Effects of Age and Gender on Autonomic Control of Blood Pressure Dynamics

Sheila R. Barnett, Raymond J. Morin, Dan K. Kiely, Margaret Gagnon, Gohar Azhar, Eric L. Knight, Jerald C. Nelson, Lewis A. Lipsitz

Abstract—Both age and gender influence cardiovascular autonomic control, which in turn may influence the ability to withstand adverse autonomic events and respond to orthostatic stress. The purpose of this study was (1) to quantify age- and gender-related alterations in autonomic control of blood pressure (BP) and (2) to examine the impact of these autonomic alterations on BP response to orthostatic stress. We measured continuous BP and R-R intervals and vasoactive peptide levels in the supine and 60° head-up tilt positions during paced respiration (0.25 Hz) in 89 carefully screened healthy subjects (41 men, 48 women, aged 20 to 83 years). Data were analyzed by gender (age adjusted) and by age group (gender adjusted). During tilt, women had greater decreases in systolic BP than men (−10.2±2 versus −1.2±3 mm Hg; \( P=0.02 \)) and smaller increases in low-frequency (sympathetically mediated) BP power (\( P=0.02 \)). Upright plasma norepinephrine was lower in women (\( P=0.02 \)). Women had greater supine high-frequency R-R interval power than men (\( P=0.0001 \)). In elderly subjects, the tilt-induced increase in low-frequency BP power was also diminished (\( P=0.01 \)), despite higher supine (\( P=0.02 \)) and similar upright norepinephrine levels compared with younger subjects. Thus, healthy women have less sympathetic influence on BP and greater parasympathetic influence on R-R interval than men. Elderly subjects also have reduced sympathetic influence on BP, but this appears to be more consistent with a reduction in vasomotor sympathetic responsiveness. (Hypertension. 1999;33:1195-1200.)

Key Words: sympathetic nervous system ■ norepinephrine ■ spectral analysis ■ hypotension

Analyses of the beat-to-beat variability of cardiac R-R intervals have been used to quantify alterations in autonomic function and predict adverse clinical events.\(^1\)\(^2\) Since both age and gender have a profound influence on the risk of cardiovascular disease and death, it is important to understand the effects of healthy aging and gender on autonomic control of cardiovascular function. Previous studies have shown reductions in heart rate (HR) variability with aging\(^3\)\(^4\) and increases in high-frequency HR variability in women compared with men.\(^5\)\(^7\) Since many studies did not rigorously screen subjects to exclude occult cardiovascular disease, it is not known whether abnormalities in short-term autonomic control of HR reflect subclinical cardiovascular disease or whether they represent “normal” age- or gender-related alterations in autonomic function.

The effects of age and gender on beat-to-beat blood pressure (BP) dynamics have been less well studied, and it is not known whether changes in the autonomic regulation of beat-to-beat BP are associated with hemodynamic impairment. Therefore, we asked the following questions: (1) Are there specific age- and gender-related alterations in the autonomic control of beat-to-beat BP dynamics in healthy individuals free of cardiovascular disease? (2) If so, what are the hemodynamic consequences of these changes during orthostatic stress?

We used spectral analysis of continuous BP and R-R interval time series obtained in the supine and head-up tilt positions to assess alterations in the short-term autonomic regulation of BP and R-R. Spectral analysis decomposes cardiovascular signals into their frequency components and quantifies the power of each component.\(^8\) During paced breathing at 0.25 Hz in the supine position, high-frequency R-R interval power (0.15 to 0.50 Hz) quantifies the amplitude of the vagally mediated respiratory sinus arrhythmia. During upright tilt, increases in low-frequency BP power (“Mayer waves,” 0.04 to 0.15 Hz) represent baroreflex-mediated increases in sympathetic vasomotor activity. The degree to which low-frequency BP oscillations are associated with oscillations in R-R interval at the same frequency (transfer magnitude) was used as a measure of cardiovascular baroreflex gain.\(^9\) Finally, we examined plasma norepinephrine level and levels of other circulating vasoactive peptides to determine their potential relationship to hemodynamic changes during orthostatic stress.

Methods

Subjects

One hundred forty-four potential subjects were recruited from the local community through newspaper advertisements and the Harvard

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From the Hebrew Rehabilitation Center for Aged Research and Training Institute (S.R.B., L.A.L., R.J.M., D.K.K., M.G.), Beth Israel/Deaconess Medical Center, Departments of Medicine (L.A.L., G.A., E.L.K.) and Anesthesia (S.R.B.), Harvard Medical School, Boston, Mass; and Quest Diagnostics Nichols Institute (J.C.N.), San Juan Capistrano, Calif.

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Hypertension is available at http://www.hypertensionaha.org
Cooperative Program on Aging subject registry. After an initial telephone screen, subjects underwent a history and physical examination, complete blood count, chemistry and lipid profile, and ECG. Subjects aged >40 years also performed a graded exercise stress test. Exclusion criteria included evidence of cardiovascular or other diseases, tobacco or alcohol use, obesity (body mass index >30 kg/m²), hypertension (systolic BP >140 mm Hg), and use of medication other than oral contraceptives (n=8). A total of 34 subjects were ineligible after screening, and 15 decided to withdraw, leaving 95 subjects who completed the study. Six of these subjects were excluded during data analysis because of frequent ectopy during prolonged cardiac monitoring. Therefore, the final sample included 89 healthy subjects. The study was approved by the Institutional Review Board of the Hebrew Rehabilitation Center for Aged, and all subjects provided informed consent.

**Instrumentation**

Subjects reported to the Cardiovascular Research Laboratory at 7:30 AM on the morning of the study in the fasting state. Premenopausal women aged 20–39 years also performed a graded exercise stress test. Baseline hemodynamic and respiratory measurements were obtained during the upright position. Subjects then performed paced breathing while in the upright position over 30 seconds. Between 5 and 15 minutes in the upright position, subjects again performed paced breathing while continuous ECG, BP, and respiratory data were collected. Blood samples were obtained at 15 minutes of upright tilt.

**Vasoactive Hormone and Peptide Assays**

Plasma was collected in tubes containing glutathione for the norepinephrine assay and in tubes containing EDTA and aprotinin for measurements of endothelin, renin (renin peptide and plasma renin activity), and aldosterone. Plasma was stored at −70°C until assayed. All assays were performed by the Corning Nichols Laboratory.

Norepinephrine was measured in a plasma extract by high-performance liquid chromatography with the use of a cation exchange column, an acetonitrile/phosphate buffer mobile phase, and electrochemical detection, with an interassay coefficient of variation (CV) of 3.9%. Endothelin was measured in an extract of plasma by a double-antibody radioimmunoassay method with endothelin-1 stan-

### TABLE 1. Mean (SE) Baseline Characteristics by Age Group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Young (20–39 y)</th>
<th>Middle (40–59 y)</th>
<th>Old (≥60 y)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>30</td>
<td>27</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>27.2 (1.0)</td>
<td>49.9 (1.1)</td>
<td>70.1 (1.1)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.0 (0.4)</td>
<td>24.2 (0.6)</td>
<td>24.5 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>59 (3)</td>
<td>61 (3)</td>
<td>56 (2)</td>
<td></td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>1030 (26)</td>
<td>1013 (32)</td>
<td>1085 (25)</td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>117 (2)</td>
<td>121 (3)</td>
<td>122 (3)</td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>62 (2)</td>
<td>68 (2)</td>
<td>66 (2)</td>
<td></td>
</tr>
<tr>
<td>FBF, mL/min</td>
<td>1.7 (0.1)</td>
<td>1.7 (0.2)</td>
<td>1.4 (0.1)</td>
<td></td>
</tr>
<tr>
<td>FVR, units</td>
<td>53 (4)</td>
<td>62 (5)</td>
<td>70 (5)*</td>
<td>0.04</td>
</tr>
<tr>
<td>Spectral power</td>
<td>R-R interval HF, ms²</td>
<td>1630 (372)</td>
<td>439 (102)*</td>
<td>234 (45)†</td>
</tr>
<tr>
<td>SBP LF, mm Hg²</td>
<td>2.7 (0.5)</td>
<td>2.5 (0.4)</td>
<td>1.7 (0.2)</td>
<td></td>
</tr>
<tr>
<td>DBP LF, mm Hg²</td>
<td>2.0 (0.4)</td>
<td>1.7 (0.3)</td>
<td>0.8 (0.1)†</td>
<td>0.0001</td>
</tr>
<tr>
<td>Transfer magnitude</td>
<td>12 (0.9)</td>
<td>10 (1.1)</td>
<td>9 (0.6)*</td>
<td>0.03</td>
</tr>
<tr>
<td>Vasoactive peptides</td>
<td>Norepinephrine, pmol/L</td>
<td>35.9 (2.2)</td>
<td>49.7 (4.6)*</td>
<td>60.7 (5.1)*</td>
</tr>
<tr>
<td>Aldosterone, pmol/L</td>
<td>0.17 (0.02)</td>
<td>0.18 (0.01)</td>
<td>0.16 (0.01)</td>
<td></td>
</tr>
<tr>
<td>Endothelin, pmol/L</td>
<td>34.8 (3.0)</td>
<td>32.5 (1.5)</td>
<td>30.5 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Direct renin, mU/L</td>
<td>18.8 (1.5)</td>
<td>21.7 (1.4)</td>
<td>18.4 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Plasma renin activity, ng/L · s</td>
<td>3.6 (0.7)</td>
<td>3.2 (0.4)</td>
<td>2.5 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBF, forearm blood flow; HF, high frequency; and LF, low frequency. All analyses are adjusted for gender.

*P value compared with young.
†P value compared with middle-aged.
**TABLE 2. Absolute Changes From Supine to Head-Up Tilt by Age Group**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young (20–39 y)</th>
<th>Middle (40–59 y)</th>
<th>Old (≥60 y)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>+17 (1)</td>
<td>+11 (1)*</td>
<td>+11 (1)*</td>
<td>0.002</td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>−232 (18)</td>
<td>−162 (22)*</td>
<td>−180 (16)</td>
<td>0.03</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>−7 (3)</td>
<td>−5 (3)</td>
<td>−7 (4)</td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>+2.7 (3)</td>
<td>+0.3 (3)</td>
<td>−0.2 (3)</td>
<td></td>
</tr>
<tr>
<td>FBF, mL/min</td>
<td>−0.6 (0.1)</td>
<td>−0.8 (0.1)</td>
<td>−0.5 (0.1)</td>
<td></td>
</tr>
<tr>
<td>FVR, units</td>
<td>+34 (7)</td>
<td>+51 (8)</td>
<td>+30 (7)</td>
<td></td>
</tr>
<tr>
<td>Spectral power</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-R interval HF, ms²</td>
<td>−1415 (371)</td>
<td>−323 (93)*</td>
<td>−106 (43)*</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP LF, mm Hg²</td>
<td>+7 (2)</td>
<td>+7 (2)</td>
<td>+4 (1)</td>
<td></td>
</tr>
<tr>
<td>DBP LF, mm Hg²</td>
<td>+3 (0.6)</td>
<td>+2 (0.5)*</td>
<td>+2 (0.2)*</td>
<td>0.02</td>
</tr>
<tr>
<td>Transfer magnitude</td>
<td>−4 (0.8)</td>
<td>−4 (1.2)</td>
<td>−2 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Vasoactive peptides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine, pmol/L</td>
<td>30 (4)</td>
<td>32 (5)</td>
<td>26 (4)</td>
<td></td>
</tr>
<tr>
<td>Aldosterone, pmol/L</td>
<td>0.06 (0.03)</td>
<td>0.09 (0.02)</td>
<td>0.08 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Endothelin, pmol/L</td>
<td>0.3 (1.3)</td>
<td>1.0 (1.0)</td>
<td>−0.3 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Direct renin, mU/L</td>
<td>5.5 (0.9)</td>
<td>5.2 (1.7)</td>
<td>1.6 (0.9)*</td>
<td>0.03</td>
</tr>
<tr>
<td>Plasma renin activity, ng/L·s</td>
<td>1.8 (0.4)</td>
<td>1.4 (0.4)</td>
<td>0.7 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

All analyses are adjusted for gender.

*P value compared with young.
†P value compared with middle-aged.

Data Processing
ECG, BP, and respiratory data were digitized at 250 Hz and displayed in real time on a personal computer (Windaq, Dataq Instruments). Continuous ECG and BP data before and during tilt were edited offline for artifact and ectopy with the use of an automated arrhythmia detection program for the ECG and manual editing for BP. Eight-minute data segments during paced breathing, with the subject supine and in the tilt position, were used for the analysis.

Beat-to-beat R-R intervals were determined from the R wave of the ECG, and beat-to-beat systolic and diastolic BPs were derived from the maximum and minimum of the arterial pressure waveform. Each R-R systolic and diastolic BP time series was interpolated by cubic spline function and resampled at 2 Hz to obtain equidistant time intervals. The resampled series were analyzed with a fast Fourier transform algorithm. The areas under the power spectra in the Mayer wave and respiratory frequencies (defined as 0.04 to 0.15 and 0.15 to 0.50 Hz, respectively) were integrated and used for statistical comparisons. HR was calculated as the reciprocal of the R-R interval (in seconds), multiplied by 60. Mean HRs and BPs were determined from the 8-minute data segments during supine and upright time periods.

Statistical Analysis
Two separate analyses were performed, 1 by age group (20 to 39, 40 to 59, and ≥60 years) and 1 by gender. We compared baseline characteristics of groups of subjects with ANCOVA, controlling for either age or gender. Supine and tilt cardiovascular variables and spectral powers were compared between the groups with 2-way (group and time) repeated-measures ANCOVA. Multiple linear regression was also used to determine factors independently associated with changes in BP power during upright tilt. All spectral data were natural log transformed to normalize their distributions. Data are expressed as untransformed mean±SE values. An α level ≤0.05 was used to determine statistical significance.

To characterize the baroreflex, we examined the linear relation (coherence) and strength of that relation (transfer magnitude) between systolic BP (input signal) and R-R interval (output signal) fluctuations in the low-frequency range (0.04 to 0.15 Hz) during supine and upright tilt conditions. We calculated the coherence and transfer magnitudes between the signals using the technique of Saul et al, with paced rather than random breathing. All analyses were performed with DaDisp software on a personal computer. Coherence was calculated from the cross-spectra and autospectra of the time series following the formula: [Cross-Spectra²/Output Signal Autospectrum]×[Output Signal Autospectrum]. The signals were considered coherent over the frequencies at which coherence values were >0.5. The complex transfer function was calculated by dividing the cross-spectra by the input autospectrum. The transfer magnitude was then derived for each subject over the low-frequency range meeting the coherence criterion.

Results
Effects of Age
Baseline Characteristics
As shown in Table 1, forearm vascular resistance (FVR) was greater in the old, and plasma norepinephrine levels were greater with increasing age. However, low-frequency diastolic BP power was lower in the older group than in the middle-aged and young. High-frequency R-R interval power and transfer magnitude were also lower in the oldest age group.

Response to Tilt
The responses to head-up tilt were similar whether absolute or relative changes were analyzed; therefore, only absolute changes...
are reported as shown in Table 2. HR and FVR increased during tilt \( (P<0.001 \text{ and } P<0.0003, \text{respectively}) \), and HR increased to a greater extent in the young than in middle-aged and old groups. 

In response to upright tilt, low-frequency systolic and diastolic BP power increased in all groups \( (P<0.0003) \). The increase in diastolic power was greater in the young than in middle-aged and old groups (Table 2). While subjects were in the upright position, both low-frequency systolic \( (P<0.01) \) and diastolic \( (P<0.0001) \) BP power were lower in the old group than in the middle-aged and young (Figure 1). Plasma norepinephrine levels increased to the same extent in all groups (Table 2 and Figure 1).

High-frequency R-R interval power fell during tilt in all ages \( (P<0.02) \) but to a significantly smaller extent in the middle-aged and old subjects than in the young group \( (P=0.001) \). There was a similar decline in transfer magnitude with posture change at all ages \( (P<0.04) \).

Direct renin increased with posture change in the young and middle-aged groups \( (P<0.06) \) but not to a significant extent in the old \( (P<0.03 \text{ for old compared with middle-aged and young groups}) \). Plasma renin activity increased with posture change in all groups \( (P<0.006) \). Aldosterone increased in the middle-aged and old groups \( (P<0.0001) \) but not in the young. However, changes in aldosterone levels were not significantly different between groups.

**Effects of Gender**

**Baseline Characteristics**

As shown in Table 3, women had smaller body mass index, higher basal HR, and greater high-frequency R-R interval power than men. There were no differences in other baseline hemodynamics, spectral powers, or circulating vasoactive peptide levels.

**Response to Tilt**

As shown in Table 4, women had a significant decline in systolic BP during tilt \( (P=0.001) \), while men did not. However, HR and FVR increased by the same extent in women and men \( (P<0.0001 \text{ for each variable}) \). In the upright position, low-frequency systolic and diastolic BP powers and plasma norepinephrine levels increased less and achieved lower values in women than in men (Table 4 and Figure 2). There was a trend toward greater reduction in high-frequency R-R power in women than in men \( (P=0.10) \). Transfer magnitudes decreased \( (P=0.0002) \), and aldosterone, direct renin, and plasma renin activity increased to a similar extent in both genders during head-up tilt.

**Multivariate Analysis**

Multiple linear regression analyses examining the effects of age, genders, body mass index, and baseline BP's and R-Rs on changes in BP power during upright tilt revealed that gender alone was related to the change in systolic BP power \( (P=0.02) \), and both age \( (P=0.0068) \) and gender \( (P=0.02) \) were related to
the change in diastolic BP power during tilt. There was no age
and gender interaction, indicating that gender-related differences
in BP dynamics were similar across all age groups.

### Discussion

#### Principal Findings

The results of this study indicate that both healthy aging and
female gender are associated with reduced low-frequency beat-
to-beat BP oscillations during orthostatic stress. These vasomo-
tor oscillations, also called Mayer waves, are thought to repre-
sent the effects of baroreflex-mediated sympathetic outflow on
the vasculature. Their attenuation with age and female gender
appears to be due to different mechanisms. In elderly subjects,
supine resting plasma norepinephrine levels were elevated, and
the norepinephrine response to tilt was the same as that in the
young. In contrast, women had lower plasma norepinephrine
responses to tilt than men and a corresponding reduction in
sympathetically mediated low-frequency vasomotor oscillations.

Second, the results show a striking dissociation between
changes in beat-to-beat BP dynamics and changes in mean
levels of forearm vascular tone. Despite a blunted increase in
the amplitude of low-frequency beat-to-beat BP oscillations
during head-up tilt, both elderly and female subjects were
able to increase mean levels of FVR to the same extent as
their younger or male counterparts.

Third, we found that women had greater declines in systolic
BP during tilt than men. This was not explained by differences in
HR, cardiovagal baroreflex gain, or various neurohumoral
modulators of vascular tone and volume status, including plasma
renin, aldosterone, and endothelin. Given their blunted plasma
norepinephrine response, orthostatic hypotension in women may
result from reduced cardiac inotropy or reduced systemic rather
than regional (forearm) vasoreactivity.

Finally, this study confirmed our previous findings that
high-frequency R-R variability in the supine position, a
marker of the vagally mediated respiratory sinus arrhythmia,
is reduced as a function of age but elevated in women across
all ages. Thus, women appear to have a more favorable
autonomic profile of reduced sympathetic and enhanced
parasympathetic activity than men, but possibly at the ex-
pense of mild orthostatic hypotension.

#### Effects of Healthy Aging on BP Variability

Although Taylor et al reported supine, resting low-frequency
diastolic BP variability to be lower in healthy older versus
younger males, only 1 study to our knowledge examined the
effect of aging on beat-to-beat BP variability during orthostatic
stress. This study compared preadolescents (aged 10 to 15
years) to young adults (aged 20 to 40 years) and elderly subjects
(aged 70 to 90 years); however, the elderly were not screened
with exercise tests to exclude the possibility of occult cardiovas-
cular disease. Consistent with our results, there was an increase
in low-frequency (referred to as “mid-frequency” in their study)
systolic and diastolic BP power during upright posture in all age
groups, but a smaller increase in the elderly subjects.
Effects of Gender on BP Variability

Little is known about the effects of gender on BP dynamics. We previously found that healthy postmenopausal women taking estrogen replacement therapy had reduced low-frequency BP variability after head-up tilt or a meal, compared with untreated age-matched female controls. It is possible that estrogen reduces beat-to-beat BP variability by increasing baroreflex sensitivity. If estrogen was solely responsible for reduced BP variability, however, one would expect to see less of a gender-related effect on BP dynamics after menopause or differences in baroreflex sensitivity between premenopausal women and men. This was not found in the present study. There may be an intrinsic difference in BP regulation in women compared with men.

Differing Effects of Age and Gender

In contrast to the parallel age-related decline in both low-frequency BP power in the tilted position (a measure of sympathetic activity) and high-frequency R-R interval power in the supine position (a measure of parasympathetic activity), gender affects these measures in opposite directions, independent of age. The effect of aging might be explained by the known age-related reduction in sympathetic vasomotor responsiveness and reduced respiratory sinus arrhythmia, which would reduce both low-frequency BP oscillations and high-frequency R-R interval oscillations in a parallel fashion. In contrast, female gender is associated with reduced muscle sympathetic nerve activity and plasma norepinephrine concentrations at rest and, as we have shown, reduced plasma norepinephrine levels during orthostatic stress. Reductions in sympathetic activity produced by β-blockade are well known to enhance the respiratory sinus arrhythmia, possibly because sympathetic activity has a restraining influence on vagal modulation of HR. In women, this could explain why reduced low-frequency BP variability (a measure of sympathetic activity) is associated with enhanced high-frequency R-R interval variability (the respiratory sinus arrhythmia).

Strengths and Weaknesses

The present study is limited by the absence of direct measures of cardiac output, systemic vascular resistance, and blood volume and by its reliance on circulating plasma norepinephrine concentration, which is an indirect measure of sympathetic nervous system activity. Nevertheless, this study provides novel data showing that healthy women have less sympathetic influence on BP and greater parasympathetic influence on R-R interval than men, despite similar spontaneous baroreflex gain. Since high sympathetic activity and low parasympathetic activity are associated with cardiovascular disease morbidity and mortality, the favorable autonomic profile seen in women may be related to their delayed onset of cardiovascular disease and increased longevity compared with men.

Acknowledgments

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References

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