Relationship Between Muscle Sympathetic Nerve Activity and Aortic Wave Reflection Characteristics in Young Men and Women

Darren P. Casey, Timothy B. Curry, Michael J. Joyner, Nisha Charkoudian, Emma C. Hart

Abstract—Increased arterial stiffness is associated with higher levels of aortic wave reflection and aortic blood pressure. Recent evidence suggests a link between muscle sympathetic nerve activity and indices of arterial stiffness. Therefore, the aims of this study were to examine the relationship between resting muscle sympathetic nerve activity and characteristics of aortic pressure wave reflection and the influence of sex on these relationships. In 44 subjects (23 females and 21 males; 25±1 years of age), we measured muscle sympathetic nerve activity via peroneal microneurography. In addition, noninvasive aortic pressure waveforms were synthesized from radial pressure waveforms obtained from applanation tonometry. Aortic blood pressure, augmentation index, wave reflection amplitude, and wasted left ventricular energy were calculated. Resting sympathetic activity (bursts/100 heart beats) was not associated with any of the aortic pressure wave reflection characteristics for all patients. However, there was a positive relationship between sympathetic activity and augmentation index (r=0.46; P=0.05) in men. Further, sympathetic activity in men was related to wave reflection amplitude (r=0.53; P<0.05) and wasted left ventricular energy (r=0.57; P<0.01). In contrast to men, women demonstrated strong inverse relationships between sympathetic activity and augmentation index (r=−0.63), wave reflection amplitude (r=−0.59), and wasted left ventricular energy (r=−0.58; P<0.01 for all). Our results suggest another possible mechanism by which young women are protected against the development of cardiovascular disease. (Hypertension. 2011;57:00-00.) ● Online Data Supplement

Key Words: sympathetic nerve activity ● aortic wave reflection ● blood pressure ● peripheral resistance ● sex

It has been demonstrated that sympathetic vasoconstrictor nerve traffic exhibits no relationship with resting arterial pressure among young healthy men and women. These observations are based on a lack of relationship between peroneal muscle sympathetic nerve activity (MSNA) and resting arterial blood pressure measured at the level of the brachial artery. However, there can be marked pressure differences throughout the arterial tree. Along these lines, persons with similar peripheral arterial pressures can have drastically different aortic systolic and pulse pressures because of greater reflected pressure wave amplitude. Increased arterial stiffness causes an increase in pulse wave velocity (PWV) and can promote an early return of reflected waves from peripheral reflecting sites to the heart during systole. Consequently, early return or increased amplitude of reflected pressure waves during systole increases ascending aortic systolic and pulse pressures and elevates left ventricular afterload. In general, increases in the amplitude of the reflected pressure waves are associated with increases in cardiovascular risk.

Recent evidence suggests a relationship between carotid-femoral PWV, an index of aortic stiffness, and MSNA in healthy men. However, whether sympathetic vasoconstrictor nerve traffic is related to aortic pressure has not been determined. Because MSNA appears to be related to PWV and the latter can have significant effects on pulsatile pressures in the aorta, we sought to examine the relationship between MSNA and aortic pressures and wave characteristics. We hypothesized that there would be a positive relationship between MSNA and indices of aortic wave reflection among persons.

Based on previous findings from our group demonstrating that regulation of peripheral arterial pressure is fundamentally different between the sexes, a second aim of our study was to examine potential sex differences in the relationship between MSNA and aortic pressures. Therefore, we also hypothesized that because the relationship between sympathetic nerve activity and total peripheral resistance (TPR) is stronger in men, they would demonstrate a stronger positive relationship between resting MSNA and measures of aortic pressure wave reflection than women.

Methods

Subjects
A total of 44 young healthy subjects (23 females and 21 males) 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). 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 study protocols were approved by the Mayo Institutional Review Board and were performed according to the Declaration of Helsinki.

**Measurements**

All studies were performed in the clinical research unit laboratory at the Mayo Clinic, where ambient temperature was controlled between 22°C and 24°C. Subjects were studied at rest in the supine position. 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 heart rate.

MSNA was recorded in the peroneal nerve posterior to the fibular head with a tungsten microelectrode, as described by Sundlöf and Wallin. The recorded signal was amplified 80,000-fold, band-pass filtered (700 to 2000 Hz), rectified, and integrated (resistance-capacitance integrator circuit; time constant 0.1 s) by a nerve-traffic analyzer.

The assessment of arterial wave reflection characteristics was performed noninvasively using the SphygmoCor system (AtCor Medical) as described previously. Briefly, high-fidelity radial artery pressure waveforms were recorded by applanation tonometry of the radial pulse in the right wrist using a pencil-type micromanometer (Millar Instruments). The radial blood pressure and waveforms were calibrated from the systolic and diastolic brachial artery blood pressure (catheter). A validated, generalized transfer function was used to generate the corresponding aortic pressure waveform (supplemental Figure I, available in an online supplement at http://hyper.ahajournals.org). 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 (AI), AI, adjusted for a heart rate of 75 (AI, at 75 bpm), roundtrip travel time of the forward traveling wave from the ascending aorta to the major reflection site and back (Δt), and wasted left ventricular pressure energy (Ew), which is the component of extra myocardial oxygen requirement attributable to early systolic wave reflection. Ew can be estimated as \(1.333 \times \text{augmented pressure} \times \Delta t \times 1.333\), where 1.333 is the conversion factor from mm Hg to dynes/cm² and Δt is the systolic duration of the reflected wave. Augmented pressure 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 blood pressure.

**Table 1. Demographic Variables in Men (n=21) and Women (n=23)**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>25±1</td>
<td>26±1</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>77±2</td>
<td>64±2*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>178±1</td>
<td>166±1*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2±0.5</td>
<td>23.3±0.4</td>
</tr>
</tbody>
</table>

BMI indicates body mass index. Data are mean±SEM. *Data are different from men (P<0.05).

cate applanation tonometry measurements were made. (For a more detailed description of the data analysis, please see the online data supplement.)

**Statistical Analyses**

Group data are expressed as means±SEM. Differences in MSNA, hemodynamic variables, and aortic wave reflection characteristics in men and women were evaluated using a 2-tailed independent t test. To access the relationships between MSNA and aortic wave reflection characteristics, linear regression analysis was performed and Pearson correlation coefficients calculated. The critical α-level was set at 0.05, and data were analyzed using SigmaStat software (version 2.03; SPSS Inc).

**Results**

Subject demographics are presented in Table 1. All 44 subjects completed the study protocol. Arterial catheter placement was unsuccessful in 4 subjects (2 males and 2 females). Therefore, TPR values were only calculated in 19 and 21 of the male and female subjects, respectively. In these subjects, an average of 3 automated brachial blood pressure readings was used to calibrate the radial pressure waveforms during the applanation tonometry measurements. In addition, Ew could not be calculated in 1 male subject. Therefore, the relationships between MSNA and Ew are reported in 20 male subjects.

**Group-Averaged Data for Neural-Hemodynamic and Aortic Wave Reflection Variables in Men and Women**

Peripheral and aortic pressures were similar between sexes (Table 2). Indices of aortic wave reflection (both AI and augmented aortic pressure [AG]) were higher in women compared with men. Consequently, Ew was greater in women compared with their male counterparts (Table 2; P<0.05). Women demonstrated a lower stroke volume and cardiac output and a higher TPR compared with men.

**Relationships Between Neural-Hemodynamic and Aortic Wave Reflection Variables**

MSNA expressed both as burst incidence and frequency did not correlate with aortic systolic, diastolic, or pulse blood pressure and indices of wave reflection when all subjects were grouped together for analysis (Table 3). There was a correlation between TPR and aortic diastolic pressure (P≤0.05) and an inverse relationship with pulse pressure amplification (P<0.05) for all subjects studied.

When we split the group into men and women, we observed sex-specific differences in these relationships.
Table 2. Neural-Hemodynamic Variables and Aortic Wave Reflection Characteristics in Men (n=21) and Women (n=23)

<table>
<thead>
<tr>
<th>Hemodynamic/Neural Variables</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td>PSBP, mm Hg</td>
<td>126±2</td>
<td>127±2</td>
</tr>
<tr>
<td>PDBP, mm Hg</td>
<td>70±2</td>
<td>71±1</td>
</tr>
<tr>
<td>PPP, mm Hg</td>
<td>56±2</td>
<td>56±2</td>
</tr>
<tr>
<td>ASBP, mm Hg</td>
<td>102±2</td>
<td>104±2</td>
</tr>
<tr>
<td>ADBP, mm Hg</td>
<td>70±1</td>
<td>70±2</td>
</tr>
<tr>
<td>APP, mm Hg</td>
<td>32±1</td>
<td>34±2</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>89±1</td>
<td>92±2</td>
</tr>
<tr>
<td>PPA</td>
<td>1.74±0.04</td>
<td>1.65±0.06</td>
</tr>
<tr>
<td>AG, mm Hg</td>
<td>4±1*</td>
<td>-2±2</td>
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<tr>
<td>Al, %</td>
<td>10±2*</td>
<td>5±2*</td>
</tr>
<tr>
<td>Ew, dyne · cm² · s</td>
<td>788±161*</td>
<td>64±2</td>
</tr>
<tr>
<td>HR, bpm⁻¹</td>
<td>62±2</td>
<td>5.0±0.2*</td>
</tr>
<tr>
<td>SV, mL</td>
<td>102±4</td>
<td>79±3*</td>
</tr>
<tr>
<td>CO, L/min⁻¹</td>
<td>6.2±0.3</td>
<td>14.8±0.7*</td>
</tr>
<tr>
<td>TPR, mm Hg/L · min⁻¹</td>
<td>14.8±0.7*</td>
<td>18.6±0.7*</td>
</tr>
<tr>
<td>MSNA, bursts/100 heart beats⁻¹</td>
<td>34±3</td>
<td>25±3</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>20±2</td>
<td>16±2</td>
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</table>

PSBP indicates peripheral systolic blood pressure; PDBP, peripheral diastolic blood pressure; PPP, peripheral pulse pressure; ASBP, aortic systolic blood pressure; ADBP, aortic diastolic blood pressure; APP, aortic pulse pressure; MAP, mean arterial pressure; PPA, pulse pressure amplification; HR, heart rate; SV, stroke volume; CO, cardiac output.

Data are mean±SEM.

*Data are different from men (P<0.05).

Table 3. Correlations Between MSNA and TPR and Aortic Pressure and Indices of Wave Reflection

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<tr>
<td>All subjects (n=44)</td>
<td>−0.11</td>
<td>0.01</td>
<td>−0.19</td>
<td>−0.19</td>
<td>−0.20</td>
<td>−0.24</td>
<td>−0.17</td>
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<tr>
<td>Males (n=21)</td>
<td>0.08</td>
<td>0.05</td>
<td>0.04</td>
<td>−0.40</td>
<td>0.46*</td>
<td>0.34</td>
<td>0.53*</td>
<td>0.57†</td>
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<tr>
<td>Females (n=23)</td>
<td>−0.20</td>
<td>0.02</td>
<td>−0.30</td>
<td>0.14</td>
<td>−0.63†</td>
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<td>MSNA (bursts/min)</td>
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Values in parentheses indicate correlations for which indices of wave reflection have been corrected for body height.

MSNA indicates muscle sympathetic nerve activity; TPR, total peripheral resistance; ASBP, aortic systolic blood pressure; ADBP, aortic diastolic blood pressure; APP, aortic pulse pressure; PPA, pulse pressure amplification.

*P<0.05; †P<0.01.

Discussion

The major new finding of the current study was that the relationships between MSNA and measures of aortic wave reflection are sex specific. Because our previous work demonstrated that sympathetic regulation of peripheral arterial pressure is fundamentally different between sexes,3 we hypothesized that the relationship between MSNA and aortic wave reflection would be stronger in men than in women. Consistent with our hypothesis, men demonstrated a positive relationship between MSNA and aortic wave reflection characteristics. However, and surprisingly, these relationships were inversely related in women. Thus, greater sympathetic activity may contribute to increased aortic wave reflection and left ventricular work in men but appears to be offset by other factors in women.

In agreement with previous studies,16,17 women demonstrated higher levels of aortic wave reflection compared with men in the current study (Table 2). These sex differences have been attributed to women being shorter with the associated shorter aorta, which, in turn, results in reflecting sites closer to the heart and earlier wave reflections.18 However, the differences in aortic wave reflection between the sexes remain in elderly men and women matched for body height.19 The goal of the present study was not to quantify sex differences in aortic wave reflection, but to determine whether the relationship between MSNA and aortic wave reflection characteristics is different in men and women.

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*P<0.05; †P<0.01.
differences in aortic wave reflection characteristics, but rather to examine the relationships between MSNA and aortic pressure wave reflection and whether these relationships differ between young men and women. Although a shorter body height may result in higher resting levels of wave reflection in women, it should not a priori influence the relationship between AIx and MSNA. In fact, correcting AIx, AG, and Ew for body height did not alter the relationship reported in this study (Table 3; values in parentheses). This suggests that the contrasting relationships between MSNA and aortic wave reflection characteristics in young men and women are independent of body height.

Increased arterial stiffness and early wave reflections are associated with several cardiovascular risk factors, including age, hypertension, diabetes mellitus, hypercholesterolemia, and atherosclerosis.4,17,20 Further, increased AIx is a strong independent risk marker for premature coronary artery disease and all-cause and cardiovascular mortality.7,21 In the present study, increased AIx and AG were associated with higher levels of MSNA in men. Moreover, men also demonstrated a significant positive relationship between MSNA and Ew, an index of myocardial oxygen demand and left ventricular work. Ew is the portion of the tension-time index curve attributed to previous reflection of the pulse pressure wave (a shortening of ∆t; supplemental Figure I) that increases central aortic pressure during systole. An increase in Ew can be interpreted as an excess amount of energy expended by the
left ventricle without a commensurate increase in flow and is associated with left ventricular hypertrophy. Interestingly, and in contrast to men, higher levels of MSNA in women were inversely related to indices of wave reflection (AIx and AG) and Ees in the present study.

High sympathetic activity is also associated with several of the conditions in which aortic wave reflection is elevated. Moreover, both MSNA and aortic wave reflection characteristics increase during commonly used laboratory stressors such as the cold pressor test and handgrip exercise. Whether sympathetic activity plays a major role in modulating the elastic properties of central arteries or the tone of peripheral muscular arteries remains unknown. Recent evidence suggests that resting MSNA levels are related to aortic stiffness in men, and short-term sympathetic activation (via cold pressor test) decreases muscular artery compliance in normotensive young humans. However, Lydakis et al demonstrated that despite similar levels of sympathetic system engagement during lower body negative pressure and isometric fatiguing handgrip exercise, only the latter resulted in an increase in blood pressure and in measures of central large artery stiffness and wave reflection. Based on these findings, the authors concluded that blood pressure rather than sympathetic activity seems to play the major role in modulating the elastic properties of the central arteries. In the current study, MSNA was not related to arterial pressure (either peripheral or aortic) in men or women. Nonetheless, in our study, MSNA was related to measures of aortic wave reflection. Interestingly, the direction of these relationships were dependent on sex.

Maneuvers that acutely increase sympathetic stimulation are associated with reductions in the distensibility of both muscular (radial) and elastic (carotid) type arteries. The sympathetic nervous system may also exert a marked tonic restraint of medium-sized and large muscular arteries in men and may have a stiffening influence on the mechanical properties of the aorta. Evidence from normotensive male rats suggests that stimulation of the α-adrenergic receptors with norepinephrine increases carotid intima media thickness and reduces lumen area, which might theoretically change the mechanical properties of this artery. Because the nature of reflected waves are dependent on the elastic properties of the entire arterial tree, changes in arterial distensibility and tone of both elastic and muscular arteries can have profound effects on the aortic pressure wave. In this context, AIx is related to arterial properties via changes in PWV. Increased arterial stiffness increases PWV and causes early return of the reflected wave from the peripheral reflecting sites to the ascending aorta. Likewise, changes in smooth muscle tone of the muscular arteries, especially those in the lower body, modify the speed of travel of the pressure wave along their length and determine when the reflected wave arrives back at the heart. Along these lines, men with higher levels of MSNA demonstrate increased levels of calf vascular resistance.

Possible Mechanisms for Discrepant Relationships in Men and Women
We were surprised and interested to note that the relationships between MSNA and aortic waveform characteristics in women were exactly opposite of those in men. These data suggest that women with high MSNA actually have a reduced aortic wave reflection and a lower index of left ventricular wasted energy compared with women with lower MSNA. In this context, previous data from our laboratory and others demonstrate that in women, high MSNA does not necessarily translate into elevated peripheral vascular resistance, as it does in men. The fact that that resting MSNA appears to have a differential effect on aortic wave form characteristics in women is further adds to the body of evidence, which suggests that sex influences the way that MSNA interacts with the vasculature.

The exact mechanisms underlying the inverse relationship between MSNA and aortic waveform characteristics in women are unclear, but there are several possible explanations. First, it appears that the β-adrenergic receptors are either more sensitive or upregulated in women versus men. Thus, concurrent β-mediated vasodilation via norepinephrine released from the sympathetic nerve terminal might offset α-mediated vasoconstriction in women. Consequently, high levels of MSNA in young women may decrease aortic waveform characteristics via decreased vascular tone or stiffness via vascular β-adrenergic receptor stimulation. Second, differences in the metabolism of norepinephrine in the vascular smooth muscle cells may exist between men and women, which could result in alterations vascular tone or stiffness. However, this can only be postulated because we have no data to support this, and it is beyond the scope of the present study. Finally, circulating estrogens increase endothelial nitric oxide availability, causing a decrease in resting vascular tone in women, and thereby have the potential to decrease indices of wave reflection. Consequently, the effect of estrogen on the vasculature might explain why MSNA was not positively related to augmentation index in the young women. However, if this was the case, then we would expect no relationship between MSNA and augmentation index. We found an inverse relationship between MSNA and augmentation index in young women, thus other factors other than the vasodilating effects of estrogen acting alone must be important in driving this relationship.

Limitations
The characteristics of the reflected wave depend on a complex set of determinants, including the speed at which the wave travels (ie, PWV). Increased arterial stiffness increases PWV and causes early return of the reflected wave from peripheral reflecting sites and thus results 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 sex differences in the relationships between MSNA and wave reflection characteristics were related to differences in aortic stiffness. We also note in this context that AIx can vary considerably among large groups of young men and women despite similar aortic PWV values.

Perspectives
This is the first study to examine the relationships between MSNA and aortic wave reflection characteristics in hu-
mans. Our current results demonstrate that young men with high MSNA have elevated levels of aortic wave reflection, whereas the relationship between these 2 variables is inversely related in young women. Although these results were unexpected, they are consistent with our recent work regarding sex differences in relationships between MSNA and peripheral vascular resistance in young healthy humans. Together, the present and previous studies provide important initial insight into sympathetic–hemodynamic interactions, which appear to have profound implications for development of cardiovascular risk. As such, our present findings add to our previous work by identifying additional mechanisms by which cardiovascular risk may be minimized in young women compared with young men. In men, our data suggest that increases in MSNA negatively affect aortic hemodynamics (variables shown to be related to cardiovascular risk) to a greater extent than in women. Importantly, cardiovascular risk profiles change dramatically at menopause, at which time potential protective influences of estrogen in women are lost, and cardiovascular risk profiles can approach or even exceed levels seen in men. To this point, future studies should address the impact of aging, specifically in women, on the relationships between sympathetic neural activity and aortic wave reflection variables.

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

Sources of Funding
This study was supported by National Institutes of Health grants HL083947 (M.J.I., N.C.H.), HL46943 (M.J.I.), AR55819 (D.P.C.), DK082424 (T.B.C.), and CTSA RR024150 (Mayo Clinic), and by Mayo Clinic Research Subcommittee Early Career Development Supplement (T.B.C.) and American Heart Association grant 2170087 (E.C.H.).

Disclosures
None.

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Hypertension. published online January 17, 2011;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Relationship between muscle sympathetic nerve activity and aortic wave reflection characteristics in young men and women

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Supplementary Data Analysis

Data were collected at 240Hz, stored on a computer and analyzed off-line with signal processing software (WinDaq, DATAQ Instruments, Akron, OH). Mean arterial pressure (MAP) was calculated as the time integral over the pulse pressure. Cardiac output was calculated as the average stroke volume measured over a 5 minute period multiplied by the heart rate measured over the same time period. Total peripheral vascular resistance was calculated as MAP/cardiac output. Mean arterial blood pressure, heart rate, stroke volume, cardiac output, TPR and MSNA were averaged from the last 5 minutes of the 15 minute rest period.

Sympathetic bursts in the integrated neurogram were identified by a custom-manufactured semi-automated analysis program<sup>1</sup>,<sup>2</sup>; burst identification was controlled visually by a single investigator (ECH). The program then compensated for baroreflex latency and associated each sympathetic burst with the appropriate cardiac cycle. MSNA was analyzed and expressed as both burst incidence (bursts 100 heartbeats<sup>1</sup>) and frequency (bursts min<sup>1</sup>). All relationships between MSNA, expressed as both burst incidence and frequency, and aortic wave reflection characteristics are presented in Table 3. For simplicity, only the relationships between burst incidence and aortic wave reflection characteristics are presented in the text of the results section. All pulse wave analysis variables were recorded and analyzed by a single investigator (DPC) and are reported as the mean of two applanation tonometry measurements for each individual. To control for the potential influence of body height on aortic wave reflection hemodynamics (AI<sub>x</sub>, AG, and E<sub>wa</sub>), each index was scaled for body height (index/body height).

Supplementary References


Figure S1. Typical high-fidelity derived ascending aorta pressure waveform with pulse wave analysis components. $P_s$, aortic systolic pressure; $P_d$, aortic diastolic pressure; $P_i$, inflection pressure where incident and reflected waves merge; $\Delta t_{\text{rt}}$, round trip travel time of reflected pressure wave to peripheral reflecting sites and back to heart; $\Delta t_s$, systolic duration of the reflected wave; ED, ejection duration. Wasted energy ($E_w$) is the energy or force the left ventricle must generate to overcome the late systolic augmented pressure due to wave reflection. Augmented pressure (AG) is defined as $P_s - P_i$. 