The Effects of Acute Beta-Adrenergic Blockade on Aortic Wave Reflection in Postmenopausal Women

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BACKGROUND
Acute beta-adrenergic blockade increases aortic-wave reflection in young women. However, it is not known whether this effect extends to postmenopausal women. We therefore examined the effect of systemic beta-adrenergic blockade on aortic wave reflection in 14 postmenopausal women with a mean age of 58 ± 2 years.

METHODS
Aortic pressure waveforms were synthesized noninvasively from high-fidelity radial pressure waveforms obtained through applanation tonometry before and during systemic beta-blockade with propranolol given in a bolus dose of 0.25 mg/kg, followed by a continuous infusion at 0.004 mg/kg/min. To further examine the effects of acute beta-blockade on aortic-wave reflection in postmenopausal women, we compared the changes in hemodynamics and indices of aortic-wave reflection with published data from a previous study with a protocol identical to that in the present study but which involved young women.

RESULTS
Acute beta-blockade increased the aortic augmentation index (AIx) in postmenopausal women (32 ± 2% vs. 35 ± 2%, P < 0.01). However, AIx adjusted for a heart rate of 75 bpm (AIx75) was unchanged (25 ± 2% vs. 24 ± 2%, P > 0.05). The changes in AIx, AIx75, and the amplitude of reflected waves (augmented aortic pressure) during beta-blockade were all substantially smaller in postmenopausal women than in their younger counterparts (P < 0.05).

CONCLUSIONS
As compared with those in our previously published study involving young women, indices of aortic-wave reflection were significantly less affected by acute systemic beta-adrenergic blockade in the postmenopausal women in the present study. Taken together, our data suggest that the negative effects (i.e. increased aortic wave reflection) of non-selective beta-adrenergic blockade are less pronounced in postmenopausal than in young women.

Keywords: aortic wave reflection; beta-adrenergic receptors; blood pressure; hypertension; menopause.

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Beta-adrenergic–blocking agents have long been prescribed as antihypertensive agents for many high-risk patients with cardiovascular diseases.1 However, beta-blockers, despite producing similar reductions in peripheral blood pressure (BP), may be less effective than other antihypertensive drugs in reducing stroke and cardiovascular mortality.2,3 The less-than-desirable cardiovascular protection provided by beta-blockers may be related to their lack of effectiveness in reducing central aortic BP and wave reflection. In this context, greater central aortic pressures and wave reflection have been observed with traditional nonvasodilating beta-blockers (i.e. atenolol) than with other antihypertensive drugs.4–10 Although the mechanisms responsible for these observations are unclear, they may be related to: (i) prolonged systolic ejection time (as a result of reductions in heart rate (HR)) and a delayed peak of the outgoing aortic pressure wave that allows pressure-wave reflections to augment the central aortic systolic pressure wave10; and/or (ii) a reduction in beta-adrenergically mediated peripheral vasodilation or an unmasking of alpha-adrenergically mediated vasoconstriction.11

The aortic augmentation index (AIx) provides information related to the contribution of wave reflection to the ascending aortic pressure waveform, and is defined as the proportion of central pulse pressure contributed by the late systolic peak, which is in turn attributed to the reflected pulse wave. Importantly, AIx is associated with cardiovascular risk as well as with all-cause and cardiovascular mortality.12,13 We previously demonstrated that acute systemic beta-blockade increased aortic wave reflection (i.e. AIx) in young normotensive adults, and that this effect was more pronounced in women than in men.14 Additionally, the mechanisms responsible for the increased wave reflection appeared to differ in...
males and females in that the beta-blocker–induced change in aortic wave reflection was associated with changes in HR in men whereas it was related to changes in total peripheral resistance (TPR) in women, in accord with a higher level of tonic beta-adrenergic vasodilator tone in younger women. Interestingly, beta-adrenergic receptor sensitivity in the peripheral vasculature appears to be lower in postmenopausal women than in their younger counterparts. With this information as a background, we conducted the present study to examine the effects of acute systemic beta-blockade on aortic wave reflection in older postmenopausal women. We hypothesized that postmenopausal women would have an attenuated change in aortic wave reflection during acute beta-blockade as compared with their younger counterparts.

METHODS

Subjects

A total of 14 postmenopausal women were enrolled in the study. Subjects provided written informed consent for their participation and underwent a standard screening. The subjects were nonsmokers without a history of cardiovascular or other chronic diseases, and were considered to be either sedentary or recreationally active (without structured exercise training) as assessed with a self-reported health-history questionnaire. One postmenopausal woman had a history of smoking, but had ceased smoking 4 years before the study. Postmenopausal women taking antihypertensive medications or hormone replacement therapy were excluded from the study. Postmenopause was defined as a period of at least 1 year since last menstruation. This was determined from the health-history questionnaire and verified by a review of the subject’s medical records. All parts of the study were performed in the laboratory of the Clinical Research Unit of the Mayo Clinic in Rochester, MN, where the ambient temperature was controlled at 22 °C to 24 °C. Procedures in the study were performed after an overnight fast, and the subjects refrained from exercise, alcohol, and caffeine for at least 24 hours before each procedure. All of the study protocols were approved by the Mayo Institutional Review Board and were conducted in accord with the Declaration of Helsinki.

Measurements

For the recording of brachial artery BP and measurement of HR, a 20-gauge, 5-cm catheter was placed in the brachial artery of the subject’s left arm under sterile conditions after the induction of local anesthesia (2% lidocaine). The catheter was connected to a pressure transducer that was positioned at the level of the heart, and arterial pressures were continuously recorded. A three-lead electrocardiogram (ECG) was used for continuous recording of the HR. Beat-to-beat stroke volume was measured from the brachial artery using Modelflow analysis (Finapres, Amsterdam, The Netherlands), which computes an aortic waveform on the basis of nonlinear pressure–volume, pressure–compliance, and pressure–characteristic impedance equations, incorporating age, sex, height, and body mass into the computations. Cardiac output (CO) was calculated as stroke volume (SV) × HR, and TPR was calculated as mean arterial pressure (MAP) ÷ CO.

Pulse wave analysis

After 15 minutes of rest in the supine position, each subject’s arterial-wave reflection characteristics were assessed noninvasively with the SphygmoCor system (AtCor Medical, Sydney, Australia) as described previously. Briefly, pressure waveforms in the radial artery were recorded with high-fidelity applanation tonometry of the radial pulse in the right wrist, using a “pencil type” micromanometer (Millar Instruments, Houston, TX). The BP and waveforms in the radial artery were calibrated from the catheter-recorded systolic and diastolic brachial artery BPs. A validated, generalized transfer function was used to generate the corresponding aortic-pressure waveform. The generalized transfer function has been validated with both intra-arterially and noninvasively obtained radial pressure waves. Pulse-wave analysis of the aortic-pressure waveform provided the following key variables of interest: aortic pressures (systolic, diastolic, and aortic pulse pressure); aortic augmentation index (AIx); AIx adjusted for an HR of 75 bpm (AIx,75); travel time of the forward-traveling pressure wave from the ascending aorta to the major reflection site of the wave and back (Δt); and wasted left-ventricular pressure energy (Ew), which is the component of extra myocardial oxygen consumption required for ventricular contraction to overcome the effect of early systolic wave reflection. The value of Ew can be estimated as [(π/4) × (augmented pressure × Δtr)] × 1.333, where 1.333 is the conversion factor for mm Hg/s to dynes·s/cm², and Δtr is the systolic duration of the reflected wave. The augmented pressure (AG) is the amplitude of the reflected wave, and is defined as the difference in amplitude between the first (forward wave) and second systolic shoulders of the aortic systolic BP wave. Only high-quality recordings, defined as those with an in-device quality index of > 80% (derived from an algorithm that includes the average variation in pulse amplitude, diastolic variation, and maximum rate of increase in the peripheral pressure waveform) were accepted for analysis. In general, two or three measurements were made to obtain two measurements with an acceptable quality index. The two highest quality recordings were averaged and used for analyses.

Nonselective systemic beta-blockade was achieved with intravenous propranolol. A 0.25 mg/kg bolus of propranolol, given over a period of 5 minutes, was followed by a continuous infusion of propranolol at 0.004 mg/kg/min to maintain beta-blockade. This dose of propranolol has been previously proven to cause total beta-blockade in adult humans. All hemodynamic and applanation tonometric measurements were repeated ~15–20 minutes after the start of the propranolol infusion. The timing of the measurements made after beta-blocker administration was chosen to mimic the protocol used in our previous study.

Statistical analyses

Group data are expressed as means ± SEM. To fully explore the effects of acute beta-blockade on aortic wave reflection
in postmenopausal women, we made comparisons of these women’s data recorded in the present study with previously data recorded in an identical protocol involving young women \((n = 15)\). Analysis of variance (ANOVA) was used to investigate baseline differences in the two groups. Changes in the continuous dependent variables were analyzed with repeated measures ANOVA. When a significant group-by-time interaction was observed, within-group comparisons of values at time points before and during beta-blockade, and between-group comparisons of postmenopausal vs. young women, were made with Tukey’s post hoc test. To assess the relationship between changes in HR, TPR, and AIx during beta-blockade, we used linear regression analysis and calculated Pearson’s correlation coefficients. All statistical analyses were done with SigmaPlot software version 12 (SPSS, Chicago, IL). An alpha-level of \(P < 0.05\) was required for statistical significance.

## RESULTS

All 14 of the postmenopausal women in the study completed the study protocol. The subjects had a mean (±SEM) age of 58 ± 2 years, were 166 ± 2 cm in height, and weighed 67 ± 2 kg (body mass index (BMI), 24.4 ± 0.6 kg/m). Hemodynamic and aortic wave reflection variables before and during systemic beta-blockade are presented in Table 1. During systemic beta-blockade, the HR and peripheral systolic and pulse pressures of the postmenopausal women in the study were reduced in comparison with those recorded before beta-blockade, whereas TPR was increased in the postmenopausal women \((P < 0.01)\). Aortic pressures were unchanged by beta-blockade \((P > 0.05)\). Beta-blockade caused a small yet significant increase in Alx \((32 ± 2\% \text{ vs. } 35 ± 2\%, P < 0.01\) (Figure 1A)), but the change in Alx was abolished after correction for HR \((\text{Alx}_{75} = 25 ± 2\% \text{ vs. } 24 ± 2\%, P = 0.27 \text{ (Figure 1B))} \). Moreover, AG and Ew remained unchanged during beta-blockade \((P > 0.05\) for both (Table 1)). There was a trend toward a modest inverse relationship between the change \((\Delta)\) in Alx and the change in HR \((\DeltaHR)\) \((r = -0.48, P = 0.08 \text{ (Figure 2)})\). Conversely, \(\Delta\text{Alx}\) was not related to \(\Delta\text{TPR}\) \((r = 0.17, P = 0.56)\).

To better understand the effect of acute beta-blockade on aortic wave reflection in postmenopausal women, we compared the results of the present study with those of our previous study of young women. As expected, the 15 women in our previous study were substantially younger \((28 ± 2\) years of age vs. \(58 ± 2\) years of age, \(P < 0.001)\) than the postmenopausal women in the present study. The young women also weighed slightly less than those in the present study \((62 ± 1\) kg vs. \(67 ± 2\) kg, \(P < 0.05)\). However, the young women were of similar height \((164 ± 1\) cm) and body mass index \((\text{BMI}, 23.1 ± 0.4\text{ kg/m2 vs. } 24.4 ± 0.6\text{ kg/m})\) to the postmenopausal women in the present study \((P > 0.05\) for both height and BMI). The group means for hemodynamic and wave-reflection variables in the young women are presented in Table 1, to make comparisons between the two study

<table>
<thead>
<tr>
<th>Hemodynamic/wave reflection variables</th>
<th>Postmenopausal women</th>
<th>Young women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre BB</td>
<td>During BB</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>59±2</td>
<td>51±2*</td>
</tr>
<tr>
<td>PSBP (mm Hg)</td>
<td>137±5†</td>
<td>132±4†</td>
</tr>
<tr>
<td>PDBP (mm Hg)</td>
<td>69±2</td>
<td>68±2</td>
</tr>
<tr>
<td>PPP (mm Hg)</td>
<td>69±4†</td>
<td>65±4†</td>
</tr>
<tr>
<td>ASBP (mm Hg)</td>
<td>129±5†</td>
<td>126±5†</td>
</tr>
<tr>
<td>ADBP (mm Hg)</td>
<td>69±2</td>
<td>68±2</td>
</tr>
<tr>
<td>APP (mm Hg)</td>
<td>60±4†</td>
<td>57±4†</td>
</tr>
<tr>
<td>PPA</td>
<td>1.18±0.03†</td>
<td>1.15±0.03†</td>
</tr>
<tr>
<td>AG (mm Hg)</td>
<td>20±2†</td>
<td>21±2†</td>
</tr>
<tr>
<td>Δt (msec)</td>
<td>146±4</td>
<td>148±5</td>
</tr>
<tr>
<td>E (dyne · cm² · s)</td>
<td>4313±538†</td>
<td>4277±537†</td>
</tr>
<tr>
<td>Ejection duration (msec)</td>
<td>351±4</td>
<td>345±6</td>
</tr>
<tr>
<td>Ejection duration (%)</td>
<td>35±1</td>
<td>29±1*</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>66±2†</td>
<td>68±3</td>
</tr>
<tr>
<td>TPR (mm Hg · L/min)</td>
<td>25.1±1.4†</td>
<td>29.0±1.9†</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

\*P < 0.05 vs. before beta-adrenergic blockade; † P < 0.05 vs. young women at same time point.

Abbreviations: ADBP, aortic diastolic blood pressure; AG, augmented pressure; APP, aortic pulse pressure; ASBP, aortic systolic blood pressure; BB, beta blockade; Δt, round trip travel time of the forward traveling wave from the ascending aorta to the major reflection site and back; HR, heart rate; E, wasted left ventricular energy; PDBP, peripheral diastolic blood pressure; PPA, pulse pressure amplification; PPP, peripheral pulse pressure; Pre-BB, before beta-adrenergic blockade; PSBP, peripheral systolic blood pressure; TPR, total peripheral resistance.

Data from young women are from previously published work.12
populations more straightforward. At baseline, the postmenopausal women had higher brachial and aortic systolic and pulse pressures than the young women \((P < 0.01)\). \(A_{I}, A_{I75}, AG,\) and \(E_{w}\) were also greater in the postmenopausal women before the administration of propranolol \((P < 0.01)\). Stroke volume was smaller in the postmenopausal women at baseline than in their younger counterparts, but did not significantly change in either group during beta-blockade.

A significant group-by-time interaction \((P < 0.05)\) was found for \(A_{I}, A_{I75}, AG,\) and \(E_{w}\). Figure 3 illustrates the change \((\Delta)\) in each of these variables during beta-blockade in postmenopausal and young women. The changes \((\Delta)\) in \(A_{I} (2.7 \pm 0.9\% \text{ vs. } 7.5 \pm 1.1\%, P < 0.01),\) \(A_{I75}\) \((-1.1 \pm 1.0\% \text{ vs. } 4.6 \pm 1.1\%, P < 0.01),\) \(AG (0.5 \pm 0.9\text{ mm Hg vs. } 2.8 \pm 0.5\text{ mm Hg, } P < 0.05),\) and \(E_{w} (-36 \pm 241 \text{ vs. } 544 \pm 116, P < 0.05)\) were all substantially smaller in the postmenopausal women than in their younger counterparts (Figure 3A–D). It should also be noted that in contrast to the relationships reported above for postmenopausal women, \(\Delta A_{I}\) was not associated with \(\Delta HR (r = -0.19, P = 0.50)\) but was positively related to \(\Delta TPR (r = 0.50, P < 0.05)\) in the younger women.

**DISCUSSION**

The present study is the first to examine the acute effects of systemic beta-adrenergic blockade on aortic wave reflection in postmenopausal women. The primary novel findings of the study are that: (i) \(A_{I}\) is increased during acute systemic beta-blockade in postmenopausal women; and (ii) the increase in \(A_{I}\) appears to be primarily mediated by the beta-blocker–induced reduction in HR. These findings are supported by the abolition of the increase in \(A_{I}\) after adjustment was made for HR (Figure 1B) and by a trend toward an inverse relationship between the change in \(A_{I}\) and HR during systemic beta-blockade (Figure 2).

When compared with those in our previous study involving an identical protocol in young women, the effects of acute beta-adrenergic blockade on aortic wave reflection were substantially attenuated in the postmenopausal women.
Beta-blockade in Postmenopausal Women

In the present study. In this context, the increase in AIx during beta-blockade was nearly 3-fold greater in the young women. Moreover, the amplitude of the reflected wave (AG) and the resultant wasted LV pressure energy (Ew) were significantly increased in young women during acute beta-blockade, whereas these indices of wave reflection were unchanged in the postmenopausal women in the present study. Because of the strong inverse relationship between AIx and HR, we also assessed changes in AIx adjusted for HR (i.e. AIx75) during beta-blockade. Interestingly, there was no change in AIx75 during beta-blockade in the postmenopausal women, whereas AIx75 was significantly increased in the young women (despite similar reductions in HR). Additionally, there was a trend (P = 0.08) toward the change in AIx being inversely related to the change in HR during beta-blockade in the postmenopausal women but not in the young women. Taken together these findings suggest that the small yet significant increase in AIx during systemic beta-blockade in postmenopausal women is mediated by a reduced HR, whereas additional factors apparently contribute to an enhanced AIx in young women.

The exact mechanisms underlying the attenuated aortic wave reflection responses to acute beta-blockade in postmenopausal women are unclear, but several possible explanations exist for them. First, decreases in HR can prolong the systolic ejection time and increase the possibility that pressure-wave reflections will augment the outgoing pressure wave during systole. In the current study, acute beta-blockade caused reductions in HR and in the relative duration of systolic ejection in postmenopausal women that were similar to those in the young women in our earlier study (Table 1). The discrepancies in aortic wave reflection in the two groups during beta-blockade are therefore not likely to be explained by differences in the timing of systolic ejection.

Figure 3 Changes (Δ) from baseline (before beta-blockade) in (A) aortic augmentation index (AIx), (B) aortic augmentation index adjusted for a heart rate of 75 bpm (AIx75), (C) augmented pressure (AG), and (D) wasted LV pressure energy (Ew) during beta-blockade in postmenopausal women (open bars) and young women (black bars). Data are mean ± SEM. *P < 0.05 vs. young women. †P < 0.05 vs. baseline (before beta-blockade). Data for young women are from a previously reported study.4
ejection. However, HR is also inversely related to central aortic pulse pressure, a variable used as the denominator in the calculation of $AI_x$. Therefore, HR-induced changes in aortic pulse pressure could potentially influence $AI_x$. Yet beta-blockade did not change aortic pulse pressures in either the postmenopausal women or the young women (Table 1). Second, the characteristics of the reflected aortic pressure wave depend on a complex set of determinants, including the speed at which the wave travels. In the present study, the travel time of the forward-traveling pressure wave from the ascending aorta to the major reflection site and back ($\Delta t_p$) was not changed during beta-blockade. Therefore, differences in reflection of the aortic pulse-pressure wave in the postmenopausal and young women in our two studies were unlikely to have come from differences in the velocity of the pressure wave. Third, it is possible that alterations in beta-adrenergically mediated vasodilation might also play a role in the age-related attenuation of aortic wave reflection during systemic beta-blockade, specifically in women. Evidence suggests that beta-adrenergic receptors are either more sensitive or are upregulated in the peripheral vasculature of young women as compared with young men. Moreover, the vasoconstrictor response to exogenous norepinephrine in the forearm is enhanced after beta-blockade in young women but not in postmenopausal women. Thus, postmenopausal women may have less peripheral vasoconstriction in response to nonselective beta-blockade than young women, which in turn might diminish a proximal shift in arterial reflection sites and the consequent increase in aortic wave reflection. Indeed, the beta-blockade–induced change in $AI_x$ was not related to changes in TPR in postmenopausal women, whereas it was in young women. Lastly, and in accord with previous reports, indices of wave reflection were substantially greater in the postmenopausal women in the present study than in their younger counterparts in our earlier study. Therefore, the attenuated responses in $AI_x$, $AI_x75$, and the amplitude of aortic wave reflection observed in the postmenopausal women might have been related to an upper limit of the effects of acute beta-blockade on aortic wave reflection in individuals with elevated baseline values of these variables. Along these lines, a previous large population study (the Anglo–Cardiff Collaborative Trial) demonstrated that age-related increases in AIx tend to plateau after the age of 50 years in women. Therefore, the findings of the present study cannot be extrapolated to other beta-blocking drugs. However, continuous treatment with newer vasodilating beta-blockers (i.e. nebivolol and carvedilol) can have favorable effects on peripheral vascular function and aortic pressure waves and stiffness.

In accord with previously reported findings, the postmenopausal women in the present study had higher peripheral and central BPs than those observed in the young women in our previous study. It could be argued that the attenuated central hemodynamic responses to acute beta-blockade in the postmenopausal women might be related to changes in beta-adrenergically mediated vascular function as a result of elevated BP. Along these lines, it has been suggested that beta-adrenergic receptor responsiveness is reduced in patients with borderline or mild hypertension. However, data from studies with experimental animals suggest that beta-adrenergic effects on the heart and peripheral vasculature are neither enhanced nor impaired during the development of hypertension. Moreover, our previous data as well as those of others clearly demonstrate that acute beta-blockade enhances aortic wave reflection in human groups with significantly different BPs.

**Perspectives**

Although beta-blockers are effective in reducing brachial BP in various patient populations, they are often associated with significantly higher mortality than are other antihypertensive agents. One common theory for this discrepancy is that traditional nonvasodilating beta-blockers (i.e. atenolol) fail to reduce, and in some cases increase, central aortic pressures and wave reflection. From a clinical standpoint, this is particularly relevant, because an increased $AI_x$ is a strong independent risk marker for premature coronary artery disease and all-cause and cardiovascular mortality. In the present study, systemic beta-blockade caused a small yet significant increase in $AI_x$ of approximately 3 ± 1%. When considered with the data from our previously published study with young women, the present findings might suggest that the negative effects (i.e. increased aortic wave reflection) of nonselective beta-adrenergic blockade are less pronounced in postmenopausal women than in their younger counterparts). This is consistent with the idea that there is a tonic level of beta-adrenergic vasodilator tone in young women that is lost with aging. In turn, the loss of beta-adrenergic tone in postmenopausal women might explain the plateauing of $AI_x$ at about the age of 50 and the minimal effects of beta-blockade on aortic wave reflection observed in the present study. On the basis of the slight increase in $AI_x$ and the lack of change in other indices of aortic wave reflection and pressures observed in the postmenopausal women in the present study, our data support the idea that nonselective beta-blockers may offer less than...
desirable cardiovascular protection despite effecting reductions in peripheral BP. However, newer vasodilating beta-blockers appear to be more beneficial in improving central hemodynamics\(^9,30–32\) and may provide better outcomes in both young and older women.

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DISCLOSURE

The authors declared no conflict of interest.

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