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Effect of aging on the cardiovascular regulatory systems in healthy women

Shahar Lavi,1,2 Ori Nevo,1,3 Israel Thaler,3 Rimma Rosenfeld,1 Lior Dayan,1 Nir Hirshoren,1 Lior Gepstein,2 and Giris Jacob1
1J. Recanati Autonomic Dysfunction Center, Medicine A, Departments of 2Cardiology and 3Obstetrics and Gynecology, Rambam Medical Center, Faculty of Medicine, Technion-Israel, Institute of Technology, Haifa Israel

Submitted 25 May 2006; accepted in final form 29 August 2006

Lavi S, Nevo O, Thaler I, Rosenfeld R, Dayan L, Hirshoren N, Gepstein L, Jacob G. Effect of aging on the cardiovascular regulatory systems in healthy women. Am J Physiol Regul Integr Comp Physiol 292: R788–R793, 2007. First published August 31, 2006; doi:10.1152/ajpregu.00352.2006.—Aging, independently from the hormonal status, is a major risk factor for cardiovascular morbidity in healthy women. Therefore, we studied the effect of healthy aging on the cardiovascular homeostatic mechanisms in premenopausal and postmenopausal women with similar estrogen levels. Twelve healthy postmenopausal women, confirmed by follicular-stimulating hormone (FSH) and luteal hormone (LH) levels, were compared with 14 normally menstruating women during the early follicular phase (young-EF), to avoid as much as possible the effects of estrogen. Systolic BP was 108 ± 1.5 vs. 123 ± 2.5 (P < 0.001), supine norepinephrine was 260 ± 30 vs. 216 ± 45 and upright 640 ± 100 vs. 395 ± 50 pg/ml (P = 0.05) in young-EF vs. postmenopausal, respectively. Plasma renin activity and aldosterone remained unchanged. Vagal cardiac tone indices decreased significantly with aging (young-EF vs. postmenopausal): high-frequency (HF) band, root mean square successive differences (rMSSD) and proportion of R-R intervals >50 ms (PNN50%) were 620 ± 140 vs. 270 ± 70 (P = 0.04), 53 ± 7 vs. 30 ± 3 (P = 0.02), and 23 ± 5 vs. 10 ± 3 (P = 0.04), respectively. LF to HF ratio was 0.85 ± 0.17 in young-EF and became 1.5 ± 0.22 in postmenopausal (P = 0.03). Both arms of the baroreflex, +BRS (29 ± 5 vs. 13.5 ± 2.5, P = 0.01) and −BRS (26 ± 4 vs. 15 ± 1.5, P = 0.02) decreased with aging. Cardiovascular α1-adrenergic receptor responsiveness significantly increased and β-decreased in postmenopausal compared with young EF (P < 0.001, both). The corrected QT intervals (QTc) were similar, whereas corrected JT intervals (JTC) and JTC to QTc ratio were prolonged in the postmenopausal group. We conclude that in young women, parasympathetic control is the main regulator of the cardiovascular system and in postmenopausal women, sympathetic tone dominates. The transition from parasympathetic to sympathetic control may contribute to the increased cardiovascular morbidity with aging.

autonomic nervous system; baroreflex; renin; QT interval

HEALTHY AGING AFFECTS THE cardiovascular circulation by alterations of the autonomic nervous system, adrenoreceptors responsiveness (3), baroreflex sensitivity (20), and other neurohumoral systems; for example, renin-angiotensin-aldosterone axis (25). Studies in healthy men showed that baroreflex buffering is reduced with age (40), and this decrease is related to an increase in basal muscle sympathetic nerve activity (MSNA) and reduction of the α1-adrenergic vascular responsiveness (10). Assessment of heart rate variability by spectral analysis in relation to sex showed that men and postmenopausal women have higher low-frequency R-R intervals (LFRRi), lower high-frequency R-R intervals (HFRRi), and an increased LF to HF ratio (29). However, the effects of aging on the cardiovascular homeostasis were mainly studied in healthy men (20, 21).

A few studies compared the cardiovascular homeostasis in postmenopausal and premenstrual women, without considering their menstrual phase. During the menstrual cycle, remarkable alterations in the homeostatic mechanisms of the cardiovascular system occur and may be confounded by hormonal status (17, 31). The failure of hormone replacement therapy to attenuate the cardiovascular morbidity that accompanies aging (37) suggests that aging is a risk factor for cardiovascular morbidity independent from hormonal status.

The purpose of the present study was to investigate the effect of healthy aging in women on the cardiovascular regulatory systems after excluding the transient effects of ovarian hormones. To do so, we compared young menstruating women during the early follicular phase (EF) to postmenopausal women.

METHODS

Subjects. Twenty-six healthy women (12 postmenopausal and 14 young) were included in the study. The postmenopausal women fulfilled the following criteria: age between 50 and 70 yr, no vaginal bleeding, and not treated by hormone replacement therapy. The healthy young subjects fulfilled the following criteria: age between 18 and 40 years, normal menstrual period without significant premenstrual symptoms, and not on an oral contraceptive. The young menstruating women were studied during the early follicular phase (young-EF) on the 2nd or 3rd day.

All subjects were physically active and underwent clinical evaluation that included review of medical history, physical examination, and ECG. Subjects were excluded if they took medications that affect the autonomic nervous system. No subjects had a history of alcohol, drug abuse, or a primary psychiatric disorder. Participants refrained from alcohol or caffeine-containing products 24 h before study sessions. All investigational procedures were performed in the J. Recanati Autonomic Dysfunction Center on subjects 4 h after ingesting the meal.
Thereafter, blood was drawn for the ovarian steroids E2 and progesterone; gonadotropines, follicular stimulating hormone (FSH) and luteal hormone (LH); catecholamines, epinephrine, and norepinephrine; plasma renin activity (PRA); and aldosterone. Subsequently, subjects rested supine for 20 min, and blood was sampled for catecholamines, PRA, and aldosterone. Afterward, blood sampling without tourniquet and for drug administration. Continuous three-lead ECG, pneumobelt and beat-to-beat radial arterial tonometric blood pressure (CBM 7000, Colin Medical Instruments, San Antonio, TX) were monitored and displayed on a computer screen and on a chart thermal array recorder (TA-6000, Gould, Valley View, OH). Data were digitized at 500 Hz by an analog-to-digital converter using the Winddaq pro+ software (WinDaq, ver. 2.27, DataQ Instruments, Akron, OH). Data were stored onto the hard disk of a personal computer for off-line analysis using locally developed software.

After the subjects rested supine for 30 min, 10 min of computer sampling were obtained for RRi and blood pressure variability (BPv). Thereafter, blood was drawn for the ovarian steroids E2 and progesterone; gonadotropines, follicular stimulating hormone (FSH) and luteal hormone (LH); catecholamines, epinephrine, and norepinephrine; plasma renin activity (PRA); and aldosterone. Then, subjects stood for 20 min, and blood was sampled for catecholamines, PRA, and aldosterone. Data were digitized at 500 Hz by an analog-to-digital converter using the Winddaq pro+ software (WinDaq, ver. 2.27, DataQ Instruments, Akron, OH). Data were stored onto the hard disk of a personal computer for off-line analysis using locally developed software.

The baroreflex sensitivity (BRS) slopes were used for the calculation of cardiac vagal tone indices, rMSSD, the square root of the mean squared differences of successive normal intervals and pNN50 (proportions of cycles in which the difference is >50 ms), which reflect mainly the cardiac vagal activity (23). Baroreflex sensitivity was calculated from the time domain data of RRi and beat-to-beat systolic BP (10-min recording), as previously described (35). The baroreflex sensitivity (BRS) slopes (+BRS and −BRS) (in milliseconds per millimeter of mercury) represent the corresponding increase and decrease in systolic BP and RRi, respectively. For analysis, the computer software selected all sequences of three or more successive heart beats in which there were concordant increases (+BRS) or decreases (−BRS) in systolic BP and RRi. The minimal change had to be 0.5 mmHg and 4 ms for R-R. A linear regression (r > 0.85) was applied to each of the sequences, and an average regression slope was calculated for the sequences detected during each recording period.

Plasma concentrations of norepinephrine and epinephrine were assayed by HPLC, in a method modified from Goldstein et al. (14). Individual QT and JT (J = ST – 80 ms) intervals were obtained from a randomized rest supine recording (DATAQ) of sequences of 1 min from lead II of a surface ECG using an electronic magnifier software to achieve the maximal precision. The QT interval was corrected according to the Bazett’s formula. A JTc was derived by subtracting the QRS duration from the QTc (6). In addition, we adjusted the JTc to the QTc by computing a ratio of JTc to QTc.

**Protocol.** Studies were conducted in a quiet, partially darkened room with an ambient temperature of ~24°C. A large antecubital intravenous heparin intravenous lock (18 gauge) was inserted to allow blood sampling without tourniquet and for drug administration. Continuous three-lead ECG, pneumobelt and beat-to-beat radial arterial tonometric blood pressure (CBM 7000, Colin Medical Instruments, San Antonio, TX) were monitored and displayed on a computer screen and on a chart thermal array recorder (TA-6000, Gould, Valley View, OH). Data were digitized at 500 Hz by an analog-to-digital converter using the Winddaq pro+ software (WinDaq, ver. 2.27, DataQ Instruments, Akron, OH). Data were stored onto the hard disk of a personal computer for off-line analysis using locally developed software.

After the subjects rested supine for 30 min, 10 min of computer sampling were obtained for RRi and blood pressure variability (BPv). Thereafter, blood was drawn for the ovarian steroids E2 and progesterone; gonadotropines, follicular stimulating hormone (FSH) and luteal hormone (LH); catecholamines, epinephrine, and norepinephrine; plasma renin activity (PRA); and aldosterone. Then, subjects stood for 20 min, and blood was sampled for catecholamines, PRA, and aldosterone. Subsequently, subjects rested supine for 30 min, and α1-adrenoceptor responsiveness was determined by recording beat-to-beat systolic blood pressure (BP) in response to graded intravenous boluses of phenylephrine, 25–250 μg. Then, β-adrenoceptor responsiveness was assessed by the heart rate changes in response to incremental boluses of isoproterenol, 0.125–1.5 μg. Phenylephrine (PHE) was determined as the dose of phenylephrine required to increase systolic BP by 20 mmHg and isoproterenol (ISO) as the dose of isoproterenol required to increase the heart rate by 20 beats per minute (bpm). We allowed 6–10 min of rest before each dose. Cuff BP was used for the calibration of the tonometric blood pressure before each administration of drug.

**Analysis.** Power spectral analyses of RRi and beat-to-beat systolic BP were calculated by the Welch periodogram method for power spectral density calculation (23). Band pass filter (BPF) was used for the calculation of cardiac parasympathetic activity, low-frequency (0.04 – 0.14 Hz) and high-frequency band pass filter (HFR) was used for the calculation of cardiac sympathetic activity (23). Baroreflex sensitivity was calculated from the time domain data of RRi and beat-to-beat systolic BP (10-min recording), as previously described (35). The baroreflex sensitivity (BRS) slopes (+BRS and −BRS) (in milliseconds per millimeter of mercury) represent the corresponding increase and decrease in systolic BP and RRi, respectively. For analysis, the computer software selected all sequences of three or more successive heart beats in which there were concordant increases (+BRS) or decreases (−BRS) in systolic BP and RRi. The minimal change had to be 0.5 mmHg and 4 ms for R-R. A linear regression (r > 0.85) was applied to each of the sequences, and an average regression slope was calculated for the sequences detected during each recording period.

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**Statistics.** Results are expressed as means ± SE. Nonpaired two-tailed t-test was used for comparison between measurements of both groups. Linear regression analysis was used for the correlation between the various parameters and for the determination of the PHE20 and ISO20. Data were analyzed with GraphPad Prism (ver. 4.03; GraphPad Software, San Diego, CA). The level selected for statistical significance was set at P < 0.05.

**RESULTS**

Subjects’ mean age, weight, height, body mass index, supine and upright BP, and heart rate are shown in Table 1. The postmenopausal women, compared with young women, had higher weight and systolic BP, without significant differences in diastolic BP and heart rate. Plasma levels of estradiol in the young group during the follicular phase were similar to those in the postmenopausal women (Table 2). Progesterone levels were higher in the young compared with the postmenopausal group. As expected, the postmenopausal women had higher plasma levels of the gonadotropines FSH and LH.

**Neurohumoral changes.** PRA, aldosterone, and plasma catecholamine concentrations are depicted in Table 2. Although, plasma catecholamine concentrations during rest supine were similar in both groups, after postural stimulation, norepinephrine levels increased more in the young group (P < 0.05, Table 2).

**Heart rate and blood pressure variability.** Frequency-domain and time-domain data for both heart rate and systolic BP are illustrated in Fig. 1. The total power of heart rate variability tended to decrease with age, 1,700 ± 250 ms² vs. 1,200 ± 150 ms² in young and postmenopausal, P = 0.13. The very low frequency (0–0.04 Hz) was similar in both groups, 590 ± 100 ms² for young and postmenopausal group, respectively. The absolute low frequency (LF RRi) remained unchanged with aging, 380 ± 80 ms² vs. 340 ± 100 ms², for young and postmenopausal groups, respectively (Fig. 1A). However, only the absolute HF RRi domain decreased significantly with aging, 620 ± 140 vs. 270 ± 80 ms² (P < 0.05), as shown in Fig. 1A. Further confirmation of these data came from the RRi time domain indices of cardiac parasympathetic activity, that is, rmSSD and pNN50% as shown in Fig. 1, B and C. As a result, LF to HF ratio was higher in postmenopausal women.

**Table 1. General characteristics, QT, and hemodynamics data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young-EF</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>28 ± 0.5</td>
<td>55 ± 1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>59.5 ± 2</td>
<td>73 ± 4</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.65 ± 0.02</td>
<td>1.64 ± 0.01</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21 ± 0.5</td>
<td>27 ± 1.4</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>108 ± 1.3</td>
<td>123 ± 2.5</td>
</tr>
<tr>
<td>Systolic BP (upright)</td>
<td>106 ± 1.3</td>
<td>122 ± 3.3</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>66 ± 2</td>
<td>72 ± 4</td>
</tr>
<tr>
<td>Diastolic BP (upright)</td>
<td>68 ± 1.5</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>Heart Rate: bpm</td>
<td>69 ± 2</td>
<td>66 ± 2</td>
</tr>
<tr>
<td>Heart Rate (upright)</td>
<td>80 ± 2</td>
<td>76 ± 2</td>
</tr>
<tr>
<td>QT, ms</td>
<td>401 ± 5</td>
<td>407 ± 8</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>426 ± 6</td>
<td>421 ± 5</td>
</tr>
<tr>
<td>JTc, ms</td>
<td>330 ± 6</td>
<td>346 ± 7</td>
</tr>
<tr>
<td>JTc/QTc</td>
<td>0.77 ± 0.005</td>
<td>0.82 ± 0.005</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. BP, blood pressure.
women compared with young-EF group: 1.5 ± 0.2 vs. 0.85 ± 0.15, respectively (P < 0.03). The total power of the frequency domain of systolic BP was higher in the postmenopausal women: 5.2 ± 0.75 vs. 9.8 ± 1.5 (P < 0.005). The LFBP band was significantly higher in the postmenopausal group, as shown in the Fig. 1A.

Baroreflex changes. Both arms of the baroreflex, (−BRS) and (+BRS), were significantly decreased in the postmenopausal women, as illustrated in Fig. 2. Further confirmation for the decrease in the +BRS was obtained from the slope of the changes in systolic BP against R-R changes after each dose of PHE (data not presented).

Adrenoreceptor responsiveness. PHE20 was higher in the young group: 175 ± 12 vs. 107 ± 15 μg (P < 0.001), as presented in Fig. 3A. Menopausal women required higher doses (almost twofold) of isoproterenol to increase their heart rate by 20 bpm. The ISO20 was 0.32 ± 0.03 and 0.6 ± 0.06 μg for the young and postmenopausal group, respectively (P < 0.001, Fig. 3B). Isoproterenol tended to cause more decrease in BP in postmenopausal women compared with young-EF. The dose required to decrease the systolic BP by 20 mmHg was 0.83 ± 0.15 and 1.12 ± 0.09 μg for postmenopausal and young-EF group, respectively (P = 0.10). (This data were detectable in nine postmenopausal and eight young-EF women.)

QTc intervals. As shown in Table 1, QT and QTc intervals were similar in the young and the postmenopausal groups. However, the pure repolarization intervals (JTC), tended to be prolonged in the postmenopausal group (P = 0.08). The ratio between the individual’s JTC to QTc was significantly higher in the postmenopausal group compared with the younger (P < 0.001).

**DISCUSSION**

The present study demonstrates that aging of healthy women is associated with the following cardiovascular autonomic alterations: 1) a decrease in the vagal tonic modulation of the heart rate in the setting of preserved sympathetic tone, and consequently predominance of the sympathetic control (significant increase in LF to HF ratio); 2) the buffering ability of the systemic baroreflex decreases by 50% in both sympathetic and vagal arm; 3) a decrease in cardiovascular β-adrenoreceptor responsiveness; 4) an increase in α1-adrenoreceptor responsiveness; 5) preservation of catecholamine levels during rest, but not during orthostatic stress; and finally 6) prolongation of JTC intervals.

Hormonal changes along the menstrual cycle are associated with complex fluctuations in the cardiovascular regulatory mechanisms. These changes correlate with plasma estrogen levels. (17, 31) Furthermore, estrogen replacement therapy affects the autonomic control of the cardiovascular system in postmenopausal women (36). Our study is novel by comparing the cardiovascular regulatory systems in two groups of women with low estrogen level and different ages. This approach enabled us to study the effects of aging without the confounding hormone effects, and indeed, similar plasma levels of estrogen were found in both groups. Our study demonstrates

<table>
<thead>
<tr>
<th>Plasma Hormone</th>
<th>Young-EF</th>
<th>Postmenopausal</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH, U/l</td>
<td>6.65±0.5</td>
<td>53±5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH, U/l</td>
<td>4.05±0.45</td>
<td>27±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estradiol, pmo/l</td>
<td>150±25</td>
<td>135±22</td>
<td>0.60</td>
</tr>
<tr>
<td>Progesterone, nmol/l</td>
<td>1.68±0.2</td>
<td>0.76±0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>PRA (supine), ng·ml⁻¹·h⁻¹</td>
<td>0.65±0.12</td>
<td>0.9±0.15</td>
<td>0.21</td>
</tr>
<tr>
<td>PRA (upright)</td>
<td>1.2±0.2</td>
<td>1.7±0.3</td>
<td>0.27</td>
</tr>
<tr>
<td>Aldosterone (supine)</td>
<td>44±6</td>
<td>60±10</td>
<td>0.19</td>
</tr>
<tr>
<td>Aldosterone (upright)</td>
<td>65±7</td>
<td>93±15</td>
<td>0.10</td>
</tr>
<tr>
<td>Norepinephrine (supine)</td>
<td>260±30</td>
<td>216±45</td>
<td>0.45</td>
</tr>
<tr>
<td>Norepinephrine (upright)</td>
<td>640±100</td>
<td>395±50</td>
<td>0.05</td>
</tr>
<tr>
<td>Epinephrine (supine)</td>
<td>24±8</td>
<td>14±4</td>
<td>0.30</td>
</tr>
<tr>
<td>Epinephrine (upright)</td>
<td>60±14</td>
<td>42±10</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. FSH, follicular stimulating hormone; LH, luteal hormone; PRA for plasma renin activity.

Fig. 1. Means ± SE of the time and frequency domain analysis, absolute frequency domain of both low-frequency (LF) and high-frequency (HF) bands (A), vagal cardiac indices root mean square differences (rMSSD) (B) and proportions of R-R intervals >50 ms (PNN50%) (C), and the sympathetic vascular domain, LFHFB (D), of both young-menstrual early follicular phase (EF) and postmenopausal women.
for the first time an integrated insight into the changes that occur with aging in the cardiovascular regulatory systems in females.

Central cardiovascular autonomic control. From a careful review of studies on sex differences (mainly middle-aged subjects), we can deduce that premenopausal healthy women may have parasympathetic predominance in the regulation of heart rate compared with age-matched men and postmenopausal women (8, 11, 24). However, other investigations show that the HFRRi is higher in women compared with aged men (2), or that HFRRi and LFRRi are similar in females and males without changing with age (4, 18, 47). These conflicting data result from the lack of consistent criteria for inclusion and age selection, as well as from not considering menstrual cycle timing. The present study extends the previous observations. We found that aging in healthy women affects mainly the cardiac vagal tone (HFRRi, rMSSD, and PNN50%). The absolute power LFRRi remains unchanged, but low frequency normalized (LFn) increases despite the partial loss of its vagal component. As a result, the LF to HF ratio is increased in the postmenopausal women. Thus the autonomic nervous system that controls the heart rate shifts from vagotonic dominance in the young women into sympathotonic dominance with aging. As recently emerged, menstruating healthy women have higher sympathetic control, assessed by both MSNA and LF to HF ratio, on the circulation during the luteal phase (high hormonal state) compared with the early follicular phase (17, 31). Therefore, future studies that consider aging in healthy women should select the proper menstrual phase. We should mention that estrogenic treatment in menopausal women causes a decrease rather than an increase in sympathetic circulatory control (7). These contrasting effects of exogenous estrogen on the circulation remain to be explored.

Previous studies show that MSNA is increased with healthy aging in both sexes (16, 30, 39). The MSNA does not correlate with the RRi spectra, as it does with the LFRRi (32). The MSNA and the LFRRi domain represent mainly the sympathetic modulation of the vasculature. According to our finding that older women have higher LFRRi, this may contribute, at least in part (vide infra), to the higher systolic BP in this older group. It is noteworthy to mention that similar to these findings, a reduced tonic cardiac vagal tone and increased sympathetic support of BP has been recently described in healthy aging men (21).

The postmenopausal women reported a lower weight in younger age and were more obese than the younger group at the time of the study, a difference that may reflect normal aging. Obesity and fat distribution may contribute to the increase in systemic sympathetic tone but not to the decrease in the vagal cardiac tone (1, 5). Although our findings indicate a shift to predominance of sympathetic activity with aging in women, catecholamine levels were not increased with aging. This may be explained by the fact that in contrast to MSNA, plasma catecholamine level is not a good surrogate marker for systemic sympathetic activity.

Baroreflex control. As established previously in normotensive healthy men (20), aging of women is also associated with decreased baroreflex buffering ability. Both arms of the systemic baroreflex are significantly blunted. This may contribute to an increase in BP, vascular sympathetic activity (LFRRi), and altered adrenoreceptors responsiveness in postmenopausal. Experimental and clinical studies have convincingly demonstrated that impaired BRS and reduced HR variability increase the risk of cardiac mortality (38, 44). Chronic estrogen treatment augments the cardiovagal arm of the baroreflex and the HR variability in postmenopausal women (18, 28). Acute increase in estrogen levels (~5- to 10-fold) along the luteal phase of the menstrual cycle is associated with similar changes in the baroreflex sensitivity (17, 43).

Adrenoreceptor responsiveness. Human isolated blood vessels obtained during surgery have a decreased contraction to PHE (selective α1-adrenergic receptor agonist) but not to α2-adrenergic receptor agonists, with aging (34). Similar results are demonstrated in healthy men with local infusion of PHE into the brachial artery (10). In contrast, systemic infusion of PHE in older healthy women (our data) and men (21) elicits augmented
cardiovascular sensitivity (higher BP response). Ganglionic blockade with trimethaphan (22) in healthy men reverses this increased responsiveness (20). Thus the increased \( \alpha_1 \)-adrenoceptor responsiveness in healthy aging women, at least in part, depends on decreased buffering ability of the baroreflex. Other factors could be involved, such as aortic and vessel stiffness (which is also applied on the baroreflex bodies), contractility, and the assigned kinetic energy to the stroke volume (41, 42).

Paucity of data exists on adrenoreceptor function in women. Previously, we described that the chronotropic response to isoproterenol is attenuated during the luteal phase (higher hormonal state) in menstruating women (17). It is known that cardiovascular \( \beta \)-adrenoreceptors sensitivity is decreased with aging (3). Boluses of isoproterenol elicit a blunted heart rate response in our aged women. This chronotropic effect of \( \beta_1 \)-adrenoreceptors is also mediated by baroreflex activation from the simultaneous vasodilatation induced by isoproterenol (\( \beta_2 \)-adrenoreceptors-mediated) (26, 46). Therefore, a blunted baroreflex response in our older subjects could easily contribute to the attenuated chronotropic and increased depressor effect of isoproterenol. \( \beta \)-Adrenoreceptor sensitivity could also account for these differences (19).

**Neurohumoral effects.** Our results indicate that female aging does not affect the rest supine catecholamines, PRA, and aldosterone. But during orthostatic stress, aged women have a blunted increase in plasma norepinephrine concentration. This latter finding is further supported by several studies. However, Geelen et al. (12) reported that old men had higher plasma catecholamine during standing compared with young men, and old and young women were comparable in this study (255 vs. 296 pg/ml, 453 vs. 497 pg/ml supine and upright, respectively). Similar findings were reported by Ng et al. (33) and Goldstein et al. (15) in normotensive and hypertensive women. Thus, although plasma catecholamine concentrations increase with aging in healthy men, it seems that this phenomenon is not present in healthy aging women (2, 12, 21). Both, MSNA and sympathetic tone (vascular and cardiac) are blunted during orthostatic stress in aging women compared with men (2). Hence, we can speculate that aging women have less sympathetic reserve (upon standing), proclaiming a priori that the MSNA is a qualitative rather than quantitative measure of the sympathetic nervous system.

A few studies examined PRA and aldosterone responses to aging and sex. These reports reveal either similar or higher supine and posture-stimulated PRA in men compared with women (2, 12). Hormone replacement therapy had conflicting results in this regard (25), although during the menstrual luteal phase, there is significant increase in these fluid regulatory hormones related to the increase in progesterone plasma levels during this menstrual phase (17). No age effect was found in this system, similar to our findings. It should be mentioned that our participants were not limited to a controlled sodium diet, and we compared the postmenopausal group to the EF phase only.

**QT intervals.** There is sufficient evidence that the sympathetic nervous system is involved in myocardial repolarization, despite conflicting results regarding the QT intervals. Withdrawal of the sympathetic control on the heart, whether in a disease state or induced by drugs, is associated with QT prolongation (9). The sympathetic tone, LF to HF ratio, is increased in our aging subjects. This ratio represents a qualitative measure on the sinus node control but not on the ventricular conduction attitude. Fluorodopa uptake by the heart was found to be reduced in older subjects compared with young (27). This may suggest that the innervation’s density of the heart is significantly reduced with aging, which may explain, at least partly, the increased repolarization time with aging. Noteworthy to mention, the JTc intervals per se is an independent predictor of cardiac events (6).

**Limitations and applications.** There is no ideal method to assess the effects of aging on the homeostatic mechanisms in women, because of the hormonal fluctuations that occur along the menstrual cycle. We may be able to learn more about the effects of aging on the studied systems from comparing postmenopausal to young women with premature ovarian failure. Our study is the first to face this dilemma by comparing postmenopausal women to menstruating women in the early follicular stage.

The parameters used for the assessment of the cardiovagal tone do not depend purely on the vagal tone and the limitations of the RRi and BPv for this purpose are discussed extensively elsewhere (13). Our postmenopausal subjects are more obese than the younger group, which may contribute to the higher sympathetic activity. However, as normal aging is associated with increased weight, we decided to accept the difference in body mass index between the groups.

Applying our proposed method for selection criteria for aging studies may be useful for future investigation involving invasive studies.

In conclusion, in healthy young women, the cardiovascular system is regulated by high vagal cardiac tone and lower sympathetic vascular control. With aging in healthy women, sympathetic control predominates. This is associated with significantly reduced systemic baroreflex buffering ability. These aging processes may underlie, at least partly, the altered cardiovascular adrenoreceptor responsiveness, and the prolongation of the myocardial repolarization period. These cardiovascular changes are similar to those described in the aging men. Accordingly, aging of the homeostatic mechanisms involved in the cardiovascular regulation are independent from sex and sex hormones.

**GRANTS**

This study was supported by a grant from Ya’el Foundation.

**REFERENCES**


