Pressure Amplification Explains Why Pulse Pressure Is Unrelated to Risk in Young Subjects

Ian B. Wilkinson, Stanley S. Franklin, Ian R. Hall, Sian Tyrrell, John R. Cockcroft

Abstract—Pulse pressure rather than diastolic pressure is the best predictor of coronary heart disease risk in older subjects, but the converse is true in younger subjects. We hypothesized that this disparity results from an age-related difference in pressure amplification from the aorta to brachial artery. Data from 212 subjects age <50 years and 230 subjects age ≥50 years were abstracted from a community database. All subjects were free from cardiovascular disease, diabetes, and medication. Peripheral blood pressure was assessed by sphygmomanometry. Radial artery waveforms recorded noninvasively by applanation tonometry were used to derive central blood pressure. Pressure amplification (peripheral/central pulse pressure ratio) was linearly related to age (r=0.7; P<0.001). There was an inverse, linear relationship between amplification and diastolic pressure in the younger group (r=0.3; P<0.001) but not in older subjects (r=0.1; P=0.2). There was no relationship in either group when the amplification ratio was calculated with nonaugmented central pressure. Amplification is reduced in older subjects because of enhanced wave reflection. In younger, but not older, subjects, amplification declines as diastolic pressure rises. Therefore, peripheral pulse pressure underestimates the effect that diastolic pressure has on central pulse pressure in younger subjects. This may explain why diastolic pressure is a better predictor of risk in this age group and suggests that assessment of central pressure may improve risk stratification further. (Hypertension. 2001;38:1461-1466.)

Key Words: blood pressure ■ arteries ■ pulse wave analysis

The importance of blood pressure as a determinant of cardiovascular risk and the benefits of treating hypertension have been firmly established. However, the precise component of blood pressure that best predicts risk has been the subject of considerable recent debate. Data from the Framingham Study, in particular, have challenged the preeminence of diastolic blood pressure and focused attention toward pulse pressure as the best measure of cardiovascular risk, at least in older subjects. The importance of pulse pressure is further supported by several other observational and interventional studies. Since pulse pressure is a surrogate measure of arterial stiffness, such data indicate that arterial stiffness is a key determinant of cardiovascular risk in older subjects. Indeed, aortic pulse wave velocity, a more robust measure of large-artery stiffness, is an independent predictor of cardiovascular risk. Paradoxically, the latest data from Framingham suggest that diastolic pressure remains the best predictor of coronary heart disease (CHD) risk in younger subjects.

Although diastolic and mean arterial pressure are relatively constant throughout the arterial tree, the systolic component and, therefore, pulse pressure vary considerably. This is due, in part, to variation in vessel stiffness and the phenomenon of wave reflection. Normally, there is considerable amplification of pulse pressure between the aorta and brachial artery. However, the degree of amplification is not fixed and is influenced by a number of factors, including age, posture, and exercise. Recently, we have demonstrated that acute changes in heart rate and blood pressure also alter pressure amplification. Therefore, peripheral pulse pressure does not always provide a reliable measure of central pulse pressure. Moreover, differences between central and peripheral blood pressure may be clinically important because aortic rather than brachial pressure determines left ventricular workload. Furthermore, aortic pulse pressure predicts the incidence of restenosis following coronary angioplasty, independently of peripheral pressure, and carotid but not brachial pulse pressure correlates with carotid intima-media thickness.

We hypothesized that a difference in pressure amplification between older and younger subjects may explain why diastolic pressure and not peripheral systolic or pulse pressure is the best predictor of CHD risk in younger subjects. In particular, we considered that the effect of blood pressure per se on amplification might differ considerably with age. Therefore, we tested this hypothesis in a group of 442 subjects.
subjects covering a wide age range, using the technique of pulse wave analysis (PWA) to assess central arterial pressure noninvasively.

**Methods**

Data were abstracted from a joint database of community-based volunteers and patients attending an open-access cardiovascular risk assessment clinic based at the Wales Heart Research Institute, University of Wales College of Medicine, Cardiff. The database contains information on ~800 subjects collected over a period of ~2 years. All subjects completed a detailed lifestyle and medical questionnaire and, after 15 minutes of seated rest in a quiet, temperature-controlled environment, duplicate recordings of peripheral blood pressure and radial artery waveforms were made by 2 trained observers (S.T., I.R.H.). Subjects with a history of cardiovascular disease or diabetes mellitus and those receiving medication were excluded, leaving a total of 442 subjects for the present analysis.

**Peripheral Blood Pressure**

Peripheral blood pressure was measured, in duplicate, in the brachial artery of the dominant hand with the validated Omron HEM-705CP oscillometric sphygmomanometer.22 Peripheral mean arterial pressure was calculated from integration of the radial pressure waveform, and pulse pressure was calculated as systolic diastolic pressure. The amplification ratio was defined as (peripheral pulse pressure/central pulse pressure), and nonaugmented amplification ratio was defined as (peripheral pulse pressure/central diastolic pressure), where $P_1$ is the height of the first systolic peak.16

**Pulse Wave Analysis**

Pressure waveforms were recorded from the radial artery at the wrist of the dominant hand with a high-fidelity micromanometer (SPC-301; Millar Instruments) and the SphygmoCor apparatus (version 6.2; AtCor Medical), as previously described in detail.16,23 The technique of PWA24 was used to generate an averaged peripheral and central arterial waveform, expressed as a percentage of the central arterial waveform, and provides a measure of systemic arterial stiffness.

**Data Analysis**

Subjects were divided into 2 predefined age groups, <50 and ≥50 years, on the basis of previous data.10,25 To investigate the effect of blood pressure on the amplification ratio, the ratio was plotted against diastolic blood pressure, and the slope and intercept were calculated by linear regression analysis. Comparisons between groups were made with repeated-measures ANOVA or unpaired Student’s $t$ tests, as appropriate. Multiple regression analysis was conducted by the “enter method” (SPSS Version 10). The average of duplicate measurements was taken for analysis; all values are reported as mean±SD. A $P$ value <0.05 was considered statistically significant.

**Results**

A total of 442 subjects (mean age, 48 years; range, 19 to 83 years; 265 men and 177 women) were identified from the database. There was no difference in heart rate or the number of smokers between the 2 genders, but men were significantly taller (1.76±0.07 versus 1.63±0.07 m; $P<0.001$) and heavier (80.3±12.5 versus 67.8±11.4 kg; $P<0.001$) and were on average 3 years younger (47±16 versus 50±14 years; $P=0.03$) than the women.

The characteristics of the 2 predefined age groups are given in Table 1. In those age <50 years, 18 (8%) had a peripheral systolic blood pressure ≥140 mm Hg and normal diastolic pressure, 4 (2%) had a diastolic pressure ≥90 mm Hg and normal systolic pressure, and 31 (15%) had both. Among the older age group, the corresponding values were 33 (15%), 7 (3%), and 88 (38%), respectively.

For the study group as a whole, there was a significant inverse, linear relationship between the amplification ratio and age ($r=0.7; P=0.001$) (Figure 1). In contrast, there was no relationship between the nonaugmented amplification ratio and age ($r=0.1; P=0.1$). There was a significant linear relationship between AIx and age ($r=0.7; P<0.001$) (Figure 2A). AIx was also related to peripheral diastolic pressure ($r=0.4; P<0.001$). A multiple regression model was constructed, with AIx as the dependent variable. Age, gender, height, heart rate, and peripheral diastolic blood pressure were entered into the model as known or likely determinants of arterial stiffness. Age, short stature, and diastolic pressure correlated positively with AIx, and there was an inverse correlation with heart rate and male gender (Table 2). The model explained ~70% of the variability in AIx observed in the study ($P<0.001$), and substituting mean arterial for diastolic pressure did not alter the analysis significantly.

**Figure 1.** Relationship between pressure amplification and age. Shown are peripheral/central pulse pressure ratio (●, solid line; $r=0.7; P<0.001$) and peripheral/nonaugmented central pulse pressure ratio (▲, dashed line; $r=0.1; P=0.1$). The linear regression lines differed significantly in slope ($−0.010$ vs $0.001$; $P<0.001$).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Mean Age, years</th>
<th>Male, No.</th>
<th>Smokers, %</th>
<th>Height, m</th>
<th>Weight, kg</th>
<th>Heart Rate, bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 y</td>
<td>212</td>
<td>35±10</td>
<td>138</td>
<td>51</td>
<td>1.72±0.10</td>
<td>75±13</td>
</tr>
<tr>
<td>≥50 y</td>
<td>230</td>
<td>61±7</td>
<td>127</td>
<td>42</td>
<td>1.70±0.10</td>
<td>75±13</td>
</tr>
</tbody>
</table>

$P$ values are mean±SD. Significance was determined by unpaired 2-tailed Student’s $t$ test.
All indices of peripheral and central blood pressure were significantly higher in the older age group (Table 3), as was AIx. Although pressure amplification was significantly reduced in the older subjects, there was no difference in the ratio of peripheral to nonaugmented central pulse pressure. To investigate the influence of blood pressure on amplification, the amplification ratio was plotted against peripheral diastolic blood pressure for each age group (Figure 3A). In those age <50 years there was a significant inverse, linear relationship between the 2 variables (P<0.001). Substitution mean arterial pressure for diastolic pressure in these analyses did not significantly alter the results (data not shown).

<table>
<thead>
<tr>
<th>TABLE 3. Peripheral and Central Hemodynamics by Age and Gender</th>
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<tr>
<td>Group</td>
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<td>-------</td>
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<tr>
<td>&lt;50 y</td>
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<td>≥50 y</td>
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<td>P</td>
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<td>Men</td>
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<td>Women</td>
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Values are mean±SD. PSBP indicates peripheral systolic blood pressure; PDBP, peripheral diastolic blood pressure; PMAP, peripheral mean arterial pressure; PPP, peripheral pulse pressure; CSBP, central systolic blood pressure; CDBP, central diastolic blood pressure; CPP, central pulse pressure; and P1, height of the first systolic peak. Significance was determined by unpaired 2-tailed Student’s t test.
As arteries stiffen with advancing age, a larger reflected pressure wave returns to the aorta earlier and increases or “augments” systolic pressure ($P_2$ becomes dominant).34 Although the shape of the brachial artery waveform also changes, $P_2$ rarely becomes positive in the arm,35 and therefore brachial pulse pressure changes less. As expected,26,37 there was a highly linear correlation between age and AIx, a quantitative measure of the contribution of wave reflection to the central pressure waveform, in the present study. AIx was also correlated with short stature and diastolic pressure and was inversely related to heart rate, as previously observed.38

To investigate the influence of blood pressure on amplification, we examined the relationship between diastolic pressure and the peripheral/central pulse pressure ratio. We chose diastolic rather than mean pressure because the latter relates to both systolic and diastolic pressure. Moreover, we specifically wanted to see whether the relationship between diastolic pressure and amplification varies with age, thus providing a potential explanation for the paradox that diastolic pressure only predicts risk in younger people.10 However, similar results were obtained when the analysis was repeated using mean pressure. As expected, there was no difference in the relationship between amplification and peripheral systolic pressure between the groups (data not shown). Amplification declined with increasing diastolic blood pressure in the younger age group but not among the older subjects. Interestingly, there was no relationship between nonaugmented amplification and diastolic pressure in either group, suggesting that the effect of diastolic pressure on wave amplification in younger subjects was due mainly to changes in wave reflection. The lack of any association between amplification and diastolic pressure in older subjects is consistent with the observation that the pulse pressure gradient along the arterial tree is similar between hypertensive and normotensive subjects.39 Together, these data indicate that changes in the intensity of wave reflection due to variation in blood pressure only affect amplification in younger subjects. Possibly, the reduced impact of blood pressure on amplification in older subjects is due to the fact there is already increased early wave reflection within a stiffened arterial tree. Indeed, although AIx was positively correlated with diastolic pressure in both age groups, the regression line was steeper in the younger subjects, indicating a larger influence of diastolic pressure on wave reflection.

**Clinical Implications**

The differing effect of diastolic pressure on amplification in the 2 age groups means that for a given increase in diastolic pressure, there is greater rise in central systolic and thus pulse pressure in younger subjects. Therefore, assessing peripheral systolic or pulse pressure in subjects age <50 years will not provide an accurate assessment of the impact of diastolic pressure on central pulse pressure. Indeed, we have previously demonstrated that acute elevation of blood pressure with vasopressor drugs in young subjects alters pressure amplification.17 Conversely, in older subjects peripheral and central pulse pressure change in parallel, and, therefore, peripheral pulse pressure may be considered a reliable surrogate of central pulse pressure across a range of blood pressures. Furthermore, peripheral pulse pressure may be a
less reliable measure of CHD risk in younger subjects because it is not a dependable surrogate for central pulse pressure. In contrast, diastolic pressure may be a better means of risk assessment because of its linear relationship with central pulse pressure, ie, diastolic pressure is a better “surrogate” of central systolic and pulse pressure in younger subjects.

Potential Limitations
In the present study PWA was used to assess central pressure noninvasively rather than assessing aortic pressure directly. Such an approach may have led to a small degree of error in central pressure estimation, but the transfer function involved has been previously validated. Moreover, intra-arterial pressure measurements are not without their own intrinsic problems and inaccuracies. Furthermore, by using a non-invasive approach we were able to study a large cohort of subjects encompassing a wide range of ages and blood pressures. In addition, the observed relationships between age and AIX and between age and amplification, are similar to those reported by previous investigators using intra-aortic recordings or carotid artery waveforms derived by planar tonometry. Finally, although pulse pressure is related to diastolic pressure, this cannot explain the relationship between diastolic pressure and amplification because no association was found in the older subjects. Moreover, diastolic pressure is fairly constant throughout the arterial tree, and since amplification is calculated as the ratio of peripheral to central pulse pressure, this will minimize any confounding relationship.

Summary
In summary, there is less amplification of the pressure waveform as it travels from the aorta to the brachial artery in older subjects because of increased early wave reflection and augmentation of central systolic and thus pulse pressure. Moreover, we have demonstrated that peripheral pulse pressure is not a reliable surrogate for central pulse pressure in younger subjects because there is an inverse relationship between amplification and diastolic pressure. In contrast, peripheral and central pulse pressures tend to change in parallel in older subjects. We believe that this important difference provides an explanation for the paradoxical observation that although peripheral pulse pressure is the best predictor of CHD risk in older subjects, diastolic pressure is superior in those age <50 years. Large prospective studies involving the assessment of central pressure are now required to address this important issue directly. Indeed, measurement of central pulse pressure with noninvasive techniques such as PWA may improve risk stratification, especially in younger subjects.

References


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