaired cardiac baroreceptor sensitivity. The fact of blunted MSA in particular at the higher levels of LBNP (−30 and −50 mm Hg) suggests the arterial baroreceptors to be responsible for our finding of baroreflex alteration in patients with vasovagal syncope.

Importantly, we also found a blunted activation of MSA during orthostatic stress in patients with a history of vasovagal syncope. Hence, neuronal-mediated sympathetic vasoconstriction is reduced during conditions of increased demand. Impaired sympathetic baroreceptor sensitivity under orthostatic stress also would contribute to a blunted MSA activation. Consequently, in these patients with vasovagal syncope alternative mechanisms of vasoconstriction must be activated to maintain blood pressure, eg, catecholamines from the adrenal glands. Indeed, increased plasma levels of epinephrine under orthostatic stress conditions, ie, tilt table, were reported in these patients.

A possible pharmacological approach to prevent patients from vasovagal fainting is β-adrenoceptor blockade. It is believed that β-blockers inhibit the ventricular mechanoreceptors and in turn lower sympathetic outflow to the muscles. However, systemic β-blockade has little effect on sympa-

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**TABLE 2. Changes in MSA, Heart Rate, and Arterial Blood Pressure During LBNP**

<table>
<thead>
<tr>
<th>LBNP (mm Hg)</th>
<th>Controls (n=8)</th>
<th>Patients With Syncope (n=10)</th>
<th>P Value Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA, bursts/min</td>
<td>31.7±10.5 (17–45)*</td>
<td>46.0±6.2 (38–55)*</td>
<td>NS</td>
</tr>
<tr>
<td>MSA, bursts/100 heart beats</td>
<td>49.5±17.2 (22–73)*</td>
<td>66.2±9.4 (47–75)*</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±9 (54–77)</td>
<td>71±12 (53–95)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>119±8 (110–131)</td>
<td>121±15 (104–148)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>69±10 (59–81)</td>
<td>72±8 (61–8–5)</td>
<td>NS</td>
</tr>
<tr>
<td>LBNP = 30 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSA, bursts/min</td>
<td>34.9±10.7 (20–61)*</td>
<td>46.4±7.6 (35–61)</td>
<td>0.022</td>
</tr>
<tr>
<td>MSA, bursts/100 heart beats</td>
<td>53.3±18.0 (27–73)*</td>
<td>64.8±12.8 (40–78)</td>
<td>0.013</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±10 (54–78)</td>
<td>74±14 (53–97)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>119±9 (109–128)</td>
<td>120±13 (103–144)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73±11 (62–86)</td>
<td>75±11 (53–89)</td>
<td>NS</td>
</tr>
<tr>
<td>LBNP = 50 mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSA, bursts/min</td>
<td>38.4±10.1 (31–65)*</td>
<td>48.3±9.6 (32–62)</td>
<td>0.002</td>
</tr>
<tr>
<td>MSA, bursts/100 heart beats</td>
<td>54.6±18.5 (40–83)*</td>
<td>64.6±15.4 (31.4–75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72±8 (59–80)</td>
<td>81±18 (54–108)*</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122±10 (109–133)</td>
<td>119±13 (104–146)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73±11 (55–90)</td>
<td>74±12 (55–90)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD (range). NS indicates not significant.

*P<0.05 compared with baseline.

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**Figure 2.** Activation of MSA during orthostatic stress induced by LBNP in patients with syncope and controls. Results are expressed in bursts/min as mean±SEM. There is a significantly blunted activation of MSA in the patients compared with controls during LBNP. *P=0.002 by ANOVA.
thетic outflow. The exact site of action therefore remains unclear; some authors reported a direct interaction with baroreceptor nerve endings, which could explain the clinical efficacy of such a therapy. However, the effectiveness of β-blockade to prevent vasovagal syncope remains controversial, as vasovagal fainting also may occur during β-blocker therapy, and randomized, placebo-controlled studies were negative. The participation of the baroreflex in pathogenesis of vasovagal syncope gives rationale for novel pharmacological approaches, which would interfere with the arterial baroreceptor system.

In conclusion, this study reports that patients suffering from vasovagal syncope have a permanent sympathetic dysregulation of vascular tone due to a dysfunctional baroreceptor reflex arc and in turn an increased MSA. These alterations of cardiovascular control essentially contribute to the pathogenesis of vasovagal syncope.

Acknowledgments

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References


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