Chronic Orthostatic Intolerance
A Disorder With Discordant Cardiac and Vascular Sympathetic Control

Raffaello Furlan, MD; Giris Jacob, MD, DSc; Marie Snell, BS; David Robertson, MD; Alberto Porta, MD; Paul Harris, PhD; Rogelio Mosqueda-Garcia, MD, PhD

Background—Chronic orthostatic intolerance (COI) is a debilitating autonomic condition in young adults. Its neurohumoral and hemodynamic profiles suggest possible alterations of postural sympathetic function and of baroreflex control of heart rate (HR).

Methods and Results—In 16 COI patients and 16 healthy volunteers, intra-arterial blood pressure (BP), ECG, central venous pressure (CVP), and muscle sympathetic nerve activity (MSNA) were recorded at rest and during 75° tilt. Spectral analysis of RR interval and systolic arterial pressure (SAP) variabilities provided indices of sympathovagal modulation of the sinoatrial node (ratio of low-frequency to high-frequency components, LF/HF) and of sympathetic vasomotor control (LFSAP). Baroreflex mechanisms were assessed (1) by the slope of the regression line obtained from changes of RR interval and MSNA evoked by pharmacologically induced alterations in BP and (2) by the index \( \alpha \), obtained from cross-spectral analysis of RR and SAP variabilities. At rest, HR, MSNA, LF/HF, and LFSAP were higher in COI patients, whereas BP and CVP were similar in the two groups. During tilt, BP did not change and CVP fell by the same extent in the 2 groups; the increase of HR and LF/HF was more pronounced in COI patients. Conversely, the increase of MSNA was lower in COI than in control subjects. Baroreflex sensitivity was similar in COI and control subjects at rest; tilt reduced \( \alpha \) similarly in both groups.

Conclusions—COI is characterized by an overall enhancement of noradrenergic tone at rest and by a blunted postganglionic sympathetic response to standing, with a compensatory cardiac sympathetic overactivity. Baroreflex mechanisms maintain their functional responsiveness. These data suggest that in COI, the functional distribution of central sympathetic tone to the heart and vasculature is abnormal. (Circulation. 1998;98:2154-2159.)

Key Words: syncope ■ baroreceptors ■ blood pressure ■ norepinephrine ■ nervous system, autonomic

Chronic orthostatic intolerance (COI) is a disabling syndrome, characterized by pronounced tachycardia and symptoms such as fatigue, lightheadedness, dizziness, palpitations, and rarely syncope, most commonly during the upright position.1–3 This condition represents one of the most frequent autonomic disorders in young subjects, and it has been described by myriad terms, including postural orthostatic tachycardia,2 hyperadrenergic orthostatic tachycardia,3 idiopathic hypovolemic,4 and hyperadrenergic orthostatic hypotension.5

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Potential pathophysiological mechanisms in COI include a \( \beta \)-adrenergic hypersensitivity,4 decreased plasma volume,47 an inappropriate venous pooling,3 and possible dysautonomia.19

The finding of increased plasma catecholamines at rest19 and during standing19–11 in patients with COI has led to the hypothesis of an abnormally enhanced sympathetic drive to the cardiovascular system as a final common pathophysiological mechanism. In addition, the exaggerated increase of heart rate (HR) in the absence of discernible changes in blood pressure (BP) during standing raises the possibility that abnormalities in the baroreflex control of HR might result in an inappropriate tachycardia.

To the best of our knowledge, there are no studies in which muscle sympathetic nerve activity (MSNA) has been recorded and the cardiac autonomic modulation concomitantly estimated in subjects affected by COI. Direct assessment of these variables is crucial if possible abnormalities in the distribution of autonomic control to the heart and vasculature are to be addressed. The aim of this study was to assess the autonomic profile of patients affected by COI while they were recumbent and during orthostatic stress, including evaluation of baroreflex control of HR and MSNA.

Methods

This study was performed in 16 patients with COI (11 women, 5 men; age, 35±2 years) and in 16 healthy control subjects (7 women, 9 men; age, 35±2 years) and in 16 healthy control subjects (7 women, 9 men; age, 35±2 years) and in 16 healthy control subjects (7 women, 9 men; age, 35±2 years).
age, 30±2 years). Patients underwent a complete medical evaluation to exclude secondary causes of orthostatic intolerance or any other relevant medical condition. Their clinical features are presented in Table 1. Drug treatment was discontinued for at least 10 days before the study.

Subjects with COI were included in this study if they had (1) sustained increase of HR of at least 30 bpm or HR >120 bpm during standing, (2) absence of orthostatic hypotension (falls in systolic/diastolic BP during standing <10 mm Hg), (3) duration of symptoms longer than 6 months, and (4) daily occurrence of at least 2 of the following symptoms: palpitations, dizziness, fatigue, light-headedness, presyncope, or syncope during upright posture.

Instrumentation Procedure and Recorded Variables
In every subject, we recorded a surface ECG and intra-arterial BP from the radial artery of the nondominant arm. In 10 COI patients and 14 control subjects, central venous pressure (CVP) was measured by means of a microtip pressure transducer (Millar Instruments Inc) located near the right atrium. Respiratory activity was monitored by means of thoracic bellows.

In both groups, MSNA was obtained with microneurography as described elsewhere. Systemic BP, ECG, CVP, integrated MSNA, and the respiratory signals were digitized at 300 samples per second and stored onto the hard disk of a personal computer for subsequent analysis. Plasma epinephrine and norepinephrine were measured on and stored onto the hard disk of a personal computer for subsequent analysis. Plasma catecholamines. Then, subjects were tilted at 15° intervals every 3 minutes until the 75° head-up position was reached. This position was maintained for a total of 30 minutes. A second 30-minute recovery period, we performed the pharmacological evaluation of baroreflex function. All the subjects received incremental doses (lasting 3 minutes) of phenylephrine or sodium nitroprusside (range, 0.1 to 2.4 μg · kg⁻¹ · min⁻¹) in a random fashion. Drug infusion was stopped when systolic BP increased or decreased by 25 mm Hg.

Data Analysis
Microneurography was considered to reflect MSNA according to criteria previously established. Satisfactory recordings of MSNA during the entire procedure were obtained in 11 COI patients and 14 control subjects. CVP values are nominal, that is, referenced to atmospheric pressure; because intrathoracic esophageal pressure was not estimated concomitantly, no atrial transmural pressure values are provided.

The principles of the software for automatic evaluation of data and for autoregressive spectral and cross-spectral analysis have been described elsewhere. There are 2 main oscillatory components, the amplitude of which is affected by changes in neural autonomic control. One is high frequency (HF, ~0.25 Hz at rest). If extracted from RR interval variability, HF is an index of the vagal efferent modulation of the sinoatrial node discharge. The other oscillatory component is indicated as low frequency (LF, ~0.1 Hz). In the case of systolic arterial pressure (SAP) variability, LF can be considered a marker of the sympathetic modulation of vasomotor activity. The LF component of RR variability (LF_RR), when expressed in normalized units (NU), might reflect primarily the sympathetic efferent modulation of the sinoatrial (SA) node and its changes. Normalization is achieved by dividing the absolute power of each component by total variance (minus the power of the very-low-frequency component) and subsequently multiplying by 100. The LF_RR/SF_RR ratio, which is independent of units of measure, may furnish a further index reflecting cardiac sympathovagal balance. However, as a ratio, LF/HF may undergo large modifications when the denominator is markedly lower than the numerator, thus emphasizing even small changes in the sympathovagal balances. Cross-spectral analysis between respiration and RR and SAP variabilities was performed because this allowed the identification of the respiratory-linked fluctuation in the different power spectra.

Baroreflex function was assessed by (1) the index α, obtained by use of cross-spectral analysis of RR and SAP spontaneous oscillations both at rest and during the tilt maneuver; it was computed as the square root of the ratio between the powers of corresponding spectral components of RR interval and SAP variabilities. A high level of...
TABLE 2. Hemodynamic and Respiratory Parameters of Control and COI Subjects at Rest and During Passive Orthostatism

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Tilt</th>
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<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>COI</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>61±2</td>
<td>77±3*</td>
</tr>
<tr>
<td>RR, ms</td>
<td>1002±29</td>
<td>798±33*</td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>127±2</td>
<td>124±6</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>71±2</td>
<td>74±3</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>4.8±0.8</td>
<td>3.7±0.3</td>
</tr>
<tr>
<td>RESP, cycles/min</td>
<td>17±1</td>
<td>16±1</td>
</tr>
</tbody>
</table>

For CVP, controls, n=10; COI, n=14. DAP indicates diastolic arterial pressure; RESP, respiratory frequency.

*p<0.05 controls vs COI.

Results

Basal Hemodynamic and Neurohumoral Data

With the patient supine, we recorded higher HR and MSNA values in COI patients than in control subjects; an example is shown in Figure 1. Conversely, systemic BP, respiratory frequency, and CVP were similar in both groups (Table 2). In addition to increased MSNA in COI patients, plasma norepinephrine was higher (P<0.05), whereas epinephrine levels were similar to those of control subjects (Table 3). In COI, the spectral marker of vagal SA node modulation HF<sub>RR</sub> (NU) was reduced and LF/HF was higher than in control subjects (Table 3). Likewise, LF<sub>SAP</sub> was greater in the group of COI patients.

Hemodynamic and Neurohumoral Response to Tilt

In response to upright tilt, HR increased in both groups, reaching, however, higher absolute values in COI patients (Figure 2 and Table 2). Blood pressure remained unchanged (although more oscillations were present in the patients), and CVP was reduced to the same extent in both groups (control subjects, -9.8±0.9 mm Hg; COI patients, -7.5±1.2 mm Hg). Compared with the recumbent position, respiratory frequency tended to increase in COI patients, whereas it remained unchanged in control subjects.

The indices of sympathetic function (MSNA, epinephrine and norepinephrine levels, and LF/HF) increased during tilt compared with supine, with higher values of norepinephrine and LF/HF in COI patients (Table 3). Maximal changes in MSNA in response to tilt were 14.9±2.3 bursts per minute in control subjects and 9.1±1.7 bursts per minute in COI patients (P<0.05). The maximal increase of LF/HF in control subjects and COI was 8.1±6.5 and 21.7±6.5, respectively. Note that MSNA increased by a larger extent in control subjects than in COI patients; conversely, the increase of LF/HF was higher in the COI group (Figure 3).

Baroreflex Function

While subjects were supine, the index α was similar (P>0.06) in COI (18.6±3.1 ms/mm Hg) and in control subjects (29.6±4.7 ms/mm Hg) (Figure 4). Analogous results were obtained when baroreceptor reflex function was determined with drug infusions. Indeed, the mean of the slopes of the regression lines relating SAP changes and corresponding RR interval modifications was similar (P>0.08) in COI (10.47±1.62 ms/mm Hg) and in control subjects (15.69±2.4 ms/mm Hg). Furthermore, the gain of baroreceptor modulation of MSNA was not different.

TABLE 3. Indices of Autonomic Activity in Control and COI Subjects at Rest and During Passive Orthostatism

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Tilt</th>
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<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>COI</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>15±2</td>
<td>24±2*</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>223±23</td>
<td>323±45*</td>
</tr>
<tr>
<td>E, pg/mL</td>
<td>36.7±9.3</td>
<td>35.6±6.3</td>
</tr>
<tr>
<td>RR variance, ms²</td>
<td>5071±1057</td>
<td>3758±1129</td>
</tr>
<tr>
<td>LF&lt;sub&gt;SAP&lt;/sub&gt;, ms²</td>
<td>1279±296</td>
<td>1238±327</td>
</tr>
<tr>
<td>NU</td>
<td>44.3±4.3</td>
<td>61.9±5.0*</td>
</tr>
<tr>
<td>HF&lt;sub&gt;SAP&lt;/sub&gt;, ms²</td>
<td>1654±442</td>
<td>1218±630</td>
</tr>
<tr>
<td>NU</td>
<td>50.7±4.1</td>
<td>31.4±44*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.0±0.2</td>
<td>3.54±0.87*</td>
</tr>
<tr>
<td>SAP variance, mm Hg²</td>
<td>9.4±1.5</td>
<td>13.3±2.0</td>
</tr>
<tr>
<td>LF&lt;sub&gt;SAP&lt;/sub&gt;, mm Hg²</td>
<td>1.7±0.3</td>
<td>5.7±1.3*</td>
</tr>
<tr>
<td>HF&lt;sub&gt;SAP&lt;/sub&gt;, mm Hg²</td>
<td>2.1±0.3</td>
<td>1.9±0.3</td>
</tr>
</tbody>
</table>

For MSNA, controls, n=11; COI, n=14. NE indicates norepinephrine; E, epinephrine.

*p<0.05 controls vs COI.
During the orthostatic stimulus (Figure 4), $\alpha$ decreased significantly in both groups, reaching lower values ($P<0.05$) in patients affected by COI (2.6±0.4 ms/mm Hg) than in control subjects (6.5±1.2 ms/mm Hg).

**Discussion**

The main findings of our study include (1) an increased sympathetic outflow to the heart and to the vessels in COI patients compared with control subjects while supine; (2) during orthostatic stress in COI subjects, a blunted increase in MSNA associated with an enhancement of HR and of the spectral index LF/HF compared with control subjects; and (3) similar arterial baroreflex control of HR and MSNA in both groups.

**Autonomic Control**

In patients with COI, we observed unique alterations of autonomic control of the cardiovascular system. These changes are already present with the patient in the recumbent position, even though many of these patients were almost completely asymptomatic at rest. Indeed, MSNA and LF_SAP were higher than in control subjects, indicating an increased sympathetic drive to blood vessels. In addition, mean HR and LF/HF were greater in COI patients than in the reference group, suggesting a shift of the sympathovagal modulation of the SA node activity toward sympathetic predominance. These observations are compatible with the presence of a hyperadrenergic condition.

During tilt, an increase in MSNA in both groups was observed. However, the degree of change in MSNA in COI patients was lower than that of control subjects. This might reflect the fact that an increased sympathetic discharge at rest could inversely influence the capability of MSNA to increase further in response to the orthostatic stimulus, as described for stressors such as lower-body negative pressure and for the cold pressor test. However, in the COI group, the blunted increase in the sympathetic efferent discharge during tilt was...
associated with a more pronounced enhancement of HR and of LF/HF index compared with control subjects. This pattern suggests that the capability of increasing sympathetic outflow to the heart was not affected by the preexisting heightened cardiac sympathetic tone at rest. Therefore, the autonomic profile of COI patients seems to be characterized during the upright position by a reduced capacity to further increase sympathetic drive to the vascular tree in the lower extremities combined with a preserved or even increased capacity of activating the cardiac sympathetic modulation and withdrawal of the vagal activity to the SA node. The importance of the reduction of the vagal-related oscillations of HF_{RR} during tilt may account for the discrepancy between the trends of LF_{SU} and LF/HF. In fact, the increase of LF/HF can be largely ascribed to the reduction of the HF component of RR variability, whereas LF_{SU} increased only slightly compared with control subjects.

Different mechanisms have been considered to account for the symptoms and the hemodynamic profile of COI patients.\textsuperscript{2,27-30} These included (1) the presence of a mild form of autonomic neuropathy,\textsuperscript{1,5,9,11} (2) the development of a hyperadrenergic state resulting from changes in circulating volume,\textsuperscript{7,8} or (3) sympathetic dysfunction emanating from the central nervous system.\textsuperscript{2,10} The blunted increase in MSNA combined with normal or increased sympathetic response to other regions (eg, cardiac) may be compatible with functional autonomic dysautonomia in the lower extremities. Although in absolute values, the increase in MSNA was similar in control subjects and in patients, the relative change is abnormal, considering that both groups had similar decreases in CVP. In keeping with this possibility, some studies have documented abnormal postganglionic sympathetic sudomotor function\textsuperscript{1,9,31} and reduced norepinephrine spillover in the lower extremities of selected patients suffering orthostatic intolerance at rest, after pharmacological stimulation, and after the cold pressor test.\textsuperscript{1,9} These observations alone, however, do not account for the increased sympathetic tone at baseline recorded in the present study and for many of the clinical findings reported in this syndrome (see below).

Alternatively, it can be argued that the increased sympathetic activity found in these patients may be the result of a compensatory mechanism secondary to venous pooling or a reduced plasma volume. However, the findings of increased HR, MSNA, LF/HF, and LF_{SAP} at rest in the subset of patients characterized in our study argues, like the previous point, against this possibility. In addition, CVP, a parameter that in absolute values, the increase in MSNA was similar in control subjects and in patients, the relative change is abnormal, considering that both groups had similar decreases in CVP. In keeping with this possibility, some studies have documented abnormal postganglionic sympathetic sudomotor function\textsuperscript{1,9,31} and reduced norepinephrine spillover in the lower extremities of selected patients suffering orthostatic intolerance at rest, after pharmacological stimulation, and after the cold pressor test.\textsuperscript{1,9} These observations alone, however, do not account for the increased sympathetic tone at baseline recorded in the present study and for many of the clinical findings reported in this syndrome (see below).

In light of these considerations, we believe that our findings are compatible with the presence of a central nervous system abnormality leading to a hyperadrenergic state.\textsuperscript{1} A strong indication is the finding of pronounced increments in resting supine plasma norepinephrine, MSNA, LF/HF, and LF_{SAP} in patients with COI. The overall increase in resting sympathetic tone is striking because it is detected even in the absence of discernible orthostatic stress. Furthermore, a central alteration of sympathetic tone is compatible with the marked BP oscillations, the pronounced tachycardia, and the changes in regional sympathetic tone during orthostatic stress found in this study and with some of the clinical features (increased anxiety,\textsuperscript{25} response to stress,\textsuperscript{25} severe migraine-like headaches,\textsuperscript{3} and response to some central therapeutic agents such as clonidine\textsuperscript{34} and phenobarbital\textsuperscript{35}) reported by others. It is also possible that some of the dissimilar findings reported in several studies (hypertension\textsuperscript{1} versus hypotension,\textsuperscript{8,11} elevated supine plasma norepinephrine and MSNA versus normal catecholamines and low norepinephrine spillover,\textsuperscript{11} therapeutic response to clonidine\textsuperscript{34} or barbiturates\textsuperscript{37} versus volume load or sympathomimetic agents\textsuperscript{36}) can be explained by the inclusion of heterogeneous groups of patients in whom a different mechanism (or a combination of several) results in similar clinical symptoms.

In this study, we evaluated sympathetic tone by 3 different complementary methods that included microneurography, plasma catecholamines, and spectral analysis of HR and BP variabilities. During tilt, plasma norepinephrine levels were markedly higher in the group of patients with COI compared with control subjects, a finding that seems to be a hallmark of orthostatic intolerance.\textsuperscript{1,9,38} However, it must be noted that the observed enhancement of plasma norepinephrine levels in COI patients may not represent, per se, an increase in central sympathetic activity. For instance, standing induces changes in blood flow redistribution, which might have reduced norepinephrine clearance, as described in other conditions.\textsuperscript{37} Conversely, the increased MSNA and LF/HF ratio indicate, at least while the patient is supine, significant enhancement of sympathetic tone compatible with a hyperadrenergic state. These observations are consistent with data of a recent investigation by Novak et al,\textsuperscript{38} who also found evidence of a hyperadrenergic state in COI patients.

In general, different hemodynamic and sympathoneural responses are evident in subjects suffering from vasovagal syncope compared with COI patients. In vasovagal subjects, we\textsuperscript{25} and others\textsuperscript{38,40} have described a blunted increase in sympathetic activity during tilt, followed by progressive decrease and total disappearance before syncope. Not surprisingly, in vasovagal subjects, the postural loss of consciousness was preceded by a constant reduction in BP, with a “blunted” increase in HR.\textsuperscript{25} This contrasts with the results obtained in COI patients, in whom BP remained unchanged and HR dramatically increased during tilt. The different hemodynamic and sympathoneural profiles have important clinical implications, because COI patients often are confused with vasovagal patients, which then may result in inappropriate therapy.

**Baroreflex Function**

In the recumbent position, COI patients and control subjects had similar baroreflex function. Therefore, the increased values of HR and MSNA observed in COI patients at rest cannot be ascribed to an impairment of the inhibitory modulation elicited by arterial baroreceptor activity. Also, the index \( \alpha \) was unchanged in the 2 groups at rest. During the tilt maneuver, \( \alpha \) decreased in both control subjects and COI patients, reaching lower values in the latter group. This observation suggests that in
this syndrome, baroreflex mechanisms still maintain their functional integrity. Finally, the reduced values of α observed during tilt in COI patients primarily reflect the important reduction of total RR variability and, consequently, of its spectral components as a result of the enhancement of cardiac sympathetic modulation and of vagal withdrawal.

Conclusions

We conclude that in a subset of patients with COI, there is the presence of sympathetic dysfunction, which is characterized, in the recumbent position, by an augmented rate of firing of cardiac and blood vessel sympathetic fibers. During the assumption of the upright posture, an attenuated increase in cardiac sympathovagal modulation toward a sympathetic predominance in patients with COI compared with control subjects. This autonomic profile is associated with a preserved sensitivity of baroreflex mechanisms.

Acknowledgments

We gratefully acknowledge the typing assistance of Isabella Ghirardelli, Varonica Watts, and Dorothea Boemer. Simona Piazza contributed to the analysis of baroreflex sensitivity data.

References

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Circulation. 1998;98:2154-2159
doi: 10.1161/01.CIR.98.20.2154

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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