Age-Specific Relationship of Aortic Pulse Wave Velocity With Left Ventricular Geometry and Function in Hypertension

Giuseppe Schillaci, Massimo R. Mannarino, Giacomo Pucci, Matteo Pirro, Johny Helou, Gianluca Savarese, Gaetano Vaudo, Elmo Mannarino

Abstract—Aortic pulse wave velocity (PWV), generally considered an intrinsic marker of arterial stiffness, might depend in part on the velocity of myocardial fiber shortening, but the relation between PWV and myocardial function in humans has been understudied. A total of 237 untreated hypertensive subjects over a wide age range (18 to 88 years) underwent aortic PWV determination and echocardiography, from which the mean velocity of circumferential fiber shortening was calculated as a measure of the velocity of myocardial shortening, and relative wall thickness was taken as a measure of left ventricular concentric remodeling. Patients were divided in 3 age groups (<40 years, 40 to 59 years, and ≥60 years). In the young, aortic PWV was directly associated with heart rate–corrected velocity of circumferential fiber shortening \((r=0.39; \ p=0.002)\) but not to relative wall thickness \((r=-0.01; \ p=0.95)\). The opposite was found in the older group, in which aortic PWV was accompanied by a concentric left ventricular geometric pattern \((r=0.44\) with relative wall thickness; \(p=0.009)\) and a reduced velocity of circumferential fiber shortening \((r=-0.54; \ p<0.001)\) and stress-corrected midwall fractional shortening \((r=-0.56; \ p<0.001)\). Intermediate values were found in the middle-aged group \((r=0.23; \ p<0.01\) with relative wall thickness; \(r=-0.07, \ p\) value not significant with velocity of circumferential fiber shortening). In conclusion, the relation between aortic PWV and the left ventricle is strongly age dependent. These data suggest that, in young people, aortic PWV is partly determined by an increased velocity of myocardial shortening. With increasing age, a relationship between aortic PWV (as a measure of arterial stiffness) and left ventricular concentric geometry emerges, which ultimately leads to a depressed ventricular systolic function. (Hypertension. 2007; 49:317-321.)

Key Words: pulse wave velocity ■ echocardiography ■ left ventricular function ■ hypertension ■ age ■ clinical science

Large-artery stiffness is increasingly recognized as an early marker of future cardiovascular disease and mortality in different clinical settings, including essential hypertension, the general population, and chronic kidney disease.\(^1\)–\(^3\) The availability of applanation tonometry-based techniques for measuring pulse wave velocity (PWV) provided a simple, accurate, noninvasive means for the determination of large-artery stiffness. Aortic PWV is considered an intrinsic measure of arterial stiffness on the basis of the Moens–Korteweg equation\(^6\) and, as a measure of aortic impedance and an integrated marker of the pulsatile component of left ventricular (LV) afterload, has been linked to a prognostically adverse cardiac phenotype, including concentric remodeling and depressed LV systolic function.\(^7\)–\(^8\) On the other hand, the pulse wave is generated by the contracting heart, and it has been hypothesized that aortic PWV might be determined in part by enhanced myocardial performance, at least in young subjects. Indeed, aortic PWV has been associated with a shortened LV ejection time in young healthy men.\(^9\) Because the initial speed of the pressure wave is mainly determined by the velocity of myocardial shortening,\(^10\) and LV ejection time is correlated with shortening velocity,\(^11\) these data can be taken as an indirect suggestion that myocardial function might influence the characteristics of the pulse pressure wave in humans.

However, the relation between aortic PWV and a direct measure of ventricular systolic performance has not been defined clearly. We explored the link between aortic PWV and LV geometry and function, as well as the influence of age on this relationship, in a large, untreated series of uncomplicated subjects with essential hypertension.

Methods

In our study, we recruited 237 subjects with essential hypertension who had been consecutively referred to our hypertension outpatient clinic by their general practitioners for baseline, off-treatment

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evaluation. All of the subjects underwent clinical examination, 2D targeted M-mode echocardiography, and tonometry planimetry--based determination of aortic PWV. Exclusion criteria were clinical or laboratory evidence of heart failure, coronary heart disease, cerebrovascular disease, echocardiographic tracings of insufficient quality, significant valvular defects, secondary causes of hypertension, serum creatinine \( \geq 120 \, \mu \text{mol/L} \) (1.4 mg/dL) in men and \( \geq 106 \, \mu \text{mol/L} \) (1.2 mg/dL) in women, major noncardiovascular disease, known diabetes or fasting glycemia \( \geq 126 \, \text{mg/dL} \), and treatment with any cardiovascular drug, including nitrates. Written informed consent was obtained from each patient, and the study protocol was reviewed and approved by the institutional ethics committee.

Aortic PWV was obtained with an automatic planimetry--based device, the SphygmoCor Vx system (AtCor), as described previously. Briefly, ECG-gated pulse waveforms were obtained sequentially over the common carotid and femoral arteries. PWV was calculated as the distance between the sampling sites measured over the surface of the body, divided by the time interval between the feet of the pressure waves. Arterial pressure waveforms were recorded by anaplasting the radial artery with a high-fidelity hand-held tonometer at the site of maximal pulsation. Pressure waveforms obtained with this method have been validated by comparing them with those obtained by a high-fidelity intraarterial transducer. Central artery waveform was derived from the radial artery waveform and pressure by using a transfer function validated previously during catheterization studies. The point at which the central arterial PWV was calculated was the instant at which the aortic PVW was augmented by wave reflection is recognized by a computer program, and the degree of augmentation is expressed either in absolute term (aortic augmentation) or as a percentage of aortic pulse pressure (aortic augmentation index).

The M-mode echocardiographic study of the left ventricle was performed under 2D control, as reported previously, by 2 investigators who were unaware of patients’ clinical data. Linear measurements were made according to the American Society of Echocardiography. LV mass was calculated according to Devereux et al as follows: \( 0.832 \times (\text{septal thickness} + \text{LV internal diameter} + \text{posterior wall thickness} + \text{LV internal diameter})^3 + 0.6 \, \text{g} \) and corrected by height in meters at the power of 2.7 to correct for the effect of overweight. Details about reading procedures and reproducibility of linear measures of LV mass in our laboratory have been reported previously. LV relative wall thickness (RWT) was calculated at end diastole as \( 2 \times \text{posterior wall thickness/LV internal diameter} \).

As described previously in detail, LV mechanics were assessed at both the chamber level, as endocardial fractional shortening, and the midwall level, according to a geometric model that takes into account the nonuniform systolic thickening of the LV wall. Fractional shortening was considered both in absolute terms and, after correction for afterload, as a percentage of the value predicted from end-systolic circumferential wall stress with regression equations from previously studied normal subjects. The VCF was calculated at the endocardium by dividing fractional shortening by the ejection time. Rate-corrected VCF was calculated by dividing the fractional shortening by the rate-corrected ejection time; this is the equivalent of multiplication of the VCF by the square root of the risk ratio interval.

Continuous variables were tested to detect substantial deviations from normality by computing the Kolmogorov–Smirnov \( Z \) score, and the assumption of satisfactory normal distribution was met for all of the examined variables. To investigate the effect of age, the relation between aortic PWV and LV properties, the subjects were split into 3 groups: \( <40 \) years, 40 to 59 years, and \( \geq 60 \) years. Divisions at 40 and 60 years were chosen to provide 3 reasonably sized groups with significantly different mean ages. The groups were compared through the use of 1-way ANOVA and Tukey’s posthoc test for multiple comparisons. Pearson’s correlation coefficients examined the bivariate associations between examined variables. Stepwise multiple linear regression tested the independent relation of several variables to aortic PWV and LV RWT. In the age group \( <40 \) years, age, sex, body mass index, mean arterial pressure, heart rate, and rate-corrected VCF were considered as explanatory variables of aortic PWV. Among subjects \( \geq 60 \) years, age, sex, body mass index, mean arterial pressure, heart rate, LV mass index, and aortic PWV were considered as explanatory variables of LV RWT. \( P<0.05 \) was considered statistically significant. Data are presented as mean\( \pm SD \).

Results

Demographic and clinical characteristics of the study subjects divided by age group are summarized in Table 1. The proportion of women increased from the first to the third age group. As expected, brachial and synthetized aortic systolic, but not diastolic, pressures increased with age. Self-reported duration of hypertension did not differ among the groups. The oldest age group showed a lower heart rate and a longer LV ejection time. Both LV mass and RWT increased with age, whereas parameters of LV shortening and velocity did not differ among groups.

Bivariate relations of aortic PWV are shown in Table 2. Age and BP values had a positive correlation with aortic PWV in each of the age groups, despite the fact that not all of the reported associations were statistically significant. No significant association between aortic PWV and LV mass index was found. In younger subjects, aortic PWV was directly associated with heart rate–corrected VCF but not with RWT or myocardial shortening parameters (Figure 1). The opposite was found in the older group, in which increasing aortic PWV was accompanied by a concentric LV geometric pattern, a reduced VCF, and a reduced endocardial and midwall shortening fraction. Intermediate values were found in the middle-aged group. A negative correlation between aortic PWV and LV ejection time was found in the young age group only. Age-related changes in the relationships between the functional and geometric properties of the left ventricle and aortic PWV are summarized graphically in Figure 2.

The above results were confirmed in multivariate linear regression analyses carried out separately in the youngest and oldest age group. Among subjects \( <40 \) years of age, aortic PWV was independently predicted by age (\( \beta=0.38; \, P<0.001 \)), mean arterial pressure (\( \beta=0.31; \, P=0.005 \)), and heart rate-corrected VCF (\( \beta=0.29; \, P=0.01 \)). After adjustment for other potential confounders, aortic PWV increased by 0.51 m\( \times s^{-1} \) for each 1-SD increase in heart rate-corrected VCF (0.23 circumferences per second) in this age group. Above the age of 60 years, the only independent predictor of LV RWT was aortic PWV (\( \beta=0.45; \, P=0.01 \)).

Discussion

In this study, we demonstrate a strong, age-dependent relation between aortic PWV and the anatomic and functional properties of the left ventricle. Aortic PWV is partly determined by an increased velocity of myocardial shortening in young people. With increasing age, aortic PWV, as a measure of arterial stiffness and ventricular afterload, becomes related to LV concentric remodeling and to depressed LV systolic function. Aortic PWV, a classical measure of arterial stiffness, is widely used to assess the elastic properties of the arterial tree and is a strong predictor of cardiovascular complications in
PWV and heart rate have been recognized by some authors, but not by others.

This study provides confirmatory evidence that large-artery stiffness is related to an array of functional and structural changes of the left ventricle, including concentric remodeling and impaired systolic function at the midwall level, both of which have been associated with an adverse prognosis. In agreement with previous results, our findings demonstrate that an elevated aortic impedance is a major stimulus for the development of LV concentric remodeling, without a significant increase in LV mass.

More importantly, the present study demonstrates for the first time that the above relationship is clearly evident in middle-aged and older hypertensive subjects only. Below 40 years, when the effects of age on arterial stiffening are less clear cut, a reverse pattern becomes apparent. Indeed, in young subjects, aortic PWV bears no relation to LV geometry or depressed systolic function, and a positive association emerges between aortic PWV and the velocity of LV chamber shrinking.

Although the impact of carotid-to-femoral PWV as a measure of vascular load on LV geometry and function has been explored extensively, the possibility of an inverse causal relationship had been understudied. It is conceivable that the velocity of pulse wave propagation along the arterial tree might be, in part, dependent on PWV traveling within the ventricular chamber. In an elegant experimental model of excised canine ventricles, Shishido et al have been able to

### TABLE 1. Anthropometric, Hemodynamic, and Echocardiographic Characteristics of 237 Hypertensive Patients Divided by Age Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;40 Years (n=61)</th>
<th>40 to 59 Years (n=141)</th>
<th>≥60 Years (n=35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34 (18 to 39)</td>
<td>49 (40 to 59)</td>
<td>66 (60 to 88)</td>
<td>. .</td>
</tr>
<tr>
<td>Men, %</td>
<td>69</td>
<td>58</td>
<td>38†</td>
<td>0.015</td>
</tr>
<tr>
<td>Body mass index, kg×m⁻²</td>
<td>26.7±4</td>
<td>27.5±4</td>
<td>28.3±4</td>
<td>0.21</td>
</tr>
<tr>
<td>Brachial systolic BP, mm Hg</td>
<td>141±15</td>
<td>151±18</td>
<td>158±21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Brachial diastolic BP, mm Hg</td>
<td>94±12</td>
<td>96±11</td>
<td>95±11</td>
<td>0.60</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±10</td>
<td>66±10</td>
<td>63±11</td>
<td>0.038</td>
</tr>
<tr>
<td>Aortic systolic BP, mm Hg</td>
<td>129±15</td>
<td>141±18</td>
<td>151±21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic diastolic BP, mm Hg</td>
<td>95±11</td>
<td>97±11</td>
<td>96±11</td>
<td>0.41</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>1.4±2</td>
<td>1.7±2</td>
<td>1.3±2</td>
<td>0.60</td>
</tr>
<tr>
<td>LV mass index, g×m⁻²⁻⁷</td>
<td>40±8</td>
<td>45±9*</td>
<td>51±10†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RWT</td>
<td>0.37±0.05</td>
<td>0.39±0.06*</td>
<td>0.42±0.07†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocardial FS</td>
<td>0.36±0.05</td>
<td>0.37±0.06</td>
<td>0.37±0.05</td>
<td>0.53</td>
</tr>
<tr>
<td>Stress-corrected endocardial FS, %</td>
<td>107±11</td>
<td>109±14</td>
<td>112±17</td>
<td>0.43</td>
</tr>
<tr>
<td>Midwall FS</td>
<td>0.17±0.02</td>
<td>0.17±0.02</td>
<td>0.16±0.02</td>
<td>0.23</td>
</tr>
<tr>
<td>Stress-corrected midwall FS, %</td>
<td>98±11</td>
<td>96±14</td>
<td>93±13</td>
<td>0.28</td>
</tr>
<tr>
<td>VCF, circ/s</td>
<td>1.25±0.2</td>
<td>1.29±0.2</td>
<td>1.23±0.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Heart rate-corrected VCF, circ/s</td>
<td>1.20±0.2</td>
<td>1.22±0.2</td>
<td>1.20±0.2</td>
<td>0.76</td>
</tr>
<tr>
<td>LV ejection time, s</td>
<td>0.294±0.02</td>
<td>0.293±0.03</td>
<td>0.307±0.03†</td>
<td>0.048</td>
</tr>
<tr>
<td>Aortic PWV, m×s⁻¹</td>
<td>7.7±1</td>
<td>9.1±2*</td>
<td>11.4±3†</td>
<td>0.001</td>
</tr>
<tr>
<td>Aortic augmentation index</td>
<td>0.21±0.12</td>
<td>0.33±0.12*</td>
<td>0.38±0.12†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or median [range]. BP indicates blood pressure; FS, fractional shortening. Aortic augmentation index is adjusted at a heart rate of 75 beats×min⁻¹.

*P<0.05 vs <40 years; †P<0.05 vs 40 to 59 years.

different clinical settings, including essential hypertension. However, several anthropometric and hemodynamic factors have been shown to influence PWV, including age and blood pressure. More recently, a positive correlation between PWV and heart rate has been recognized by some authors, but not by others.

This study provides confirmatory evidence that large-artery stiffness is related to an array of functional and structural changes of the left ventricle, including concentric remodeling and impaired systolic function at the midwall level, both of which have been associated with an adverse prognosis. In agreement with previous results, our findings demonstrate that an elevated aortic impedance is a major stimulus for the development of LV concentric remodeling, without a significant increase in LV mass.

More importantly, the present study demonstrates for the first time that the above relationship is clearly evident in middle-aged and older hypertensive subjects only. Below 40 years, when the effects of age on arterial stiffening are less clear cut, a reverse pattern becomes apparent. Indeed, in young subjects, aortic PWV bears no relation to LV geometry or depressed systolic function, and a positive association emerges between aortic PWV and the velocity of LV chamber shrinking.

Although the impact of carotid-to-femoral PWV as a measure of vascular load on LV geometry and function has been explored extensively, the possibility of an inverse causal relationship had been understudied. It is conceivable that the velocity of pulse wave propagation along the arterial tree might be, in part, dependent on PWV traveling within the ventricular chamber. In an elegant experimental model of excised canine ventricles, Shishido et al have been able to
measure PWV within the left ventricle. In that study, intraventricular systolic PWV was found to be an accurate, preload-independent measure of ventricular contractility.\textsuperscript{10} Data in humans regarding the relation between aortic PWV and LV myocardial shortening are limited, however. In 15 normal healthy subjects, Drinnan et al\textsuperscript{28} found that changes in pulse transit time, from which PWV is calculated, follow changes in heart rate, thus suggesting indirectly that PWV may be influenced by myocardial function. Nu¨rnberger et al\textsuperscript{9} have shown that aortic PWV had an inverse relation with LV ejection time in young healthy men. A short ejection time has been related to a high myocardial shortening velocity\textsuperscript{11} and does not seem to be affected by changes in cardiac afterload.\textsuperscript{29,30} Taken together, the previous studies suggest the existence of a relation between myocardial function and aortic PWV in humans. However, LV ejection time is at most a very indirect measure of myocardial shortening velocity, and, to our knowledge, no data have been published on the relation between myocardial function and aortic PWV at different ages.

By showing that the cardiac correlates of aortic PWV vary with age, these data provide a conceptual framework for understanding the clinical implications of aortic PWV. In the young, when the effects of age on the structure of the arterial wall have not yet developed, aortic PWV is highly influenced by the velocity of LV chamber shrinking. As patients get older, aortic PWV becomes determined primarily by large-artery stiffness and is most strongly associated with LV concentric remodeling.

Despite the cross-sectional nature of this study, it does not allow us to establish definite causal relationships; the idea that the relation observed in young subjects between PWV on the 1 hand and VCF and LV ejection time on the other hand can be attributed to myocardial function is supported by the observation that changes in cardiac afterload do not affect LV ejection time.\textsuperscript{29,30} Moreover, indices of velocity of fiber shortening, such as VCF, seem to be more sensitive than those reflecting the extent of shortening in assessing the early functional consequences of pressure-overload hypertrophy.\textsuperscript{31} Indeed, alterations in LV preload significantly influence the relation between systolic wall stress and the extent of fiber shortening, whereas they have little effect on the relation between stress and the velocity of shortening.\textsuperscript{32–34}

**Perspectives**

A complex interplay exists between aortic PWV and the left ventricle in hypertensive subjects, which is driven by 2 different biological relationships. In middle-aged and older subjects, PWV is overwhelmingly determined by aortic stiffness, and the associated increase in vascular load superimposed on the left ventricle results in concentric remodeling and depressed systolic function, all of which have an adverse prognostic significance. In the young, aortic PWV is determined to a significant extent by the velocity of LV chamber shrinking. The age-specific interactions of PWV with LV structure and function imply that aortic PWV might have a different clinical and prognostic impact at different ages. Properly designed, prospective studies are needed to verify this hypothesis.
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Disclosures

None.

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