Impairment in Cardiac Autonomic Regulation Preceding Arterial Hypertension in Humans
Insights From Spectral Analysis of Beat-by-Beat Cardiovascular Variability

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Background—Subjects in the upper-normal range of arterial pressure have an excess cardiovascular risk, which suggests that other factors, such as impaired autonomic regulation, might be implicated. This study was designed to assess whether noninvasive markers of cardiac and vascular autonomic regulation might already be altered in subjects with high-normal arterial pressure levels.

Methods and Results—We performed an observational study on a population comprising 300 subjects of both sexes with arterial pressure ranging from 90/60 to 210/120 mm Hg, who were divided into 3 groups (each n=100) with average systolic pressures of 103, 133, and 163 mm Hg. Autonomic regulation was inferred from spectral analysis of RR interval and systolic arterial pressure variability, considering rest and stand-induced changes, to account for sympathetic excitatory components. Significant alterations in markers of sinoatrial regulation (increased low-frequency normalized units, reduced high-frequency normalized units, and α-index) were already apparent in subjects in the second tertile, ie, those with arterial pressure within normal limits. Markers of vascular regulation instead showed significant alterations in the third (hypertensive) tertile. In response to standing, changes in markers of sinoatrial modulations were gradually reduced, whereas those of vascular regulation were increased. A tight link between progression of arterial pressure and the continuum of changes in autonomic markers as shown by simple correlation analysis appeared strongly affected by age and was spread across many spectral analysis–derived variables. Hypertensive autonomic dysregulation was particularly apparent in the youngest group.

Conclusions—RR-variability parameters might prove useful to assess, with longitudinal studies, the mechanistic role of autonomic impairment in the increased risk of prehypertensive conditions. (Circulation. 2002;106:2673-2679.)

Key Words: nervous system, sympathetic hypertension aging prevention

Expert national committees recommend that subjects with established hypertension, defined as arterial pressure values exceeding 140 mm Hg systolic and 90 mm Hg diastolic, should receive antihypertensive treatment to reduce their increased cardiovascular risk.1 Despite the fact that in population studies, even small reductions in arterial pressure load might appear useful, the clinical benefits of lowering arterial pressure are far from optimal, particularly with regard to coronary risk.2 Cardiovascular events such as sudden coronary death, myocardial infarction, and stroke might easily occur at pressure values below this threshold,3 and antihypertensive treatment might prove valuable, at least in selected cases, even in patients who do not reach the hypertensive limit.4 Accordingly, the usual dichotomous approach to hypertension, distinguishing between normotensive and hypertensive subjects, might be suboptimal. Limited compliance with individual variations, such as spontaneous or seasonal shifts in arterial and autonomic baseline values,5 the “white coat” effect,6 or measurement bias,7 would be particularly confounding in subjects with borderline values, contributing to uncertain diagnosis.8 Most recent guidelines suggest further dividing the pressure range,9 focusing also on high-normal values. The demonstration that subjects in the upper-normal range of pressure (notably, those with systolic arterial values between 130 and 135 mm Hg10 ) show an excess event rate argues in favor of a linear relationship11 between arterial pressure and cardiovascular risk, which supports the use of continuum models. Moreover, risk should be considered in the context of its multifactorial nature, which derives from interaction with other unfavorable genetic, behavioral, or metabolic elements, such as smoking, stress,12 sedentary lifestyle, dyslipidemia, or endothelial dysfunction.11 Among possible components of increased risk, studies showing the presence of several anomalies in autonomic markers such as reduced heart rate variability,13 decreased baroreflex sensitivity,14,15 increased sympathetic activity,16,17 and altered auto-
nomic responsiveness\textsuperscript{18} in arterial hypertension support a
mechanistic role of excitatory sympathetic circuits.\textsuperscript{19,20} The
present observational study was therefore designed to assess
whether noninvasive markers of cardiac and vascular auto-
nomic regulation, viewed as part of a continuum, might
already be altered in subjects with high-normal arterial
pressure levels.

Methods

Study Population
This study considered 300 nonobese (body mass index <26) subjects
(169 men, 131 women) whose sitting systolic arterial pressure (SAP)
ranged from 90 to 210 mm Hg and whose diastolic arterial pressure
ranged from 60 to 120 mm Hg. All subjects were nonsmokers and
free of any disease or disturbance (except arterial hypertension), as
determined by history, physical examination, and routine laboratory
tests. Left ventricular hypertrophy was ruled out by ECG criteria.
Half of the study population had been referred because of clinical
diagnosis of arterial hypertension, whereas the second half was
recruited from healthy hospital staff, medical students, and relatives.
Subjects were instructed to avoid alcohol and caffeinated beverages
for the 12 hours preceding the study, to abstain from heavy physical
activity the day before, and after a light breakfast, to come to the
laboratory between 8:30 AM and 12:30 PM on the day of the study.
All subjects were instructed about the study procedure and gave their
informed consent. None were taking any medication (treated hyper-
laboratory between 8:30AM and 12:30 PM on the day of the study.
Subjects were instructed to avoid alcohol and caffeinated beverages
recruited from healthy hospital staff, medical students, and relatives.

Autonomic Evaluation
After a preliminary 10-minute period, to allow for stabilization, a
10-minute rest period was obtained in all subjects, followed by a
7-minute period of active standing. During the last 2 periods,
recordings were performed. The ECG (CMS) and respiratory signal
were recorded with a 2-way radiotelemetry system (Marazza),
whereas the arterial pressure waveform was continuously assessed
noninvasively with a plethysmographic device (Finapres, Ohmeda),
the average error of which was estimated to be \( \pm 2.6 \pm 0.4 \) mm Hg,
according to Bland and Altman,\textsuperscript{7} with a standard sphygmomanom-
er. Data were acquired with a personal computer equipped with an
analogue-to-digital board (Data Translation) with an acquisition rate
of 300 samples per channel per second.

From the simultaneous autoregressive spectral analysis of RR
interval and SAP variability, a series of autonomic indexes was
subsequently computed offline, as described previously,\textsuperscript{21–25} which
provided markers of autonomic regulation of the sinoatrial (SA)
node, the arterial vasculature, and overall baroreflex gain (\( \alpha \)-index).\textsuperscript{15} In all subjects included in the study, respiratory rate
coincided with the high-frequency (HF) component of RR variability
and is therefore presented in Tables 1 and 2.

Statistical Analysis
Data are presented as mean\( \pm \)SEM (except age, which is shown as
mean and range, Table 1). The study population was divided into 3
groups of equal size (n=100) according to ranks of SAP, as
measured by Finapres, to focus on the high-normal range of pressure.
One-way ANOVA was used to assess the significance of differences
between the 3 groups (Tables 1 and 2), whereas paired \( t \) test was used to
assess the effects of stand-induced changes (stand-rest). Simple
and partial correlation analyses were used to estimate the relationship
between SAP and time- and frequency-domain indices of cardiovas-
cular variability, with further control for age and sex (Table 3). To
demonstrate graphically the simultaneous influence of age, as in
Figure 3, subjects were further divided into 3 age groups, and cells
presented in every panel of the illustration provide data that refer to
the youngest and eldest tertiles. (The middle age tertile is not
included for clarity.) A \( P \) level <0.05 was considered significant.

Results
An example of the spectral profile of RR variability and respiration in
a normotensive and a hypertensive subject is shown in Figure 1. Notice in the latter case the clear shift in
spectral distribution toward the LF component at rest and its
diminished increase with standing up. Respiration, in both
cases, clearly coincides with HF range.

### TABLE 1. Descriptive Statistics of RR Interval and SAP Variability in 300 Subjects Under Resting Conditions

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Age, y</th>
<th>RR, ms</th>
<th>VARRR, ms(^2)</th>
<th>LF, mHz</th>
<th>LF, ms(^2)</th>
<th>LF, NU</th>
<th>HF, mHz</th>
<th>HF, ms(^2)</th>
<th>HF, NU</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>33(16–60)</td>
<td>881±12</td>
<td>3506±306</td>
<td>109±2</td>
<td>934±103</td>
<td>47.8±1.8</td>
<td>274±5</td>
<td>1076±138</td>
<td>40.2±1.7</td>
</tr>
<tr>
<td>II</td>
<td>42(16–70)</td>
<td>841±12</td>
<td>2107±248</td>
<td>97±2</td>
<td>565±9</td>
<td>60.9±1.7</td>
<td>273±6</td>
<td>405±98</td>
<td>29.7±1.6</td>
</tr>
<tr>
<td>III</td>
<td>48(15–81)</td>
<td>847±13</td>
<td>1491±137</td>
<td>90±3</td>
<td>451±48</td>
<td>58.1±2.1</td>
<td>272±6</td>
<td>279±40</td>
<td>32.0±1.8</td>
</tr>
</tbody>
</table>

### TABLE 2. Stand-Induced Changes: Descriptive Statistics of RR Interval and SAP Variability in 300 Subjects

<table>
<thead>
<tr>
<th>Tertile</th>
<th>RR, Ms</th>
<th>VARRR, ms(^2)</th>
<th>LF, mHz</th>
<th>LF, ms(^2)</th>
<th>LF, NU</th>
<th>HF, mHz</th>
<th>HF, ms(^2)</th>
<th>HF, NU</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>−134±6§</td>
<td>−784±242§</td>
<td>−12±3§</td>
<td>−15±94</td>
<td>30.6±1.6§</td>
<td>−1±8</td>
<td>−822±131§</td>
<td>−24.3±1.5§</td>
</tr>
<tr>
<td>II</td>
<td>−96±7§</td>
<td>−79±161</td>
<td>−4±3</td>
<td>316±101§</td>
<td>18.7±1.8§</td>
<td>1±5</td>
<td>−290±91§</td>
<td>−16.3±1.6§</td>
</tr>
<tr>
<td>III</td>
<td>−80±7§</td>
<td>−87±101</td>
<td>0±3</td>
<td>−11±50</td>
<td>13.4±2.1§</td>
<td>6±5</td>
<td>−185±35§</td>
<td>−13.3±1.8§</td>
</tr>
</tbody>
</table>
Descriptive statistics at rest are presented in Table 1. Average SAP (by Finapres) was respectively 103 ± 1, 133 ± 1, and 163 ± 1 mm Hg in the 3 groups. With increasing pressure level, from tertile I to tertiles II and III, resting values of RR interval, RR variance, and both LFRR and HFRR in absolute units decreased significantly. Likewise, the center frequency of the LFRR component and the baricenter of the whole spectrum decreased significantly. With regard to components, LFRR in normalized units and LF/HF ratio in tertiles II and III were significantly higher than in tertile I, whereas HFRR in tertiles II and III was significantly lower than in tertile I. These changes overall indicate that with rising pressure groups, RR spectral power distribution shifts toward the LF end of the spectrum. Differences in markers of SA node modulation, slightly affected by age and sex, were greater between tertiles I and II than between tertiles II and III. Conversely, differences in autonomic indicators derived from arterial pressure, such as SAP variance and the LF/HF component, which increased with rising pressure levels, became more pronounced in tertile III. The α-index, a measure of baroreflex gain, was progressively reduced with rising pressure level across all tertiles. In brief, alterations in autonomic markers, particularly those that reflect SA node modulation, were already well apparent in tertile II, at a systolic arterial pressure well below the usual upper limit of normal (ie, 140 mm Hg), whereas changes in markers of sympathetic modulation of arterial pressure reached significance only in tertile III, well above the hypertensive limit.

The extent of changes induced by standing in heart rate variability parameters (Table 2) was progressively reduced with rising pressure tertile, with these variations particularly evident for LFRR in normalized units and for HFRR in both normalized and absolute units. The standing-induced reduction in α-index was progressively smaller with rising pressure groups. Standing-induced changes in SAP-derived parameters (such as SAP variance and LFSSAP component), conversely, increased with growing pressure tertile. Overall, responses to standing in indices of SA node and SAP regulation appeared divergent: whereas with growing pressure tertile, markers of RR modulation changed less with active orthostatism, the reverse occurred with markers of SAP modulation, which increased more.

**Correlation Between SAP and Spectral Variables**

To further characterize the continuum of changes, individual simple correlations between SAP and spectral analysis-derived indices were computed (see Table 3). The majority of autonomic indices, considering both their resting values and changes induced by stand, were highly significantly linked with SAP, albeit, not surprisingly, with moderate values of correlation (Figure 2 illustrates highest-ranking variables and the wide scatter of individual data points). Correlations were also controlled for age and for sex because of the strong link of age with SAP (r = 0.528, P < 0.001) and because of the reported possible influence of sex on autonomic dysregulation in hypertension. Many of the markers of SA modulation, such as RR variance, absolute LFRR, and HFRR, were thus no longer significantly linked to the continuum of SAP. Conversely, for others, such as the α-index and stand-induced changes in RR interval, LFRR (expressed in normalized units), the baricenter of the RR-interval spectrum, and LFSSAP, the partial correlation, although indicating a clear influence of age but a minimal influence of sex, signaled an independent, highly significant link with SAP. After controlling for age...
and sex, resting RR interval, frequency of LF RR, and LF SAP power had a weakly significant link with SAP.

The combined effects of age and arterial pressure tertiles on most significant cardiac and vascular autonomic variables are depicted in Figure 3, which shows that a pressure-linked, age-dependent progressive derangement of SA node regulation was more apparent in the youngest tertile. Changes in autonomic markers of vascular regulation (eg, variance SAP) were more apparent in tertile III and were less sensitive to age.

**Discussion**

This study provides new evidence in human hypertension of a progressive impairment in autonomic regulation that is already present in subjects with arterial pressure values below the upper limit of normalcy and is more apparent on markers of SA node regulation. The link between progression of arterial pressure and the continuum of changes in autonomic markers appears strongly affected by age and spreads across many variables, none of which can be reliably singled out as the most significant indicator. Impaired autonomic regulation of the SA node is particularly apparent in the youngest group.

Impaired autonomic regulation was assessed with a noninvasive approach, based on multiparametric evaluation, that considered indices derived from time- and frequency-domain analysis of RR and SAP beat-by-beat variability to simultaneously address multiple aspects of information about cardiac and vascular control. Notably, it must be stressed that because none of the techniques used in the present clinical study can provide a direct measure of autonomic nerve activity to the heart or blood vessels, only indirect inferences can be drawn from the present data, based on probability and error levels and on interpretative mod-
els,26 as shown by a large body of experimental and clinical evidence.25 The use of dynamic protocols26 that include, in addition to resting values, changes produced by sympathetic activation, eg, through standing-induced baroreceptor unloading29 or moderate exercise,15 might reveal autonomic disturbances that are not otherwise apparent.

The significant alterations in RR-variability parameters and in α-index values (a measure of baroreflex gain15) present at rest in the still normotensive tertile II subjects suggest a change in the interaction between the 2 autonomic arms that modulate the SA node toward sympathetic predominance and vagal withdrawal, which occurs at arterial pressure values below the upper limit of normalcy. This finding should be contrasted with the observation that a significant modulation of age and, to a lesser extent, of sex,25 is suggested by prior studies12 on healthy students exposed to real-life long-term stress that induced diminished responses of the SA node and increased the response of the vasculature to stand-mediated sympathetic excitation.

The importance of a continuum of changes11 is emphasized by the significant correlation between arterial pressure and the majority of markers of RR and SAP variability, which also shows the large spread of information across RR-variability parameters, as previously reported for normotensive subjects.30 The use of partial correlations to control for the well-known effects of aging on autonomic regulation in hypertension25 leads to a loss of significant links between pressure levels and absolute, but not normalized, power of markers of autonomic regulation of the SA node. This finding further supports the different information imparted by normalized or absolute markers of autonomic oscillations.21–24 Considering present data in the context of the different information26 provided by absolute and normalized powers of RR-variability components, we might hypothesize a clear and early disturbance of oscillatory properties of RR variability in human hypertension, already evident in the prehypertensive31 pressure levels of tertile II. This disturbance appears to be characterized by a shift in spectral power distribution toward the lower end of the frequency axis, as shown by normalized units (but not by absolute units, owing to the simultaneous reduction in variance), and further documented by a lower center frequency of LFRR and of the baricenter of the RR autospectrum.24 Although we did not specifically address the

**Figure 1.** Example of RR-interval variability and respiration spectra, at rest (left) and during active stand (right) in normotensive subject (110/80 mm Hg, 40 years old) and moderately hypertensive subject (150/90 mm Hg, 52 years old). Notice in hypertensive subject prevalence of LF component at rest and its lack of increase with standing. Respiratory spectrum contains in both subjects a major component synchronous with HF component of RR variability. Spectra of SAP variability are not shown for simplicity. PSD indicates spectral power distribution; a.u., arbitrary units; and RESP, respiration.

**Figure 2.** Simple linear correlations between resting SAP values and selected markers of SA node (left) and vascular autonomic regulation (right). Autonomic markers were selected according to rank of significance of correlation, as shown in Table 3. nu indicates normalized units; Δ, stand-rest; VAR, variance.
issue of sex influences, it appears from the present data that controlling in addition for sex might slightly modify our findings, if at all.

In conclusion, the present investigation revealed that in subjects with arterial pressure values in the upper normotensive range, noninvasive markers of cardiac and vascular regulation were already altered. These alterations, which were particularly apparent in the youngest group, suggest that disturbances in autonomic regulation that precede overt arterial hypertension might explain in part the increased risk of cardiovascular events even in hypertensive patients with optimal blood pressure control.

Although the cross-sectional design is an important intrinsic limitation, the present study suggests that RR-variability parameters, as in the case of ischemic heart disease and heart failure, might provide a useful functional outcome to assess the efficacy of integrated management of the increased risk of prehypertensive conditions. Accordingly, hypertension treatment should not be limited to achieving a reduction in blood pressure but should also aim to treat the mechanisms underlying high blood pressure states.

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References
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