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Gender-Related Differences in the Central Arterial Pressure Waveform

CHRISTOPHER S. HAYWARD, BMEDSC, MBBS, FRACP, RAYMOND P. KELLY, MD, FRACP, FACC

Sydney, Australia

Objectives. **This study investigated the effect of age and gender on central arterial hemodynamic variables derived from noninvasive tonometric carotid pressure waveforms.**

Background. **Women have a greater age-related increase in left ventricular (LV) mass than do men and are more likely to experience symptomatic heart failure after infarction despite their higher ejection fraction. In studies of these changes, ventricular afterload is incompletely defined by brachial blood pressure (BP) measurements. We hypothesized that there exist gender differences in pulsatile vascular load, as revealed by pressure waveform analysis, which may produce suboptimal afterload conditions in women.**

Methods. **Data from 350 healthy normotensive subjects (187 female) aged 2 to 81 years were analyzed in decade groups. Augmentation index (AIx, the difference between early and late pressure peaks divided by pulse pressure) was used as an index of pulsatile afterload, and the ratio of diastolic to systolic pressure-time integral gave a subendocardial viability index. Heart rate, BP, ejection duration and maximal rate of pressure rise (dP/dt_{max}) were also determined.**

Results. **Male subjects had a slightly higher systolic pressure until age 50. Female subjects had higher systolic pressure augmentation after the 1st decade, a difference that was significant after age 30 ($p < 0.005$ for each decade). In both males and females there was a strong age dependence for AIx ($r = 0.77$, $p < 0.001$ for females, $r = 0.66$, $p < 0.001$ for males). Although males had a larger body size and higher systolic pressure, systolic pressure-time integral was similar in males and females across all age groups. Diastolic pressure-time integral was consistently lower in females because of their shorter diastolic period. Subendocardial viability index was lower in females across the entire group. Differences in stature and heart rate may contribute to these findings.**

Conclusions. **These new data may help to explain previous findings in women of an age-related increase in LV mass and excess symptomatic heart failure that are not explained by differences in brachial BP.**

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It is known (1) that women have significantly lower morbidity and mortality from ischemic heart disease than do men until after the age of the menopause. However, they have been found (2–4) to undergo age-related incremental left ventricular hypertrophy (LVH) to a greater extent than men. Women also have excess symptomatic heart failure after myocardial infarction despite smaller infarctions or better maintained left ventricular (LV) ejection fractions (5–8) than those of similarly aged men. This gender difference is not completely explained by risk factors. Although women in the SOLVD registry (9) had less ischemic disease than did men, they still had a significantly higher incidence of mortality or hospital admission due to heart failure. Postmyocardial LV rupture rates are disproportionately high in women, accounting for up to half of reported cases (10–12), despite the lower overall incidence of coronary artery disease in women. It has been noted (13,14) that women form the great majority of patients with hypertensive hypertrophic cardiomyopathy. These data suggest that women have inappropriately high vascular loading conditions compared with those in men.

With aging there is an increase in LV pulsatile afterload due to changes in the vascular tree (15). This is attributed to a decrease in large arterial compliance with age (16). Previous studies (17,18) have shown that the central (carotid) arterial pressure waveform also changes in a continuous fashion with age. The age-related changes in carotid waveform are explicable by increased pulsatile load and quantified by the augmentation index (AIx), the ratio of the augmented systolic pressure to the pulse pressure in central arteries such as the carotid and aorta (18,19). Patterns of pressure waveforms have been correlated with aortic impedance (19), an accurate measure of pulsatile vascular afterload (15,20). Conditions in which the pulsatile load on the LV is increased, such as aging or hypertension, are those where AIx is higher (15,21). Indeed AIx correlates with the degree of LVH in humans both at normotensive and hypertensive levels (22,23). Furthermore, a late peaking systolic pressure (and thus higher AIx) causes more LVH than does an early peak (and so lower AIx) even for similar systolic pressures (24).

Because of the previously observed gender-related differences in the effect of age on LV structure and on symptomatic

From the Cardiology Department, St. Vincent's Hospital, Sydney, New South Wales, Australia. Dr. Hayward is the recipient of a Postgraduate Medical Research Scholarship from the National Health and Medical Research Council of Australia, Canberra, Australian Capital Territory, Australia.

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Address for correspondence: Dr. Raymond Kelly, Cardiology Department, St. Vincent's Hospital, Victoria Street, Darlinghurst, New South Wales 2010, Australia. E-mail: rkelly%prvnw1@svh.unsw.edu.au.

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Abbreviations and Acronyms

AIx = augmentation index
BP = blood pressure
dP/dt_{max} = maximal rate of pressure rise
DPTI = diastolic pressure-time integral
LV = left ventricle (ventricular)
LVH = left ventricular hypertrophy
SVI = subendocardial viability index
TTI = tension-time index

heart failure, we hypothesized that there are gender-related differences in pulsatile vascular load as indicated by AIx and other features of the central arterial pressure waveform.

Methods

Patients. Four hundred seven subjects ranging in age from 2 to 81 years were recruited from a community-based population and excluded if they had a history of valvular heart disease or treated heart disease. Of these subjects, 82 were current smokers and 28 were receiving monotherapy for hypertension. Subjects with a resting tachycardia (heart rate >110 beats/min) or hypertension (blood pressure [BP] ≤160/95 mm Hg) were excluded from analysis. BP or heart rate criteria excluded 32 subjects from further analysis; a similar number of male and female subjects (17 and 15, respectively) were excluded on this basis. Twenty-five additional subjects were excluded because of incomplete data. The remaining 350 healthy subjects form the basis of this report. This study is a subset of patients previously reported (18). Subjects were classified into age decades for analysis. Demographic details for this group are shown in Table 1.

Data acquisition. Carotid artery pressure waveforms were obtained by applanation tonometry (Millar Instruments), which has previously been validated as an accurate indicator of changes in aortic pressure waveform (25,26). Eight seconds of continuous pulses were recorded for each subject. Each recording was ensemble-averaged, giving an averaged waveform for each subject. This averaged waveform was then calibrated to the arithmetic mean (pulse pressure + 1/3 diastolic BP) and diastolic BP of the brachial sphygmomanometric BP obtained at the time of pulse recording as has been used previously (27). We used this technique because it was previously found (28,29) that the mean and diastolic BP remain almost constant during pressure waveform propagation to the periphery. Pressure-dependent variables characterizing the carotid waveform were derived from this calibrated waveform.

Measurements. Averaged waveforms were analyzed by using a customized semiautomated waveform analysis program written in ASYST (Macmillan Software Company). Definition of the timing and magnitude of systolic peaks was based on derivatives of the pressure waveform depending on the type of waveform "A" or "C" (19), as previously described (Fig. 1)

Table 1. Demographics of Study Subjects

Decade	Subjects (no.)	Age (yr)	Height (m)	Weight (kg)	Brachial SBP (mm Hg)	Carotid SBP (mm Hg)	DBP (mm Hg)	Carotid PP (mm Hg)	Heart Rate (beats/min)
1									
M	23	8.0 (2.0)	1.29 (0.12)	27.2 (6.4)	101.9 (12.9)	87.2 (12.1)	60.0 (8.4)	27.2 (7.6)	89.0 (12.4)
F	18	8.4 (1.3)	1.33 (0.10)	30.9 (6.2)	96.4 (11.0)	84.2 (10.4)	62.1 (8.0)	22.1 (5.8)*	92.8 (10.1)
2									
M	37	14.2 (2.3)	1.66 (0.13)	55.0 (12.8)	122.2 (15.6)	107.8 (15.0)	68.0 (8.2)	39.8 (10.0)	82.6 (11.5)
F	39	15.3 (2.7)	1.60 (0.10)*	52.8 (11.5)	118.6 (14.6)	104.7 (14.1)	71.2 (9.4)	33.5 (8.9)†	90.6 (9.8)†
3									
M	18	25.2 (3.1)	1.78 (0.06)	77.1 (11.7)	136.7 (12.9)	118.7 (10.9)	77.9 (6.9)	40.9 (8.7)	79.8 (11.8)
F	23	25.9 (3.1)	1.65 (0.08)‡	57.2 (9.4)‡	119.1 (10.7)‡	104.6 (9.1)‡	73.3 (8.3)	31.3 (5.9)‡	85.5 (14.0)
4									
M	32	35.6 (3.4)	1.78 (0.09)	80.9 (13.7)	129.7 (11.0)	115.7 (11.8)	77.7 (7.5)	38.0 (7.9)	73.4 (11.8)
F	30	36.0 (3.0)	1.65 (0.06)‡	61.6 (10.9)‡	120.6 (11.3)†	106.6 (10.7)†	75.9 (8.9)	30.8 (6.9)‡	82.5 (9.1)†
5									
M	17	44.2 (2.9)	1.75 (0.06)	77.7 (10.4)	133.4 (14.0)	117.9 (11.0)	81.6 (6.4)	36.3 (8.9)	77.8 (13.2)
F	20	44.8 (3.2)	1.62 (0.06)‡	60.4 (9.5)‡	122.9 (13.6)*	109.9 (12.3)*	74.9 (6.6)†	34.0 (8.3)	80.1 (11.7)
6									
M	16	56.2 (2.9)	1.77 (0.07)	80.4 (8.0)	129.2 (9.0)	116.4 (7.4)	80.0 (6.3)	36.4 (5.3)	73.6 (9.6)
F	28	56.1 (2.8)	1.64 (0.07)‡	65.9 (11.4)‡	130.4 (16.0)	116.1 (13.8)	79.7 (9.4)	36.4 (8.9)	82.2 (9.4)†
7+									
M	20	67.8 (5.2)	1.74 (0.08)	74.5 (11.0)	136.5 (15.2)	121.4 (12.4)	77.4 (7.8)	44.0 (11.4)	73.2 (10.3)
F	29	67.9 (5.8)	1.59 (0.06)‡	60.5 (11.5)‡	137.0 (12.1)	121.1 (12.1)	75.7 (8.8)	45.4 (10.7)	79.1 (10.5)
All									
M	163	32.6 (20.1)	1.68 (0.19)	65.9 (21.7)	126.0 (17.3)	111.2 (16.1)	73.6 (10.4)	37.6 (9.9)	78.8 (12.9)
F	187	36.7 (20.4)	1.59 (0.12)‡	56.6 (14.1)‡	121.9 (16.9)*	107.7 (15.5)*	73.7 (9.9)	34.0 (10.2)†	84.7 (11.6)‡

*$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$. Unless otherwise indicated, data are expressed as mean value (±SD). DBP = diastolic blood pressure; F = female; M = male; PP = pulse pressure; SBP = systolic blood pressure.

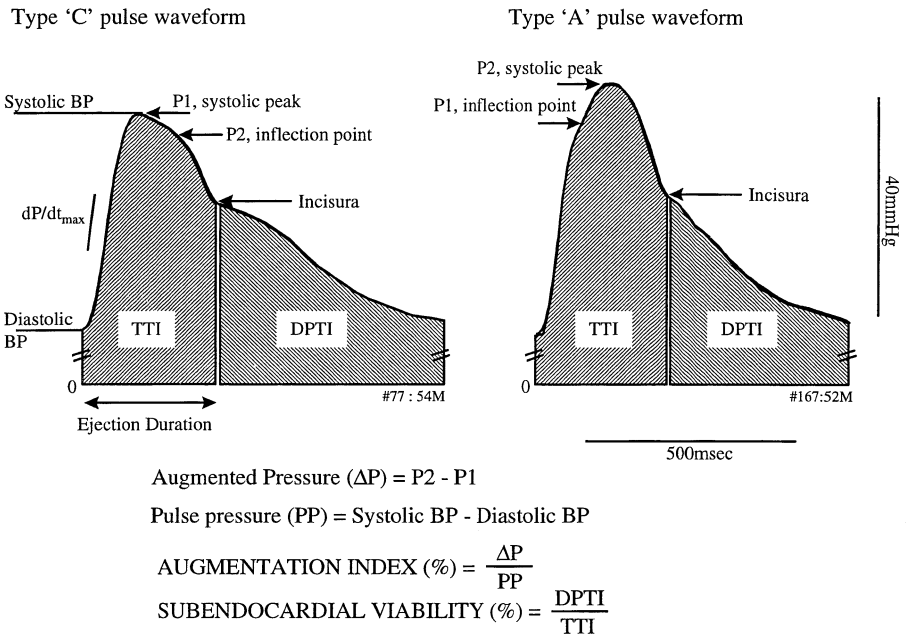


Figure 1. Definitions of derived variables as seen for an individual carotid waveform according to the classification of Murgo et al. (19). Type "C" is defined by a dominant initial pressure peak with an inflection on the pressure waveform downstroke, whereas type "A" is defined by a dominant late systolic peak and a shoulder with inflection on the upstroke. Type "B" is intermediate, with no obvious inflection. Augmentation index is calculated by the ratio of the difference between the pressure at the respective peaks or inflections (P2 − P1) divided by the pulse pressure (Systolic BP − Diastolic BP). Tension-time index (TTI) is the pressure-time integral during systole, and diastolic pressure-time index (DPTI) is the corresponding integral in diastole. Subendocardial viability is the ratio of DPTI to TTI. Schematic for dP/dt_{max} is shown.

(18). This allowed the features of the waveform to be characterized, including maximal rate of pressure rise (dP/dt_{max}), pressure at inflection (type A) or peak (type C) (P1), pressure at second peak (type A) or inflection (type C) (P2), time of first (TP1) and second (TP2) systolic peak, augmented pressure (AugP = P2 − P1), and ejection duration (Fig. 1). AIx was defined as the ratio of augmented pressure to the pulse pressure (AugP/[Central systolic BP − Diastolic BP]) (Fig. 1) (18,19,22,23).

Further derived indexes of the arterial pulse waveform were also studied. As an index of systolic stress, the tension-time index (TTI) of Sarnoff et al. (30) was calculated from the systolic pressure-time integral. LV end-diastolic pressure was assumed to be zero for all subjects as left atrial or pulmonary pressures were not available. The diastolic pressure-time integral (DPTI), and the ratio of the two, subendocardial viability index (SVI) were also determined (30–32) (Fig. 1).

After individual waveforms had been characterized, each subject's averaged waveform was then allocated to the appropriate decade (0 to 10 years to decade 1, 11 to 20 years to decade 2 and so on) for each gender. Representative decade waveforms were then obtained by ensemble averaging according to each age decade and gender group by aligning the foot of the upstroke for each waveform. The waveforms were averaged over the 1st 545 ms (which corresponds to the cutoff heart rate of 110/min), to ensure waveform data points for every subject.

Statistics. Unpaired *t* tests were used for gender comparison of individual demographic variables in each decade. Multiple linear regression models for AIx, SVI and dP/dt_{max} were derived by using backward regression analysis with cutoff of $p < 0.05$ for inclusion and $p > 0.10$ for exclusion from the final model (SPSS for Windows 6.1, SPSS Inc.). Multiple regression analyses are reported for the entire study group (n = 350) as well as for adults only (age ≥18 years, n = 245). Gender was coded as male = 1 and female = 2. Two-tailed significance was set at $p < 0.05$.

Results

The subjects studied were well distributed across each gender and age decade (Table 1). For the entire group, males were taller and heavier from the 3rd decade on. They also tended to have higher brachial and calculated carotid systolic BP between the ages of 20 and 50 years. Diastolic pressure differed only in the decade 41 to 50 years. Central pulse pressure was higher in younger males, although this difference disappeared from age 40 onward. Heart rate was higher in women in all decades ($p < 0.001$ for entire group).

There was a continuous change in the shape of the carotid arterial waveform with age in both genders (Fig. 2). Expressed quantitatively, there was a strong age dependence for AIx for both females ($r = 0.77$, $p < 0.001$) and males ($r = 0.66$, $p < 0.001$). Furthermore, the shape of the waveform in females differed consistently from that of the waveform in males. From the 4th decade on, the central arterial pulse waveform in women was characterized by a prominent secondary late systolic peak. In males, this late peak became dominant after the 5th decade but was of smaller magnitude than the late peak in women of a similar age. Expressing this gender difference quantitatively, females had a consistently higher AIx than did males after the 1st decade (Fig. 3). This difference was very significant ($p < 0.005$) from the 4th decade (that is, from age 30 onward). Differences in carotid pulse pressure also became insignificant after the 4th decade.

To determine the independent predictors of the change in

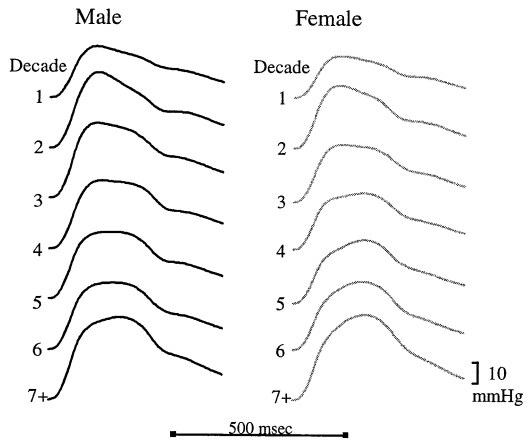
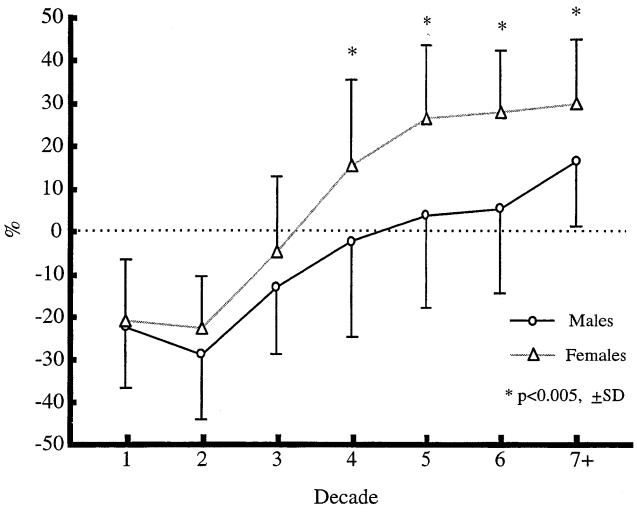


Figure 2. Calibrated averaged decade waveforms by gender (to scale).

AIx, a multiple linear regression model was derived for the entire group and for adult subjects (Table 2). Of the independent variables entered into the equation, gender, age, heart rate, mean BP, dP/dt_{max} and height all independently influenced AIx. Ejection duration and weight did not contribute to the final equation after accounting for these variables. This model was a good predictor of changes in AIx (adjusted $r^2 = 0.70$ for the entire study cohort or $r^2 = 0.60$ for adults; $p < 0.0001$ for both models). Results for the coefficients in the equation (Table 2) are expressed in clinically meaningful units of measurement to allow comparison of relative magnitude of change in AIx per unit change in each variable. Variables are displayed in order of magnitude of coefficient for the units shown. Female gender had a greater coefficient than did either 10 years of age or 10 mm Hg and was independent of concomitant differences in height, BP and heart rate. Ejection duration was excluded from the final model using backward regression, most likely because of its close correlation with heart rate ($r = 0.78$, $p < 0.001$). If heart rate was not included in the model, ejection duration remained an independent predictor of variation in AIx (coefficient 7.7 ± 0.4/10 ms). The remaining coefficients were similar to those shown in Table 2. Weight remained nonsignificant even when heart rate was not included in the model.

Figure 3. Augmentation index results for each decade.



Although males had higher brachial systolic BP than did females until the last two age decades (Table 1), TTI was surprisingly similar for all decades, (Fig. 4). This is explained by differences in the shape of the pressure waveform (Fig. 2) and heart rate. Primarily because of their faster heart rate, females had a consistently lower DPTI than did males for each decade. This difference remained significant from age 20 onward (Fig. 4). The ratio of these two variables, the SVI, reflecting relative diastolic perfusion to systolic work, was again consistently lower in women (Fig. 4). To account for differences in individual heart rates, a regression model was created (Table 3). Not surprisingly, heart rate was the dominant determinant of SVI as shown by the relative magnitude of regression coefficient. Even after accounting for heart rate, however, gender was still an independent predictor of SVI. dP/dt_{max}, BP, age and weight also contributed significantly to the variation in SVI, although to a lesser extent.

Discussion

This study shows that females differ significantly from males in central arterial pressure waveforms as assessed by carotid artery tonometry. This technique has been shown (25,26) to accurately reflect changes in aortic pressure waveform and, therefore, to be a valuable tool for examining central pressure hemodynamics. AIx was used as the primary end point in this study as it is an index of arterial pulsatile load and may therefore be helpful in explaining previously documented gender differences in LV mass (2–4).

Importance of the central arterial pressure waveform. Freis et al. (17) first noted the existence of two systolic maxima in their noninvasive study of the carotid waveform in 80 subjects. This observation was further invasively defined and correlated with aortic impedance measurements by Murgo and colleagues (19), who categorized waveforms into those with a shoulder on the upstroke (type A) with a late systolic peak; those with a shoulder or inflection on the downstroke (type C) with a dominant early peak; or intermediate (type B). The importance of this classification of the pressure waveform lies in the correlation with impedance, which is an accepted measure of external load placed on the ventricle by the vasculature (20). Kelly et al. (18) showed that the flow waveform changes with age to a lesser extent than does the pressure waveform, allowing inference of impedance changes to be made from pressure recordings alone. Type A pulses in the study of Murgo et al. were associated with increased fluctuation around characteristic impedance, indicating greater intensity of wave reflection (33) and, thus, increased pulsatile load. Previous studies (34,35) have shown the importance of impedance in affecting ventricular performance, although only relatively small studies (15) are possible with invasive measurements.

Table 2. Multiple Linear Regression Analysis Results With Augmentation Index as the Dependent Variable*

		All Subjects (2 to 81 yr) (n = 350)			Adults (≥18 yr) (n = 245)		
Variable	Units	Coefficient (SE)	p Value	R^2	Coefficient (SE)	p Value	R^2
Gender	Female	+11.6 (1.8)	< 0.0001	0.08	+13.0 (2.8)	< 0.0001	0.13
Mean BP	/10 mm Hg	+7.4 (1.0)	< 0.0001	0.15	+8.3 (1.1)	< 0.0001	0.03
Age	/10 yr	+7.0 (0.5)	< 0.0001	0.49	+4.8 (0.7)	< 0.0001	0.26
Heart rate	/10 beats/min	−6.9 (0.7)	< 0.0001	0.17	−7.1 (0.9)	< 0.0001	0.09
dP/dt	/100 mm Hg/s	−4.2 (0.6)	< 0.0001	0.03	−4.1 (0.7)	< 0.0001	0.09
Height	/10 cm	−3.7 (0.7)	< 0.0001	0.02	−5.7 (1.4)	< 0.0001	0.18
Ejection duration			0.73	0.12		0.13	0.13
Weight			0.51	0.06		0.79	0.06

*Adjusted R^2 value for entire study group, 0.70, $p < 0.0001$; for adult population, 0.60, $p < 0.0001$. R^2 values shown are for univariate analysis for each variable. Ejection duration and weight were not included in the final equation ($p > 0.05$) for either analysis. BP = blood pressure; dP/dt = rate of rise of pressure.

Previous studies using AIx. Several previous studies (17–19,36,37) have confirmed age-related changes in arterial pressure contour with age in apparently healthy persons. The current study confirmed age to be an important determinant for both genders ($r = 0.77$, $p < 0.001$ for females; $r = 0.66$, $p < 0.001$ for males). Differences in gender have been noted previously; however, previous studies (38) have been smaller and analyzed across wider age categories. Vaitkevicius and colleagues (36) found no difference in pressure augmentation between men and women. One reason may be the smaller number of subjects in their study, especially of women (50 subjects spread across 70 years). Nonetheless it is surprising that no difference was seen, given that in our study gender was the strongest determinant of augmentation both for the entire group and for adult subjects, independent of differences in other baseline variables (Table 2).

Determinants of systolic augmentation. The secondary peak in the central systolic pressure waveform has been attributed to wave reflection (19). A major determinant of intensity of wave reflection is the distance to reflecting sites. Previous investigators (38) have suggested that body height is a significant inverse determinant of augmentation due to earlier wave reflection. This is one factor that is significantly different between men and women from an early age (Table 1). We found a significant negative correlation between height and augmentation ($r = -0.42$ for subjects ≥18 years, $p < 0.0001$). This correlation existed for both men and women ($r = -0.29$, $p < 0.005$ and $r = -0.26$, $p < 0.005$, respectively). The importance of height can be seen in Figure 5, where subjects are from a single age decade (51 to 60 years). It can be seen in this decade that the higher augmentation in women is associated with their shorter stature. The important role of wave

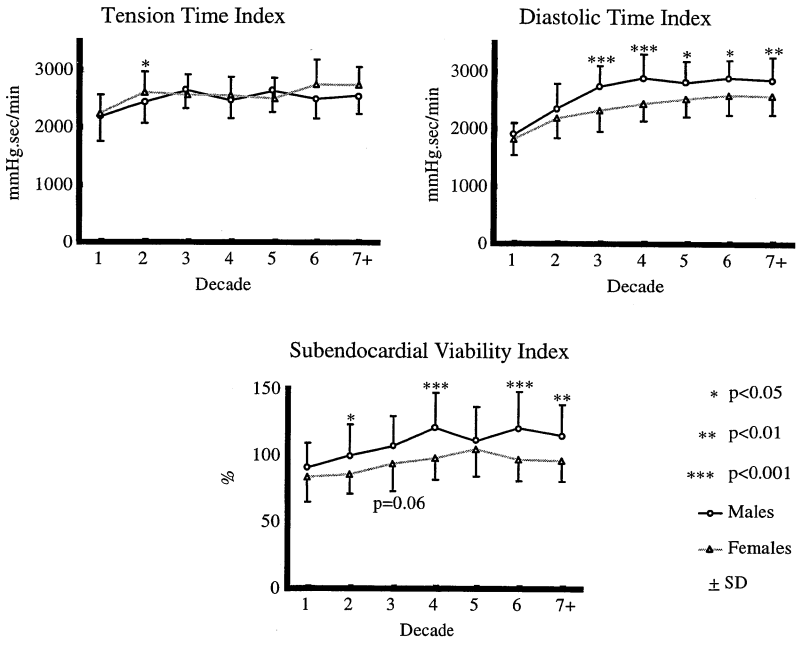


Figure 4. Tension-time (TTI) and diastolic pressure-time (DPTI) indexes for each decade. Subendocardial viability index (SVI, the ratio of DPTI to TTI) is also shown. Although males have a higher systolic BP, the TTI is similar across all ages. DPTI is consistently lower in females, yielding a consistently lower SVI.

Table 3. Multiple Linear Regression Analysis Results With Subendocardial Viability Index as the Dependent Variable

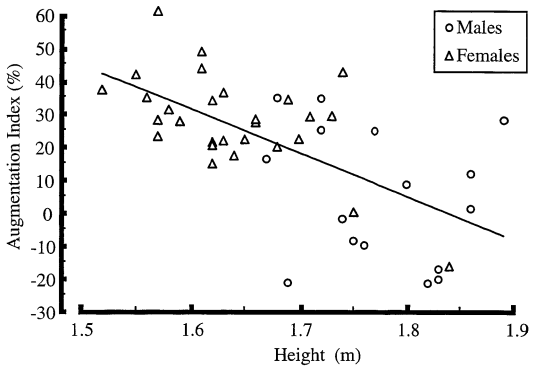
		All Subjects (2 to 81 yr) (n = 350)			Adults (≥18 yr) (n = 245)		
Variable	Units	Coefficient (SE)	p Value	R^2	Coefficient (SE)	p Value	R^2
Heart rate	/10 beats/min	−16.2 (0.4)	< 0.0001	0.81	−17.0 (0.6)	< 0.0001	0.78
Gender	Female	−5.2 (1.1)	< 0.0001	0.10	−4.1 (1.7)	0.015	0.15
dP/dt	/100 mm Hg/s	−2.9 (0.4)	< 0.0001	0.01	−3.3 (0.5)	< 0.0001	0.03
Mean BP	/10 mm Hg	+2.4 (0.6)	0.0001	0.02	+3.0 (0.8)	< 0.001	< 0.01
Age	/10 yr	−1.3 (0.3)	< 0.0001	0.06	−0.9 (0.4)	0.049	< 0.01
Weight	/10 kg	+1.2 (0.4)	0.0025	0.11	+1.5 (0.5)	0.006	0.07
Aug index	/10%		0.17	0.11	−0.8 (0.4)	0.031	0.03
Height			0.22	0.12		0.40	0.10

Adjusted R^2 value for both entire study group and adults, 0.85, $p < 0.0001$. R^2 values shown are for univariate analysis for each variable. Height was not included in the final equation ($p > 0.05$) in either analysis. Augmentation (Aug) index was included only in the adult analysis. Abbreviations as in Table 2.

reflection and pulsatile load on ventriculovascular interaction is shown in recent findings from the Cardiovascular Health Study (39), which found that short stature is associated with concentric LV remodeling.

Although the AIx itself has been suggested to be an index of decreased arterial stiffness with consequent early wave reflection (36), the prominence of the late systolic peak in women occurs at too early an age for that to be the sole mechanism. Laogun and Gosling (40) showed that women had significantly greater aortic compliance than men until after age 55 years. This gender and age difference has been further confirmed by Sonneson et al. (41) using a different noninvasive technique for the distal aorta. In a study of urban Chinese, Avolio et al. (16) found aging differences, but no gender differences, in pulse wave velocity. Karpanou and colleagues (42) found that menopause had a marked adverse effect on aortic root function in hypertensive women. In the current study we found that women had consistently higher pressure augmentation, even after the 1st decade. If arterial stiffness played a significant role in systolic augmentation, menopause might be expected to be associated with a further increase in augmentation. This was not seen in our study (Fig. 3). It seems likely, therefore, that the distance to reflecting sites was as important as actual arterial stiffness in this study. A further important contributor to arterial wave reflection is the reflection coefficient. Pharmacologic agents with similar hypotensive effect may have different effects on reflection coefficient and therefore wave reflection (43). Gender differences in reflection coefficient were not able to be assessed by this study.

Figure 5. Augmentation index versus height for a single decade (ages 51 to 60 years, n = 44). There is a strong relation with height (r^2 = 0.39, $p < 0.0001$). Equation shown with coefficient (standard error). Women in this age group can be seen to be shorter and have an associated higher augmentation index.



Augmentation Index (%) = - 132.4 (25.0)*Height (m) + 243.0 (42.4)

A change in pressure waveform contour could also be related to changes in cardiac ejection with a shift of stroke volume later into systole. Freis et al. (17) showed a close relation of the first systolic peak with the peak in aortic flow. This relation was subsequently confirmed by Kelly et al. (18) and underscores the importance of the interaction between cardiac ejection and vascular properties in the formation of the pressure pulse contour. Analysis of the determinants of carotid dP/dt_{max} (which corresponds with the rapid ejection phase) showed gender to remain significant even after accounting for individual central systolic BP (adjusted $r^2 = 0.41$, $p < 0.0001$ for equation, significant independent variables: systolic BP, $p < 0.0001$; gender, $p < 0.01$; and ejection duration, $p < 0.001$). Age was not a significant predictor of variability in dP/dt_{max}. In this study, female gender was associated with decreased carotid dP/dt_{max}. This finding is not accounted for by differences in BP, as both BP and gender independently contributed to carotid dP/dt_{max}. These results suggest that the gender differences also exist in cardiac ejection. This may be a further contributor to the gender differences in pressure wave contour independent of vascular factors (such as wave reflection) that do not affect the initial systolic pressure upstroke.

Subendocardial viability. The second important finding from this study is the significant gender difference in the ratio of DPTI to TTI. This ratio has been shown to correlate well with the ratio of subepicardial to subendocardial blood flow and represents an index of subendocardial viability (31,44). Although men had a significantly higher brachial systolic BP in the middle decades (Table 1), at no age was the TTI signifi-

cantly higher for men (Fig. 4). This occurred even though ejection duration was similar for each decade and for the group as a whole (male 323.5 ± 20.1 vs. females 321.9 ± 20.7 ms, p = 0.46). This further underlies the importance of considering not only the systolic pressure recording but also the pulse contour when assessing ventricular afterload. The gender difference in DPTI is not unexpected owing to the dependence of diastolic duration on heart rate and the faster heart rates of the women (Table 1).

Possible clinical implications of differences in AIx. Although casual BP has not been found (4,45) to correlate tightly with LV mass, some recent studies (22,23) have shown a good correlation between LV mass and AIx. A reason for this apparent anomaly may be the modulating effect of pulsatile as compared to mean vascular load as a significant impetus to myocyte hypertrophy. The gradual increase in LV mass with age in women (2–4) may, therefore, be considered an appropriate mechanism to normalize LV wall stress in the face of increased pulsatile load. Matsuzaki et al. (24) studied the effect of alterations in pulsatile load on LV mass by proximal and distal aortic banding in rats. Whereas both methods resulted in similar increases in systolic pressure, distal banding was associated with a late systolic peak in the aortic pressure waveform (type A waveform), and induced significantly greater LVH than did proximal aortic banding, which resulted in a type 'C' waveform. The differences were attributed to wave reflection returning late in systole in the distal banded aortas and therefore greater pulsatile load for the heart. Furthermore, the ability of pharmacologic agents to limit LVH in spontaneously hypertensive rats has been related (46) to their effect on pulsatile vascular afterload. Although hydralazine and zofenopril decreased systolic BP to a similar extent, hydralazine was associated with greater wave reflection, increased characteristic impedance and more LVH.

Other determinants of LV mass. LV mass has also been shown to vary significantly with body height, weight, heart rate and sympathetic activity. Men and women react differently to these variables (47). Whereas Marcus et al. (4) found that women have increased LV mass with age in univariate analysis, only weight remained significant in multivariate analysis. It has been suggested that gender differences in expression of LVH may be related to the modulating effect of estrogen on ventricular hypertrophy. Estrogen and its metabolites indeed have been shown (48–50) to have antiproliferative effects on vascular or ventricular smooth muscle. A difficulty with a hormonal explanation for gender differences in age-related LV mass increases is the lack of an apparent acceleration or deceleration in the degree of hypertrophy at the time of the menopause in women (2,3). The complexity of hemodynamic and genetic interaction was illustrated in recent work (51) showing significant gender differences in LV contractile gene expression in aortic banded rats.

Clinical implications of the SVI. It has been assumed that impaired large artery compliance, by increasing systolic load and decreasing diastolic pressure, would impair ventricular perfusion, which occurs predominantly in diastole (52). Although this rationale is theoretically sound, a recent study in open chest dogs by Saeki et al. (53) found that the increase in systolic work was adequately compensated for by increases in systolic coronary perfusion. This finding does not take into account the important issue of the faster heart rate in women, which had a dominant effect on SVI (Table 3). A possible clinical implication of the lower SVI is that in states of ischemia or increased work, such as may be found after myocardial infarction, women may be further predisposed to heart failure after infarction despite their typically smaller infarction (5–9). A lower SVI is of further significance in women because of their higher relative LV wall thickness.

Another possible clinical manifestation of the lower SVI in women is in the pathogenesis of syndrome X, which is predominantly found in women (54,55). Mechanisms proposed to explain the trial of chest pain, positive stress tests and normal coronary angiography include altered pain perception (56), coronary endothelial dysfunction (57) and the hypoestrogenic state in postmenopausal women (55). Although these help to explain symptoms, not all are able to explain the mechanism of regional hypoperfusion seen on nuclear cardiac scanning or electrocardiographic changes found on stress testing. Ferro et al. (58) found that diastolic perfusion time was important in determining ischemic threshold, both in patients with coronary disease and in those with syndrome X.

Study limitations. This study aimed to determine gender-related differences in hemodynamic variables derived from pressure waveforms. Although we do not have echocardiographic data to allow direct correlation of AIx with LV mass, previous studies have shown a good correlation between AIx and LVH. Gender-related cardiac ejection differences also cannot be determined from this study. Furthermore, without echocardiography, a small number of subjects with unrecognized valvular or myocardial disease may have been included. Notwithstanding these limitations, the current study shows a consistent gender difference in central arterial pressure waveforms across a wide spectrum of ages that has not been previously described in detail. The changes seen in central waveforms provide an explanation for the gender-related LV mass increase documented previously. A possible hemodynamic mechanism for the previously described, though unexplained, increase in heart failure in women after myocardial infarction and for symptomatic hypoperfusion in syndrome X is also discussed. Longitudinal and clinical outcome studies examining the effect and nature of central pressure waveforms are required for confirmation of the hypotheses generated by the current study.

Conclusions. Central arterial hemodynamics as assessed by carotid tonometry show significant gender-related differences in systolic pressure augmentation as well as in subendocardial ratio. These differences may be relevant in the adaptation of women to pressure overload states and may be involved in the genesis of LVH. The combination of hemodynamic load, higher relative wall thickness and lower subendocardial ratio in women may further help to explain their susceptibility to heart failure in states of cardiac stress.

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