Acute β-Adrenergic Blockade Increases Aortic Wave Reflection in Young Men and Women
Differing Mechanisms Between Sexes
Darren P. Casey, Timothy B. Curry, Michael J. Joyner, Nisha Charkoudian, Emma C. Hart

Blood Vessels

Abstract—Acute β-adrenergic blockade increases aortic wave reflection; however, the mechanisms remain unclear. Evidence suggests that β-adrenergic receptor sensitivity in the peripheral vasculature differs between sexes. Therefore, the goal of this study was to examine whether β-adrenergic blockade alters aortic wave reflection to a similar extent in young men and women. In 31 subjects (16 men and 15 women; 26±1 years) noninvasive aortic pressure waveforms were synthesized from high-fidelity radial pressure waveforms via applanation tonometry before and during systemic β-blockade (0.25 mg/kg bolus, followed by 0.004 mg/kg per minute of continuous infusion of propranolol). β-Blockade increased aortic augmentation index and wave reflection amplitude (aortic augmented pressure) in both sexes (P<0.01). Although the increase in augmentation index was not significantly different between sexes (7.5±1.1% versus 4.6±1.5%; P=0.07), the increase in aortic augmented pressure was greater in women compared with men (2.8±0.5 versus 1.4±0.5 mm Hg; P<0.05). Aortic augmentation index adjusted for a heart rate of 75 bp increased in women (4.1±1.1%; P<0.05) after β-blockade, whereas it was unchanged in men (0.6±1.3%; P=0.33). Moreover, the change in aortic augmentation index was inversely associated with the change in heart rate only in men (r=−0.54; P<0.05). Our data suggest that aortic wave reflection is increased to a greater extent in women after systemic β-blockade, and enhanced aortic wave reflection appears to be mediated by a reduced heart rate in men, whereas the mechanism is unclear in women. (Hypertension. 2012;59:145-150.)

Key Words: aortic wave reflection ■ blood pressure ■ β-adrenergic receptors ■ sex

β-adrenergic blockers are among the oldest and most widely used antihypertensive agents currently available for clinical use. β-Blocker therapy is effective in reducing brachial artery blood pressure (BP) and is often recommended for many high-risk patients with cardiovascular diseases.1 However, evidence suggests that β-blockers may be less effective than other antihypertensive drugs in reducing stroke and cardiovascular mortality despite similar BP reductions.2–4 One explanation for the less-than-desirable cardiovascular protection provided by β-blockers is their lack of effectiveness in reducing central aortic BP and wave reflection. Along these lines, treatment with traditional nonvasodilating β-blockers (ie, atenolol) is associated with greater central aortic pressures and wave reflection compared with other antihypertensive drugs.5–11 It has been postulated that the β-blocker induced reduction in heart rate (HR) prolongs systolic ejection time and delays the peak of the outgoing wave, thus causing the pressure wave reflections to augment the central aortic systolic pressure wave.11 Therefore, the benefits of HR reduction may be negated by the simultaneous increase in aortic pressure and wave reflection.

Acute and prolonged β-blockade also leads to an increase in systemic vascular resistance.12–15 Presumably, this is because of a reduction in β-mediated peripheral vasodilation and/or an unmasking of α-adrenergically mediated vasoconstriction.14 Theoretically, an increased peripheral vasoconstriction could cause a shift of arterial reflection sites proximally and contribute to the enhanced aortic wave reflection during β-blockade, independent of a reduced HR. Previous work indicates that peripheral vascular β-adrenergic receptor sensitivity is enhanced in young women compared with men of a similar age.16 Consequently, forearm vasoconstrictor responses to norepinephrine are blunted in young women because of concurrent β-adrenergic–mediated vasodilatation. Thus, it is possible that β-adrenergic receptor–mediated vasodilatation is enhanced in young women and offsets the vasoconstrictor effects of norepinephrine. Therefore, sex-specific differences may exist in wave reflection characteristics during β-blockade. With this information as background, we tested the hypothesis that acute β-blockade would increase aortic wave reflection in both sexes, but that the increase would be greater in women. Because the sex-specific differences in wave reflection characteristics during β-blockade are thought to contribute to enhanced aortic wave reflection in women, we hypothesized that sex-specific differences may exist in wave reflection characteristics during β-blockade. With this information as background, we tested the hypothesis that acute β-blockade would increase aortic wave reflection in both sexes, but that the increase would be greater in women. Because the sex-specific differences in wave reflection characteristics during β-blockade are thought to contribute to enhanced aortic wave reflection in women, we hypothesized that sex-specific differences may exist in wave reflection characteristics during β-blockade. With this information as background, we tested the hypothesis that acute β-blockade would increase aortic wave reflection in both sexes, but that the increase would be greater in women. Because the sex-specific differences in wave reflection characteristics during β-blockade are thought to contribute to enhanced aortic wave reflection in women, we hypothesized that sex-specific differences may exist in wave reflection characteristics during β-blockade. With this information as background, we tested the hypothesis that acute β-blockade would increase aortic wave reflection in both sexes, but that the increase would be greater in women. Because the sex-specific
differences in β-adrenergic–mediated vasodilatation have been demonstrated in younger adults, we chose to test our hypothesis in a similar age group. Although hypertension-related β-blocker usage is less common in young adults compared with older individuals, these drugs are used clinically for the treatment of cardiac arrhythmias, migraines, and anxiety in younger patients.

Methods

Subjects
A total of 31 young healthy subjects (16 men and 15 women) were studied. Subjects completed written informed consent and underwent a standard screening. All were healthy, nonobese, nonsmokers, and were not taking any medications (except for oral contraceptives in some women). All of the studies were performed in the clinical research unit laboratory at the Mayo Clinic, where ambient temperature was controlled between 22°C and 24°C. Studies were performed after an overnight fast, and subjects refrained from exercise, alcohol, and caffeine for ≥24 hours. Female subjects were studied during the early follicular phase of the menstrual cycle or the placebo phase of oral contraceptives. All of the study protocols were approved by the Mayo Institutional Review Board and were performed according to the Declaration of Helsinki.

Measurements

Brachial Artery BP and HR Measurements
A 20-gauge, 5-cm catheter was placed in the brachial artery of the left arm under sterile conditions after local anesthesia (2% lidocaine). The catheter was connected to a pressure transducer, which was positioned at the level of the heart and interfaced with a personal computer to monitor arterial pressure. A 3-lead ECG was used for continuous recording of HR. Beat-to-beat stroke volume was measured from the brachial artery using Modelflow analysis, which computes an aortic waveform based on nonlinear pressure-volume, pressure-compliance, and pressure-characteristic impedance equations, incorporating age, sex, height, and body mass. Cardiac output was calculated as stroke volume×HR, and total peripheral resistance (TPR) was calculated as mean arterial pressure/cardiac output.

Pulse Wave Analysis
After 15 minutes of supine rest, the assessment of arterial wave reflection characteristics was performed noninvasively using the SphygmoCor system (AtCor Medical, Sydney, Australia), as described previously. Briefly, high-fidelity radial artery pressure waveforms were recorded by applplanation tonometry of the radial pulse in the right wrist using a “pencil type” micromanometer (Millar Instruments, Houston, TX). The radial BP and waveforms were calibrated from the systolic and diastolic brachial artery BPs (catheter). A validated, generalized transfer function was used to generate the corresponding aortic pressure waveform. The generalized transfer function has been validated using 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, aortic augmentation index (A1), A1 adjusted for an HR of 75 (A1@75 bpm), roundtrip travel time of the forward traveling wave from the ascending aorta to the major reflection site and back, and wasted LV pressure energy (Ew), which is the component of extramyocardial oxygen requirement attributed to early systolic wave reflection:

\[ Ew = \frac{(\pi^4)AGx\Delta t}{a^{3.33}} \]

where 1.333 is the conversion factor for millimeters of mercury per second to dynes per second per centimeter squared, and \( \Delta t \) is the systolic duration of the reflected wave. Augmented pressure (AG) is the amplitude of the reflected wave and is defined as the difference between the first (forward wave) and second systolic shoulders of the aortic systolic BP. Only high-quality recordings, defined as an in-device quality index of >80% (derived from an algorithm including average pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform), were accepted for analysis. In general, 2 to 3 measurements were performed to get 2 measurements with an acceptable quality index.

Systemic β-Adrenergic Blockade
We showed previously that the β1- and β2-adrenergic receptors in the peripheral vasculature contribute to peripheral resistance in women but not in men. In the present study we aimed to block all of the β-adrenergic receptors on the vasculature to assess whether there would be sex-specific changes in indices of aortic wave reflection. Therefore, nonselective β-blockade was achieved using intravenous infusion of propranolol. A 0.25-mg/kg bolus of propranolol (administered over 5 minutes) was followed by a continuous infusion of 0.004 mg/kg per minute of propranolol to maintain β-blockade. This dose of propranolol has been proven previously to cause total β-blockade in adult humans. All of the hemodynamic and applplanation tonometry measurements were repeated ~15 to 20 minutes after the start of the propranolol infusion.

Statistical Analyses
Group data are expressed as mean±SEM. ANOVA was used to analyze baseline differences between sexes. Changes in the continuous dependent variables were analyzed using repeated-measures ANOVA. When a significant group-by-time interaction was observed, within-group comparisons between time points and between-group comparisons at each time point were performed using the Tukey post hoc analysis. To assess the relationship between changes in HR and TPR and AIx during β-blockade, linear regression analysis was performed and Pearson correlation coefficients calculated. All of the statistical analyses were performed using SigmaStat software (version 2.03, SPSS Inc). An α-level of P<0.05 was required for statistical significance.

Results
Subject demographics are presented in Table 1. All 31 of the subjects completed the study protocol. Beat-to-beat stroke volume could not be calculated from the brachial artery waveform in 3 subjects (1 man and 2 women). Therefore, TPR values were only calculated in 15 and 13 of the male and female subjects, respectively. Baseline (pre-β-blockade) HR, peripheral and aortic BPs, and ejection duration were not different between sexes (Table 2). However, women demonstrated a higher AIx, AIx@75 bpm, AG, and TPR compared with men (P<0.01; Table 2). Consequently, Ew was greater in women compared with their male counterparts (P<0.01; Table 2).

During systemic β-blockade via propranolol infusion, HR and peripheral systolic and pulse pressures were reduced in both sexes (P<0.01; Table 2). Aortic pressures were unchanged by β-blockade in both groups. The reduction in peripheral pulse pressure without commensurate changes in aortic pulse pressure resulted in a decreased pulse pressure.
amplification ($P<0.01$; Table 2). AIX, AG, $E_w$, and TPR were increased during $\beta$-blockade in both sexes ($P<0.01$; Table 2). However, the increases in AG (2.8±0.5 versus 1.4±0.5 mm Hg; $P<0.05$) and $E_w$ (544±116 versus 308±101 dyne·s/cm²; $P<0.05$) were greater in women during $\beta$-blockade compared with men. Although the increase in AIX was not significantly greater in women compared with men during $\beta$-blockade (7.5±1.1% versus 4.6±1.5%; $P=0.07$; Figure 1A), the increase in AIX@75 bpm was substantially greater in women (4.1±1.1% versus 0.6±1.2%; $P<0.05$; Table 2 and Figure 1B). The change ($\Delta$) in AIX was inversely associated with $\Delta$HR in men ($r=-0.54$; $P<0.05$; Figure 2) but not in women ($r=-0.19$; $P=0.50$). Conversely, $\Delta$AIX was positively related to $\Delta$TPR in women ($r=0.50$; $P<0.05$) but not in men ($r=0.17$; $P=0.54$).

**Discussion**

The major new findings of the current study were as follows: (1) acute $\beta$-adrenergic blockade increased aortic wave reflection in young men and women; (2) aortic wave reflection was increased to a greater extent in women during systemic $\beta$-blockade; and (3) the increase in aortic wave reflection during acute systemic $\beta$-blockade appeared to be caused by different mechanisms between sexes. That is, increases in aortic wave reflection characteristics in men during systemic $\beta$-blockade were predominantly driven by a reduction in HR, whereas other mechanisms in addition to a reduced HR likely contributed to the enhanced wave reflection in women. Taken together these data suggest that $\beta$-blocking drugs may affect central artery hemodynamics differently in men and women.

Our finding that acute $\beta$-blockade with intravenous propranolol enhanced aortic wave reflection in young healthy adults is in agreement with a previous report in hypertensive patients. However, those authors did not report whether there were any sex differences in aortic wave reflection during $\beta$-blockade. Moreover, it should also be noted that all of the hemodynamic measurements (in the previous report) were made after premedication with chlorpheniramine.
Therefore, it is unclear whether the changes in aortic hemodynamics during β-blockade were affected by previous antihistamine administration. To our knowledge this is the only other study to examine the acute effects of β-blockade on aortic wave reflection.

Long-term treatment with traditional nonvasodilating β-blockers (eg, atenolol) is associated with increased central aortic pressures and wave reflection compared with alternative antihypertensive therapy.5–11 From a clinical standpoint, this is particularly relevant, because increased AIx is a strong independent risk marker for premature coronary artery disease and all-cause cardiovascular mortality.27,28 Along these lines, a meta-analysis of 9 studies, which included atenolol trials, demonstrated that mortality was significantly higher with this agent, despite similar reductions in brachial BP, compared with other antihypertensive drugs.29

Increases in aortic wave reflection during both short- and long-term β-blockade have been attributed to their HR-lowering effect. It has been postulated that the reduced HR prolongs systolic ejection duration and allows the reflected wave a greater opportunity to appear in late systole rather than in diastole, thus increasing indices of wave reflection (ie, AIx).14,30 However, this concept would require pulse wave velocity (PWV) to remain unchanged during β-blockade. In this context, some studies have demonstrated an effect of β-blockers to lower aortic PWV,31–33 whereas others have not.7 In the present study, AIx was increased during propranolol infusion in both men and women (Table 2). However, after adjusting the AIx for HR (ie, AIx@75 bpm) only the women showed a significant increase (Table 2 and Figure 1B). Moreover, the change in AIx was inversely related to the change in HR during β-blockade in men but not in women (Figure 2). Therefore, men with a greater increase in AIx had a greater reduction in HR during β-blockade. These findings suggest that increases in aortic wave reflection in young men during β-blockade are because of a reduced HR, whereas additional factors likely contribute to an enhanced AIx in young women.

The exact mechanisms underlying the enhanced aortic wave reflection during β-blockade in women are unclear, but there are several possible explanations. First, the greater aortic wave reflection in women during β-blockade could have resulted from an increase in arterial PWV as a consequence of changes in arterial stiffness. Along these lines, increases in aortic PWV cause early return of the reflected wave from peripheral reflecting sites and, thus, result in a greater AIx. A limitation of the present study was that we did not assess aortic PWV. Therefore, we are unable to evaluate whether the greater increases in aortic wave reflection characteristics in women during β-blockade were related to differences in aortic stiffness. Second, decreases in HR can prolong systolic ejection time and increase the likelihood that pressure wave reflections will augment the outgoing pressure wave during systole. In the present study, the decrease in HR during propranolol infusion was similar between men and women. In addition, systemic β-blockade did not alter the absolute systolic ejection duration in men and women (Table 2). When expressed relative (percentage) to the duration of the cardiac cycle, the change in systolic ejection duration during β-blockade was similar between the sexes (Table 2). Taken together, these results suggest that differences in the timing of systolic ejection likely do not explain the enhanced aortic wave reflection in women during β-blockade. Another potential cause for the enhanced aortic wave reflection during β-blockade in women might be related to differences in peak aortic blood flow velocity. Klinke et al14 demonstrated that propranolol decreases the peak aortic blood flow velocity in men. However, it is currently unclear whether sex-related differences in the aortic blood velocity during propranolol exist.

Lastly, acute and prolonged β-blockade increases systemic vascular resistance,12–15 likely by reducing the β-mediated peripheral vasodilation and/or by unmasking a degree of α-adrenergic–mediated vasoconstriction.14 It appears that the β-adrenergic receptors are either more sensitive or upregulated in young women versus men.16 Moreover, we have demonstrated recently that the β-adrenergic receptors offset α-adrenergic vasoconstriction in young women but not young men.17 Along these lines, young men demonstrate a positive relationship between muscle sympathetic nerve activity and TPR, whereas this relationship is absent in young women. However, during β-blockade, the relationship between mus-
cule sympathetic nerve activity and TPR became positive in young women. Therefore, women may have greater peripheral vasoconstriction (in addition to HR changes) in response to nonselective β-blockade. The increased peripheral vasoconstriction could cause a shift of arterial reflection sites proximally, which, in turn, would result in earlier wave reflection and thereby enhance aortic wave reflection in women. In this context, the ΔTPR during β-blockade in the present study was related to the ΔAIx in women but not in men.

**Experimental Considerations**

In the present study propranolol (a nonselective β-adrenergic antagonist) was used to examine the impact of β-blockade on indices of aortic wave reflection. Therefore, we cannot extrapolate the current findings to other β-blocking drugs, especially newer vasodilating β-blockers (ie, nebivolol and carvedilol). These β-blockers have been shown to have favorable effects on peripheral vascular resistance, arterial distensibility, aortic pressures, wave reflection characteristics, and stiffness. Therefore, the use of vasodilatory β-blockers may offset any deleterious hemodynamic effects of HR reduction by decreasing wave reflection from the periphery. It is also important to note that, with the development of newer and more selective β-blockers, the use of propranolol as an antihypertensive agent has been reduced over the last several years. However, propranolol and other nonselective β-blockers are still commonly used in the treatment of cardiac arrhythmias, benign tremors, migraines, and heart failure.

The current findings are limited to young normotensive men and women. However, previous findings have demonstrated that acute β-blockade (via propranolol) increases aortic wave reflection in hypertensive patients. Unfortunately, other than age, the authors did not report information related to patient demographics or if any possible sex-related differences existed in the hemodynamic responses to β-blockade in their subjects. Therefore, it is unclear whether the sex differences observed in the present study can be extrapolated to other populations with or at risk for cardiovascular disease (ie, hypertension) that would likely receive β-blockers. Lastly, the findings of the current study are limited to the effects of acute β-blockade on central artery hemodynamics. Whether similar sex differences exist in response to long-term β-blockade therapy needs to be examined further.

**Perspectives**

Several studies have reported that antihypertensive medications can have substantially different effects on central aortic pressure and wave reflection, despite a similar impact on brachial BP. Along these lines, conventional β-blockers appear to be less effective in protecting against cardiovascular events compared with other antihypertensive agents. The reduced effectiveness of β-blockers is thought to be a consequence of the failure to reduce aortic BPs and wave reflection. Our current findings suggest that the negative effects (ie, increased aortic wave reflection) of conventional β-blockers may be greater in women. Interestingly, data from a recent, large (~18 000 patients) international study in patients with currently treated or newly diagnosed hypertension suggest that women receive β-blocker therapy more frequently than men. Taken together with the present data, this might suggest that sex should be considered before β-blocker therapy, especially when nonselective β-blockers are considered. To this point, future studies should address whether long-term β-blockade has a greater impact on aortic wave reflection in women compared with men.

**Acknowledgments**

We are grateful to the study volunteers for their participation. We also thank Shelly Roberts, Jean Knuston, Karen Krucker, Christopher Johnson, Nancy Meyer, and Pam Engrav for their technical assistance.

**Sources of Funding**

This study was supported by National Institutes of Health grants HL083947 (to M.J.J. and N.C.), HL46493 (to M.J.J.), AR55819 (to D.P.C.), DK082424 (to T.B.C.), and CTSA RR-024150 (Mayo Clinic), and by Mayo Clinic Research Subcommittee Early Career Development Supplement (to T.B.C.) and American Heart Association grant 2170087 (to E.C.H.).

**Disclosures**

None.

**References**


10. Polonia J, Barbosa L, Silva JA, Bertoquini S. Different patterns of peripheral versus central blood pressure in hypertensive patients treated
Acute β-Adrenergic Blockade Increases Aortic Wave Reflection in Young Men and Women: Differing Mechanisms Between Sexes
Darren P. Casey, Timothy B. Curry, Michael J. Joyner, Nisha Charkoudian and Emma C. Hart

Hypertension. 2012;59:145-150; originally published online November 21, 2011;
doi: 10.1161/HYPERTENSIONAHA.111.182337

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/59/1/145

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/