Aortic Input Impedance Increases With Age in Healthy Men and Women

Luciano Mazzaro, Stephen J. Almasi, Robin Shandas, Douglas R. Seals, Phillip E. Gates

Abstract—Aortic input impedance represents the hydraulic load presented by the systemic circulation to the left ventricle of the heart and is increased in patients with cardiovascular disease. Aging is a strong independent risk factor for cardiovascular disease and could exert this effect partly through an increase in modulus of aortic input impedance. We used a novel noninvasive technique to determine aortic input impedance in 71 healthy men and women aged 20 to 69 years. We found that the aortic input impedance spectrum was shifted rightward with advancing age, characterized by a 37% increase in the frequency of the minimum modulus between the third and seventh decade (P<0.0001). The frequency of the minimum modulus correlated with age in all subjects (r=0.48; P<0.0001), in men (r=0.43; P<0.005), and in women (r=0.53; P=0.001). Although several physical characteristics were associated with the frequency of the minimum modulus (bivariate correlation), a regression model that included age and these physical characteristics showed that age was the only independent predictor of the frequency of the minimum modulus. We conclude that aortic input impedance increases with advancing age in healthy men and women. This increase in aortic input impedance may be an important mechanism by which age increases the risk of cardiovascular disease in humans. (Hypertension. 2005; 45:1101-1106.)

Key Words: aorta ■ applanation tonometry ■ Doppler echocardiography ■ hemodynamics ■ ventricular-vascular coupling

In humans, age-associated alterations to the structural and functional properties of the arterial system are a key antecedent to cardiovascular disease.1,2 Of particular importance is an increase in the stiffness of the large elastic arteries with advancing age and associated changes in arterial hemodynamics. One hemodynamic consequence of vascular stiffening is an increase in left ventricular afterload.3 Although ventricular afterload is commonly inferred from the measurement of peripheral artery blood pressure, the zenith and nadir of a peripheral artery pressure cycle provides limited physiological insight into the pulsatile and nonpulsatile loads encountered by the left ventricle. The aortic input impedance (AII) modulus, determined from central blood pressure and aortic blood flow measurements and defined as the ratio of pressure to flow harmonics, more comprehensively characterizes the hydraulic load presented by the entire arterial system to the left ventricle throughout ventricular ejection.2,3

Previously, AII has been measured in humans using invasive and noninvasive methods of blood pressure and blood flow. Invasive measurements of aortic blood flow and pressure require aortic catheterization and have been limited to small clinical cohorts,4,6,7 providing limited insight into the influence of healthy aging on AII. Noninvasive studies of AII have typically reported several parameters derived from the AII frequency spectrum, but there is no consensus regarding the most appropriate parameter. In a recent uncertainty analysis, we found that the frequency corresponding to the first minimum value of the AII (Fmin) was a more reliable and sensitive index of AII compared with characteristic impedance (unpublished observations). This is consistent with our findings in an in vitro mechanical model and invasive measurements in the pulmonary artery.8 To date, the effect of adult aging on AII using this noninvasive approach has not been reported. The purpose of the present study was to use this technique to determine, for the first time to our knowledge, AII in a cohort of healthy men and women over a broad age range. We also determined if AII was associated with arterial stiffness and specific physical characteristics of the subject cohort that are known to change with advancing age and that are associated with increased risk of cardiovascular disease.

Methods

Subjects

All subjects were rigorously screened for cardiovascular disease, diabetes, and hyperthyroidism as described previously.9-11 Post-
Subject Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SEM (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass, kg</td>
<td>71±2</td>
</tr>
<tr>
<td>Total body fat, %</td>
<td>25±1</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>53±1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24±1</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.82±0.01</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173±1</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>107±1</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>64±1</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>79±1</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>44±1</td>
</tr>
<tr>
<td>Physical activity, met/h/wk</td>
<td>59±6</td>
</tr>
<tr>
<td>VO2,max, mL·kg·min⁻¹</td>
<td>42±1</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L mg/dL</td>
<td>4.8±0.1 187±4</td>
</tr>
<tr>
<td>HDL, mmol/L mg/dL</td>
<td>1.4±0.1 55±2</td>
</tr>
<tr>
<td>Triglycerides, mmol/L mg/dL</td>
<td>1.1±0.1 94±6</td>
</tr>
<tr>
<td>LDL, mmol/L mg/dL</td>
<td>2.9±0.1 113±4</td>
</tr>
<tr>
<td>Glucose, mmol/L mg/dL</td>
<td>5.0±0.1 89±1</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; SEM, standard error of mean.

menopausal women were included irrespective of hormone replacement therapy and eumenorrheic women were studied during the menstrual cycle early follicular phase (days 3 to 8). Subjects did not take part in regular physical activity, were not taking medication, did not smoke, had no history of alcohol abuse, and had not experienced illness or significant weight loss in the previous 2 months. Of 95 subjects screened, 71 healthy men and women (n=37/34, respectively) aged 20 to 69 years met the inclusion criteria. Subject characteristics are shown in the Table. The Human Research Committee of the University of Colorado at Boulder approved the study and all procedures, and volunteers gave their written informed consent before participation.

Central Arterial Blood Pressure

The central blood pressure waveform was obtained from the right common carotid artery and used as a surrogate of aortic blood pressure. The waveform was recorded using planimetric tonometry (TCB-500; Millar) and calibrated using the right brachial artery. This procedure has been validated previously as a noninvasive measure of central blood pressure and the technique is well-established in our laboratory. With the subject in a supine position, ∼30 blood pressure cycles were recorded from the right common carotid and right brachial arteries after a constant baseline had been established over a 10-second period. The blood pressure waveforms were digitized and stored with a concurrent ECG signal on a personal computer using a digital physiological recorder (DI-730-USB; Datua Instruments; 14-bit resolution, 100-Hz sampling rate). The brachial blood pressure waveform was assigned systolic and diastolic values from sphygmomanometric blood pressure readings and used to calculate mean brachial blood pressure by numerical integration. The carotid blood pressure waveform was then calibrated using the mean and diastolic brachial pressures.

Ascending Aortic Blood Flow

Ultrasound echocardiography was used to obtain ascending aortic blood flow with a 3.25-MHz mechanical annular array transducer (CFM 800; VingMed Sound A/S). The transducer was placed in an apical long axis view with the subject in the left lateral decubitus position, and blood flow was recorded using low-pulsed repetition Doppler (pulse repetition frequency = 4 KHz). The Doppler sample volume was located immediately superior to the aortic valve leaflets within the centerline of the vessel. Blood flow velocity was recorded from an average of 15 cardiac cycles. The wall filter was minimized to obtain complete Doppler envelopes with a well-defined baseline. Using EchODisp software (GE Medical Systems Inc) the digital maximum frequency envelope of the Doppler spectrogram at 10-ms increments was extracted and saved with the corresponding ECG segment. Internal diameter of the aortic root was obtained using M-mode imaging from a parasternal long-axis view. Finally, aortic blood flow was calculated from Doppler blood flow velocity and internal aortic diameter.

Estimation of Aortic Input Impedance Modulus

All was derived from frequency domain analysis of central blood pressure and central blood flow waveforms. The AII modulus is defined as the ratio of pulsatile blood pressure to pulsatile blood flow at the aortic root and characterizes the properties of the systemic circulation. Because pressure and flow waveforms were recorded from different sites, the phase lag between the waveforms was corrected by aligning the foot of the pressure wave with the onset of the aortic flow wave.

Use of Fmin as an Index of AII Modulus

With greater AII, the AII modulus spectrum, and therefore the Fmin, is shifted rightwards. We therefore used Fmin as an index of the AII modulus spectrum for statistical analyses. Fmin was determined from the AII modulus spectrum and found using an algorithm in the Matlab programming environment. Although characteristic impedance can also be calculated from the average modulus of all the harmonics >2 Hz or above Fmin, we chose not to use this measurement as an index of AII because it is susceptible to large uncertainty content in the high-frequency harmonics of the AII spectrum, and it can be inaccurate when calculated from data where the minimum frequency is reached at higher frequencies.

Arterial Stiffness

Carotid augmentation index was used as an index of arterial stiffness and calculated from the tonometric carotid blood pressure waveform as described previously. Briefly, the inflection point in the forward wave, caused by reflection from the periphery, was identified, and ΔP was calculated as peak pressure minus the pressure at the inflection point. Augmentation index was calculated as ΔP/pulse pressure and expressed as a percentage of pulse pressure.

Other Measurements

Blood chemistries, body composition, maximal aerobic capacity, habitual physical activity, and brachial artery blood pressure were determined using standard techniques as described in our laboratory previously.

Statistical Analyses

All statistical analyses were conducted using SPSS for Macintosh (SPSS 11; SPSS). To determine main effects, we used 1-way ANOVA with subjects grouped by decade of age. Regression analysis was used to determine if age predicted Fmin and a regression model that included specific physical characteristics and age was used to determine which variables predicted Fmin. From the regression model, part (semipartial) correlation coefficients were used to determine the independent contributions of each variable to Fmin. Pearson r was used for all bivariate correlation analysis.
Results
With advancing age the AII modulus was shifted rightward, characterized by an increase in Fmin. When subjects were grouped by decade, 1-way ANOVA showed that Fmin was significantly increased with age (P<0.0001; Figure 1) and was 37% higher in subjects in their seventh decade compared with those in their third decade. Age significantly correlated with Fmin in the pooled group (Figure 2A; r=0.48; P<0.0001) and regression analysis showed that age was a significant predictor of Fmin (R²=0.23; P<0.0001). When subjects were analyzed according to sex, age correlated with Fmin in both men (Figure 2B; r=0.43; P=0.004) and women (Figure 2C; r=0.53; P=0.001), and regression analysis revealed that age predicted Fmin in men (R²=0.19; P=0.008) and women (R²=0.28; P=0.001).

When subjects were grouped by decade, arterial stiffness was increased with age in the entire cohort (P<0.0001), in men (P<0.0001), and in women (P=0.02). Age was associated with arterial stiffness in the entire cohort (Figure 3A), in men (r=0.68, P<0.0001), and in women (r=0.53, P=0.001). Fmin was also associated with arterial stiffness in the entire cohort (Figure 3B), in men (r=0.34, P=0.02), and in women (r=0.47, P=0.003).

In the entire cohort, Fmin was positively associated with percent body fat (r=0.30; P=0.006), fasting triglycerides (r=0.28; P=0.01), and diastolic blood pressure (r=0.21; P=0.04), and was negatively associated with maximal aerobic capacity (r=−0.33; P=0.02). A regression model that included these physical characteristics and age significantly predicted Fmin (R²=0.27; P=0.01), but age was the only independent predictor of Fmin (part correlation=0.33; P=0.003).

Discussion
The present study is the first to characterize the decade-by-decade change in left ventricular afterload caused by changes in AII in healthy humans over a broad age range and has provided 4 primary novel findings. First, our results indicate that AII increases gradually from the third to the fifth decade of life but is markedly higher in the sixth and seventh decades. Second, AII was similarly increased with age in both healthy men and women. Third, although several physical characteristics correlated with AII, regression analysis showed that age was the only factor that independently predicted AII. Finally, to our knowledge, this is the first study to show an association between AII and large artery stiffness in healthy adults.

Age and AII
Cardiovascular aging is associated with stiffening of the large elastic arteries, augmented systolic blood pressure caused by early wave reflection, and an increase in the mass of blood above the aortic valve caused by widening of the aortic root. In combination, these factors are thought to increase AII, increasing afterload throughout systole, and thus increasing the amount of work performed by the left ventricle to eject blood. Despite this assertion, evidence of an increase in AII in healthy, unmedicated, unseeded humans is limited. Our data are
consistent with reports of increased AII in older adults\textsuperscript{5–7,14–17} and extend these findings by showing, for the first time to our knowledge, per decade changes in AII. These novel data indicate that age has only small effects on AII until the sixth decade, after which AII increases abruptly and remains elevated into the seventh decade. The marked rightward shift in AII modulus in older adults, characterized by an increase in F\textsubscript{min}, is consistent with the idea of a shift in energy to the low-frequency harmonics.\textsuperscript{16} Because most of the energy of the left ventricular ejection wave is contained in the low-frequency range, greater ventricular power is needed to overcome this additional energy content in the AII modulus to maintain ventricular–vascular coupling and adequate cardiac output.\textsuperscript{16} This increase in AII has been postulated to contribute to the age-associated increase in left ventricular mass, diastolic dysfunction, and risk of heart failure.\textsuperscript{18–20}

However, more research is needed to determine whether the age-associated increase in AII is mechanistically linked to left ventricular aging, heart disease, and heart failure, or whether this reflects an independent aging process in adjacent areas of the cardiovascular system.

The age-associated increase in AII is thought to be mediated in part by stiffening of the large elastic arteries. Consistent with this, we found that augmentation index was increased with age and was associated with AII in men and women. However, in addition to large artery stiffening, AII is increased as a result of earlier wave reflection and by an increased hydraulic load caused by aortic root widening. The relative contribution of these factors to the age-associated increase in AII is unclear and controversial.\textsuperscript{21,22} Moreover, the left ventricle may increase its mass and perhaps exaggerate pump function independently of large-artery stiffening.\textsuperscript{23} Our finding of an age-associated increase in AII and alteration to ventricular–vascular coupling across decades highlights the need for greater understanding of the physiological and mechanical changes to the cardiovascular system with adult aging and their associations with cardiovascular disease morbidity and mortality.

Inspection of the age–F\textsubscript{min} scatterplot reveals a tendency for greater heterogeneity among subjects in the sixth and seventh decades. This suggests that some individuals maintain AII at levels comparable to younger and middle-aged subjects, whereas others have much higher values. Whether this apparent predisposition to increase AII with age increases vulnerability to future cardiovascular disease is currently unknown. Longitudinal studies are needed to determine the importance of age-associated increases in AII to the progression of cardiovascular diseases and whether this can be modified through lifestyle\textsuperscript{13} or pharmacological interventions.\textsuperscript{24}

**Sex and AII**

In a previous sex comparison study, noninvasive input and characteristic impedance were higher in the oldest age tertile in women compared with men.\textsuperscript{25} The authors did not report a statistical analysis of the effect of age on impedance within each sex, but the data indicate an age-associated increase in input and characteristic impedance in women but not in men. This is in contrast to the present findings in which AII increased in both sexes with age. Moreover, our regression analyses showed that age was a strong predictor of AII in men and women. The discrepancy between these data may be explained by differences in the way AII was derived based on our analysis of measurement uncertainty from invasive, noninvasive, and in vitro measurements;\textsuperscript{8} F\textsubscript{min} was the best index of AII, whereas higher-frequency harmonics used to calculate characteristic impedance have a much greater uncertainty. The lower variability in F\textsubscript{min} may have allowed us to detect the age-related increase in F\textsubscript{min} in men.

Although estrogen may have some protective effects against cardiovascular disease in premenopausal women, the present study suggests that the increase in AII with age is similar between men and women. Consistent with this finding, the age-associated increase in systolic blood pressure also is similar in men and women across this age range.\textsuperscript{1,26} The Baltimore Longitudinal Study on Aging has shown that aortic root diameter (ultrasound), arterial stiffness (pulse wave velocity), and the augmentation of blood pressure mediated by early wave reflection (augmentation index) are increased with age and show similar correlations with age in both men and women.\textsuperscript{1} All of these factors likely contribute to an increased AII and may explain the similarity in the present study between the men and women with respect to the age-associated increase in AII.

We should emphasize that estrogen-deficient postmenopausal women and those using hormone replacement therapy
were included in the subject cohort in the present study to maintain a representative sample. Although it is possible that the inclusion of both of these groups of postmenopausal females may have added variability to our results (this cannot be determined with the present sample size), any effect would have acted only to weaken the association of AII with age. We were able to show a significant age related increase in AII despite any such potential influence. Nevertheless, the influence of hormone status on AII in postmenopausal women clearly is an important question to be addressed in future studies.

AII and Physical Characteristics
Several subject characteristics correlated with AII, suggesting a role in the age-associated increase in AII. However, regression analysis indicated that age was the only significant independent predictor of AII. Although these analyses may have benefited from a larger sample size, this finding demonstrates the profound effect of aging on the cardiovascular system and highlights the need to identify the mechanisms that underlie cardiovascular aging per se.

Recent studies have highlighted the influence of body fatness on arterial stiffness and left ventricular structure and function. Body fatness correlated with AII in the present study but did not predict AII independently of age. However, our cohort of healthy men and women were not obese and average body mass index was in a normal range, perhaps reducing our ability to identify an influence of body fatness on AII. Clearly, determining the effect of body fatness on AII is an important goal of future research in this area given the current overweight/obesity epidemic and the established negative influence of obesity on cardiovascular health.

Invasive methods to determine AII present a high subject burden, cannot ethically be performed in large numbers of healthy subjects, and require sedation that may affect blood pressure and blood flow. To overcome these limitations, we used noninvasive procedures that have been validated previously and that are well-established in our laboratory. However, this approach has a number of limitations. Noise can be introduced to applanation tonometry and Doppler aortic blood flow signals are affected by user skill and ease/difficulty of data acquisition between subjects. This approach also requires the assumption that the noninvasively obtained carotid blood pressure waveform is a good estimate of the aortic blood pressure waveform, as established previously. The use of noninvasive measurements also means that central blood pressure and central blood flow cannot be obtained simultaneously. However, manual alignment of the foot of the blood pressure waveform with the onset of aortic blood flow overcomes this problem. Moreover, alignment of cardiac cycles in the time domain does not significantly affect the frequency domain based AII calculations. A better frequency resolution may have allowed us to more accurately determine $F_{\text{min}}$. However, our frequency resolution was comparable to previous studies and was sufficient to detect a main effect of age in our subject cohort.

The study was conducted on 71 carefully screened, unmedicated, inactive adults. Although larger subject numbers strengthen cross-sectional studies, our cohort was sufficient to establish a statistically significant increase in AII with advancing age, addressing the primary purpose of the study. To facilitate further research in this area with more precise measurements, technological developments should reduce the dependence on user skill to obtain noninvasive central blood pressure measurements. Digital output of blood pressure and blood flow signals with access to raw Doppler data also are needed for frequency domain analysis.

Conclusion
AII was increased with advancing age in a group of carefully screened healthy men and women with a broad age range. The increase in AII was similar between men and women. When specific physical characteristics were considered, only age independently predicted AII. This study shows, for the first time to our knowledge, that $F_{\text{min}}$ is a sensitive index of the age-related change in AII.

Perspectives
Aging is an integral part of the pathophysiology of cardiovascular disease, which, along with cancer, is the leading cause of death in the United States. Aortic input impedance characterizes the mechanical properties of the entire arterial tree and provides insight into ventricular–vascular coupling. We found that AII was increased with age in men and women and was particularly high in the sixth and seventh decades of life. This increase in AII increases ventricular afterload, increasing the work required for ventricular–vascular coupling and the maintenance of cardiac output. The contribution of AII to the pathophysiology of cardiovascular diseases is unknown but greater AII has been postulated to be associated with increased left ventricular mass and altered diastolic function in older adults. Further research is needed to understand the association of AII with cardiovascular disease morbidity and mortality, the underlying mechanisms of the age-associated increase in AII, and strategies to reduce AII with aging.

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References


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