Impact of Chronic Psychosocial Stress on Autonomic Cardiovascular Regulation in Otherwise Healthy Subjects

Daniela Lucini, Gaetana Di Fede, Gianfranco Parati, Massimo Pagani

Abstract—Elevated psychosocial stress might favor the occurrence of cardiovascular disease; however, mechanisms are incompletely understood. We hypothesized that patients (n=126; 44±1 years of age) referred to an internal medicine clinic because of symptoms related to chronic psychosocial stress would demonstrate signs of autonomic dysregulation compared with controls (n=132; 42±1 years of age). We used autoregressive spectral analysis of RR interval variability to obtain indirect markers of sympathetic and of vagal (respectively, low-frequency and high-frequency components, both expressed in normalized units) oscillatory modulation of sinoatrial node, as well as of sympathetic vasomotor regulation (low-frequency component of systolic arterial pressure variability) and of cardiac baroreflex sensitivity (α-index). Higher values of systolic and diastolic arterial pressure (respectively, 124±1 versus 117±1 mm Hg and 80±1 versus 75±1 mm Hg; both P<0.001), altered markers of autonomic regulation (increased normalized low-frequency and reduced high-frequency component of RR variability, P<0.005; increased-low frequency component of systolic arterial pressure variability, P<0.002), and reduced baroreflex sensitivity (19.3±1.4 versus 23.0±2.0 ms/mm Hg; P<0.05) were observed in patients compared with controls. Autonomic responses to active standing were also blunted in stressed patients. Autonomic markers were significantly correlated to stress perception score and were capable of discriminating between controls and patients with a high degree of accuracy. Chronic real-life stress in humans appears associated to increased arterial pressure and to impaired autonomic regulation of cardiovascular functions. The combination of sympathetic predominance, vagal withdrawal, and blunted baroreflex sensitivity might represent a treatable mechanistic link between psychosocial factors and future incidence of hypertension. (Hypertension. 2005;46:1201-1206.)

Key Words: autonomic nervous system ■ stress ■ risk factors ■ baroreflex ■ behavior ■ hypertension, arterial

Mechanisms by which psychosocial factors increase the risk of cardiovascular diseases are various and complex, and among them, sympathetic overactivity seems to play a pivotal role.1,2 Acute stress might induce short-lasting rises in arterial pressure and heart rate, impair endothelial function, and reduce the threshold for arrhythmia and sudden death.3–6 Chronic stress may also facilitate the occurrence of atherosclerosis by way of the attendant elevated sympathetic activity, acting directly or in combination with inflammation,8 elevated cortisol levels,9 and unhealthy behaviors,10 or other disturbances such as the metabolic syndrome.11 Stress may also reduce baroreflex performance,2,12 thus impairing one of the major cardioprotective autonomic reflex mechanisms,13 ultimately favoring the occurrence of hypertension.

The mechanistic role of autonomic dysregulation in the context of stress has been explored in a variety of animal or laboratory models11,14,15; however, so far, relatively few studies have addressed the association between autonomic dysfunction and real-life stress in humans,2,12 probably because stress may elude accurate quantification16 because it consists of several (inter-related) elements, and its effects are characterized by pronounced between subjects’ variability. In fact, response to stress may be difficult to assess even in the controlled laboratory environment.

Computer analysis of spontaneous blood pressure and heart rate fluctuations has been suggested to offer an insight into autonomic cardiovascular regulation,17,18 with no need of external stimulation on the cardiac and vascular targets. This approach thus appears well suited to explore the impact of stress on autonomic cardiovascular control and the possible effects of suggested countermeasures.19,20

The aim of our study was to test whether patients with symptoms of chronic psychosocial stress, in absence of clinically manifested illness, show signs of autonomic dysregulation, as assessed through a noninvasive approach based on spectral analysis of cardiovascular variabilities.
Breakfast, to come to the laboratory between 8:30 AM and 12:30 PM. To avoid heavy physical activity since the day before and, after a light meal and caffeinated beverages for the 12 preceding hours, to abstain from tobacco products. Informed consent. Our institution ethics committee approved the protocol of the study.

Disorders IV. The sensitivity of arterial baroreflex control of RR interval was assessed by the α-index (average of the square root of the ratio between RR interval and systolic blood pressure spectral powers in the LF and HF regions).

Monovariate and bivariate spectral analysis of RR interval variability and respiration were used to ensure that in all subjects included in the study, respiratory rate coincided with the HF component of RR variability, and no respiratory entrainment was present.

Statistics
Data in the text, figures, and tables are presented as means±SEM. Nonparametric tests (Mann–Whitney, Kruskal–Wallis, and Jonckheere–Terpstra) with Monte Carlo procedure were used to determine the significance of the observed differences as appropriate. Simple nonparametric correlation was used to assess the statistical link between stress scores and indices of autonomic cardiovascular regulation. Discriminant analysis was used to assess the integrated capacity of several psychometric and autonomic variables to correctly classify subjects as controls or patients. A P value <0.05 was considered significant. All computations were performed with a commercial statistical package (SPSS 13).

Results
Stress Evaluation
None of the control subjects reported any particular source of stress in their lives, as per enrollment criteria, whereas the chronic psychosocial stress reported by patients was related to personal problems (relationships with partners, friends, relatives, etc) in 24.3%, social work problems (possibility to lose job, mobbing, personal relationships with managers or other employees, dissatisfaction with their role or salary, lack of social support, etc) in 27.2%, and relatives’ health problems (caregiving, worry for relative’s health status, etc) in 48.5%. The presence of attendant somatic symptoms was assessed by spontaneous reporting during consultation and by self-administered questionnaire. The majority of patients (76%) reported the same symptom/symptoms in both evaluations. Symptoms reported more frequently were related to heart, respiratory system, gastrointestinal tract, or muscle disturbances.

Overall Stress Perception Scale
Patients showed a significantly higher perception of stress compared with controls (respectively, 6.3±0.2 versus 3.2±0.2; P<0.001).

### Methods

**Study Population**

This study considers 288 consecutive subjects who, in the period 2001 to 2003, asked our advice because of symptoms related to stress lasting >3 months. A total of 162 subjects were excluded because of the presence of concomitant diseases, pharmacological treatment, or cigarette smoking, alcohol, or food abuse; the remaining 126 subjects (from now on defined as “patients”; 44±1 years of age) who did not report any stress-related symptoms were enrolled. A total of 132 healthy volunteers of similar age (42±1 years) who did not report any stress-related symptoms were enrolled as “controls” (Table 1). The absence of clinically manifested disease was determined by history, physical examination, and laboratory and routine tests. Body mass index was 23.3±0.3 kg/m² in patients and 23.0±0.3 kg/m² in controls. BMI was determined by history, physical examination, and laboratory and routine tests. Body mass index was 23.3±0.3 kg/m² in patients and 23.0±0.3 kg/m² in controls. All subjects were assessed by a clinical psychologist through a semistructured interview to establish the presence (patients) or absence (controls) of chronic psychosocial stress, the presence of stress-related symptoms, and to exclude patients with psychiatric diseases (with particular attention to depression and somatoform disorders) following Diagnostic and Statistical Manual of Mental Disorders IV criteria.

As in a previous study on the autonomic effects of acute stress, all subjects completed a self-administered questionnaire providing nominal self-rated scales that focused on overall stress perception and stress-related symptoms.

**Autonomic Evaluation**

After a preliminary 10-minute rest period in supine position, allowed for stabilization, blood pressure, ECG, and respiratory activity were recorded over a 10-minute supine baseline and over a subsequent 7-minute period of active standing.

To minimize possible emotional bias of the recording procedure, the ECG (CM5) and the respiratory signal were recorded in all subjects with a 2-way wireless radiotelemetry system while arterial pressure waveform (obtained in all patients and 83 controls) was continuously assessed noninvasively by Finapres device (Ohmeda).

The accuracy of this device in tracking beat-by-beat blood pressure changes has been documented previously. Data were acquired with a personal computer using an acquisition rate of 300 samples/channel per second.

From the simultaneous autoregressive spectral analysis of RR interval and systolic arterial pressure (SAP) variability, a series of indexes indirectly reflecting autonomic cardiovascular modulation were derived. RR interval spectral powers were quantified in the low-frequency (LF; 0.03 to 0.14 Hz) and the high-frequency (HF; 0.15 to 0.35 Hz) regions. LF spectral powers were normalized according to the formula $P_{LFnorm}=\left(\frac{P_{LF}}{VAR_{RR}}\right)\times100$, where $P_{LFnorm}=LF$ powers in normalized unit; $VAR_{RR}=tot$ variance; and $VLF=very low frequency component <0.03 Hz; similar normalization was performed for HF powers. LF/HF of RR interval variability power ratio was also computed. SAP spectral powers were quantified in the LF region (0.33 to 0.14 Hz) and reported in absolute units.

The sensitivity of arterial baroreflex control of RR interval was assessed by the α-index (average of the square root of the ratio between RR interval and systolic blood pressure spectral powers in the LF and HF regions).

Monovariate and bivariate spectral analysis of RR interval variability and respiration were used to ensure that in all subjects included in the study, respiratory rate coincided with the HF component of RR variability, and no respiratory entrainment was present.

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### Overall Stress Perception Scale

Patients showed a significantly higher perception of stress compared with controls (respectively, 6.3±0.2 versus 3.2±0.2; P<0.001).

### Table 1. Study Population*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>132</td>
<td>126</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42±1</td>
<td>44±1</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% male</td>
<td>38.2</td>
<td>44.4</td>
</tr>
<tr>
<td>% female</td>
<td>61.8</td>
<td>55.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0±0.3</td>
<td>23.3±0.3</td>
</tr>
<tr>
<td>Smoke (% smokers)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drugs (% subjects on medication)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Sedentary life</td>
<td>46.66</td>
<td>46.34</td>
</tr>
<tr>
<td>% Occasional</td>
<td>30.66</td>
<td>20.73</td>
</tr>
<tr>
<td>% Regular light</td>
<td>22.66</td>
<td>32.90</td>
</tr>
<tr>
<td>% Regular heavy</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*No statistical differences between controls and patients were present in any of these variables.
Subjective Stress-Related Somatic Symptoms Questionnaire

The total subjective stress-related somatic symptoms questionnaire (4S-Q) score was significantly higher in patients compared with controls (respectively, 57.2 ± 2.7 versus 19.7 ± 2.2; P < 0.001). A significant correlation was found between stress perception scale and 4S-Q scores (r = 0.58; P < 0.001).

Autonomic Evaluation

SAP and diastolic arterial pressure (Table 2), although still in the normal range, were significantly higher in patients compared with controls, whereas heart rate appeared significantly reduced in patients (60.3 ± 1.2 versus 66.1 ± 0.9 bpm; P < 0.005). No significant difference between patients and controls was found when considering RR interval variance and absolute values of RR interval LF and HF spectral components. Conversely, the LF component of RR interval variability (LF_{RR}) expressed in normalized units (Table 2; Figure 1) was significantly higher in patients, whereas the HF component of RR interval variability (HF_{RR}), also expressed in normalized units, was significantly smaller in patients than in controls. LF/HF ratio (Table 2) was significantly more elevated in patients. No significant differences between the 2 groups were observed regarding total variance of RR interval variability. Similar differences were also observed considering males and females separately (Table 3).

During active standing, a stimulus that physiologically enhances sympathetic drive to sinoatrial (SA) node, we observed a significantly smaller increase of normalized LF_{RR} (Figure 1) and a significantly smaller reduction of normalized HF_{RR} in patients compared with controls, whereas, again, no difference was observed when considering absolute values.

Patients were also characterized by greater (P < 0.02) LF component of SAP variability (LF_{SAP}; respectively, 4.9 ± 0.6 versus 2.8 ± 0.3 mm Hg) and by a reduced α-index, expression of baroreflex sensitivity in the frequency domain (respectively, 19.3 ± 1.4 versus 23.0 ± 2.0 ms/mm Hg; P < 0.005). Respiratory rate was slightly lower in patients than in control subjects (14.2 ± 0.3 versus 15.7 ± 0.3 cycles/min; P < 0.005).

Correlation Between Psychological and Autonomic Indices

Overall stress perception scale score showed significant correlations with arterial pressure and several autonomic indices; notably, the strongest link was with SAP (r = 0.263; P < 0.001). Regarding the correlations with spectral indices of RR interval variability, only normalized but not absolute spectral components were significantly linked to stress perception (Table 4). Similar significant, albeit weaker, correlations were found considering 4S-Q scores; again, correlations with absolute spectral components of RR interval variability were not significant.

To assess the integrated capacity of used indices to correctly categorize the study subjects into either controls or patients, discriminant analysis was also performed. Figure 2 shows that, whereas the combination of psychological and autonomic variables provided a correct classification in ≈90%, the separate use of all psychometric or all autonomic variables reduced correct classification to ≈80%. Notably, progressively restricting the number of variables to the top-ranking 10 and subsequently 5, determined a further trivial loss of classification capacity. When only the 3 top-ranking variables (resting SAP, rest–stand difference of LF_{RR} in normalized units, and α-index at rest) were used, the correct classification was still near 80% (79.5% for the original cases and 77.6% for the cross-validated cases).

Discussion

In this study on patients with symptoms of chronic psychosocial stress, we observed signs of cardiovascular dysregu-
tion, as shown by higher values of arterial pressure and altered markers of autonomic control.

The potentially confounding influences of chronic or psychiatric conditions,25 or of drugs and behaviors affecting symptom profile or cardiovascular regulation, were carefully avoided by the selection procedure.

Although still in the normal range, patients of this study were characterized by slightly but significantly higher values of SAP and diastolic arterial pressure levels compared with controls. As with real-life stressors of shorter duration,2 the level of perceived stress was correlated to arterial pressure values. Whether stress may contribute by its association with higher arterial pressure levels to the elevated cardiovascular risk observed in patients with arterial pressure in the high-normal range27 remains to be assessed.

### TABLE 3. Descriptive Statistics of RR Interval Variability in Male and Female Controls and Patients Under Resting Conditions

<table>
<thead>
<tr>
<th>Variance</th>
<th>LFRR</th>
<th>HFRR</th>
<th>α-index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mHz</td>
<td>ms²</td>
<td>nu</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>2238±76</td>
<td>796±177</td>
<td>60±2</td>
</tr>
<tr>
<td>Patients</td>
<td>2569±295</td>
<td>923±157</td>
<td>65±2</td>
</tr>
<tr>
<td></td>
<td>47±1</td>
<td>84±2</td>
<td>523±85</td>
</tr>
</tbody>
</table>

### TABLE 4. Simple Correlation Between Indices of Autonomic Cardiovascular Regulation and, Respectively, Stress Perception Scale Score and 4S-Q Score

<table>
<thead>
<tr>
<th>Autonomic Indices</th>
<th>Correlation With Stress Perception Scale Score</th>
<th>Correlation With 4S-Q Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Units</td>
<td>r</td>
</tr>
<tr>
<td>RR</td>
<td>ms</td>
<td>0.173</td>
</tr>
<tr>
<td>VARRR</td>
<td>ms²</td>
<td>−0.013</td>
</tr>
<tr>
<td>LFRR</td>
<td>mHz</td>
<td>−0.205</td>
</tr>
<tr>
<td>LFRR</td>
<td>ms²</td>
<td>0.007</td>
</tr>
<tr>
<td>HFRR</td>
<td>nu</td>
<td>0.153</td>
</tr>
<tr>
<td>HFRR</td>
<td>mHz</td>
<td>−0.168</td>
</tr>
<tr>
<td>HFRR</td>
<td>ms²</td>
<td>−0.103</td>
</tr>
<tr>
<td>HFRR</td>
<td>nu</td>
<td>−0.191</td>
</tr>
<tr>
<td>LF/HF</td>
<td></td>
<td>0.175</td>
</tr>
<tr>
<td>ΔLFRR</td>
<td>nu</td>
<td>−0.217</td>
</tr>
<tr>
<td>ΔHFRR</td>
<td>nu</td>
<td>0.203</td>
</tr>
<tr>
<td>SAP</td>
<td>mm Hg</td>
<td>0.263</td>
</tr>
<tr>
<td>DAP</td>
<td>mm Hg</td>
<td>0.176</td>
</tr>
<tr>
<td>α-Index</td>
<td>ms/mm Hg</td>
<td>−0.212</td>
</tr>
</tbody>
</table>

### Significant correlations are printed in bold characters.

The intriguing finding of a slightly lower heart rate observed in patients compared with controls should be contrasted with the well-known tachycardia produced by acute psychological stress. Recent studies28 on nonanesthetized instrumented mice subjected to prolonged stress show that after an initial increase in heart rate, a subsequent adaptation determines a clear bradycardia after about a week of continued exposure to stress. Chronic instrumentation avoided the hyper-responsiveness produced by handling and novelty, thus allowing the development over time of the unexpected bradycardia. Likewise in our patient population, the lack of any form of drug treatment, smoking, and use of a totally noninvasive wireless approach might have kept experimental bias to a minimum, thus allowing the emergence of a modest bradycardia. In line with this finding, Furlan et al29 reported a modest bradycardia in humans exposed to chronic work-related stress. Patients also displayed a slower respiratory rate,30 which, as shown previously with direct recordings of muscle sympathetic nerve activity,31 might have induced a dissociation between indices of average autonomic tone and of oscillatory autonomic modulation.

Our study provides new information on the selective role of different autonomic oscillatory mechanisms using markers derived from autoregressive spectral analysis of cardiovascular variabilities.18 A unique property of this technique derives from its ability to provide indices not only of the power of individual components but also, as with the Wiegner–Wille approach,32 of their center frequency, thus describing more comprehensively the oscillatory behavior of cardiovascular autonomic centers. Increases in sympathetic drive are signaled by a relative increase in the normalized power of the LF component (whereas nonsignificant changes were observed in absolute spectral power) and in a leftwards shift of its center frequency because it occurs with upright posture32 in normal individuals or with essential hypertension.33 A similar leftwards shift in the LF frequency with sympathetic stimulation was also shown by broadband spectral analysis in elderly subjects.34

Patients of this study, compared with controls, presented clear differences in spectral profile: the LFRR (in normalized units) and LF/HF were all elevated at rest, whereas the increase of these measures with active orthostatism was blunted. Simultaneously, the center frequency of the LF component was shifted to the left. Overall, these changes
suggest a predominant oscillatory sympathetic modulation of the SA node\textsuperscript{18,35,36} and a reduced responsiveness to excitatory stimuli. As in subjects with high normal arterial pressure,\textsuperscript{34} a concomitant derangement of vagal oscillatory modulation of the SA node is suggested by smaller resting HF$_{\text{RR}}$ and by reduced baroreflex sensitivity (assessed by the $\alpha$-index). Given the major protective role of this vagally mediated reflex mechanism in the setting of coronary artery disease,\textsuperscript{13} this finding might partly account for the well-known facilitating influence of stress on ischemia-linked arrhythmias and sudden death.\textsuperscript{3,32} Furthermore, the increased LF$_{\text{SAP}}$ suggests the presence in this patient population of enhanced sympathetic vasomotor modulation, as it occurs in acute mental stress,\textsuperscript{2} with a strong potential to also induce endothelial dysfunction in this instance.\textsuperscript{5} These data are in line with the results of broadband spectral analysis of arterial pressure fluctuations in elderly subjects exposed to postural sympathetic activation.\textsuperscript{34}

No differences were observed in resting RR variance, suggesting that this simple time domain measure of heart rate variability, although reduced in patients with hypertension,\textsuperscript{38} may be suboptimal to assess the influence of chronic real-life stress on autonomic cardiac regulation in absence of manifested cardiovascular disease.

Whether our reported changes contribute to the increased cardiovascular risk observed in chronic stress remains speculative, although our findings are in line with previous animal experiments showing a strong influence of sympathetic activation on stress-induced coronary artery disease.\textsuperscript{5,7}

In keeping with previous observations in acute stress,\textsuperscript{2} a strong association was also found between levels of perceived chronic stress and somatic symptoms, as assessed by 4S-Q questionnaire. Although the molecular mechanisms of this link were not examined, recent experimental data\textsuperscript{39} suggest that stress-mediated sympathetic overstimulation might increase protein kinase C activity in central structures, such as the prefrontal lobe, leading to a dysregulation of thought, affect, or behavior. Such a frontal cortical dysfunction might interfere with individual autonomic response patterns\textsuperscript{40} to potentially stressful situations, disturbing the interactions between cognitive appraisal and general state of health, which, in turn, reflects the interplay between genetic factors, behaviors, and lifestyle choices.\textsuperscript{10,41} This mechanism might also be playing a role in other clinical conditions, such as orthostatic intolerance\textsuperscript{42} or chronic fatigue,\textsuperscript{43} in which subjective symptoms accompany alterations of autonomic regulation.

### Study Limitations

In this observational study, we did not measure sympathetic nerve activity directly, which requires invasive techniques.\textsuperscript{23} We only inferred\textsuperscript{44} information on resting autonomic oscillatory properties and responses to an excitatory stimulus indirectly from spectral analysis of RR interval and SAP variability.\textsuperscript{10,35}

### Perspectives

Using a noninvasive, wireless approach, based on spectral analysis of short-term cardiovascular variability, we observed that chronic real-life stress in humans appears associated to an increase in arterial pressure and to impaired autonomic regulation of cardiovascular functions. Sympathetic predominance, vagal withdrawal, and baroreflex impairment might represent the autonomic counterpart of the complex psychophysiological changes underlying the increase in cardiovascular risk associated to chronic stress.\textsuperscript{16} Optimizing the autonomic profile with behavioral or pharmacological means\textsuperscript{45} might thus represent a testable strategy to reduce the link between psychosocial factors and future incidence of hypertension.\textsuperscript{33,46,47}

### Acknowledgments

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### References

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