Amplification of the Pressure Pulse in the Upper Limb in Healthy, Middle-Aged Men and Women

Patrick Segers, Dries Mahieu, Jan Kips, Ernst Rietzschel, Marc De Buyzere, Dirk De Bacquer, Sofie Bekaeart, Guy De Backer, Thierry Gillebert, Pascal Verdonck, Luc Van Bortel; for the Asklepios investigators

Abstract—Central-to-peripheral amplification of the pressure pulse leads to discrepancies between central and brachial blood pressures. This amplification depends on an individual’s hemodynamic and (patho)physiological characteristics. The aim of this study was to assess the magnitude and correlates of central-to-peripheral amplification in the upper limb in a healthy, middle-aged population (the Asklepios Study). Carotid, brachial, and radial pressure waveforms were acquired noninvasively using applanation tonometry in 1873 subjects (895 women) aged 35 to 55 years. Carotid, brachial, and radial pulse pressures were calculated, as well as the absolute and relative (with carotid pulse pressure as reference) amplifications. With subjects classified per semidecade of age, carotid-to-radial amplification varied from ≈25% in the youngest men to 8% in the oldest women. Amplification was higher in men (20±14%) than in women (13±12%; P<0.001) and decreased with age (P<0.001) in both. Amplification over the brachial-to-radial path contributed substantially to the total amplification. In univariate analysis, the strongest correlation was found with the carotid augmentation index (−0.51 in women; −0.47 in men; both P<0.001). In a multiple linear regression model with carotid-to-radial amplification as the dependent variable, carotid augmentation index, total arterial compliance, and heart rate were identified as the 3 major determinants of upper limb pressure amplification (R²=0.36). We conclude that, in healthy middle-aged subjects, the central-to-radial amplification of the pressure pulse is substantial. Amplification is higher in men than in women, decreases with age, and is primarily associated with the carotid augmentation index. (Hypertension. 2009;54:414-420.)

Key Words: cardiovascular physiology ■ blood pressure ■ large arteries ■ wave reflection ■ hemodynamics

It has long been demonstrated that, when the blood pressure waveform is measured along the arterial tree, it changes continuously in shape and amplitude.1,2 In large- and medium-sized arteries, the systolic upstroke of the wave generally becomes steeper from the central aorta toward the periphery, whereas the amplitude also increases, mainly through an increase in the peak value (systolic blood pressure) of the waveform. Overall, the minimum (diastolic) and mean (mean blood pressure) values, and especially the difference between both, change little from one location to the other.3 These are well-known features described in physiological textbooks, and these phenomena can be explained on the basis of wave travel and reflection. The heart generates a forward-running pressure wave, which is reflected in the periphery. The measured pressure at any location is, thus, composed of this forward component, as well as backward components, arising from reflections.4,5 The closer the blood pressure is measured to the reflection site (ie, the further in the periphery), the earlier the forward and backward waves will interact, leading to the steeper systolic upstroke and the more peaked appearance of pressure waves. This explains why the radial pressure wave is much more peaked than the central aortic or carotid pressure wave. This change in shape can be quantified via the so-called “form factor,” expressing the ratio of the difference between its mean and minimum value over the amplitude of a wave.

Until only a few years ago, pressure wave amplification received little or no attention and was thought to be relevant only when studying hemodynamics or arterial (patho)physiology. It may, however, have an important impact on clinical patient management.6,7 Diagnosis and treatment of (hypertension and cardiovascular) patients is quasi solely on the basis of the blood pressure values measured noninvasively using a cuff-based approach at the level of the brachial artery (BA), a peripheral vessel. Given the information above, it is clear that systolic blood pressure at the BA overestimates central...
blood pressure, which is the blood pressure faced by the heart. This should pose no specific problem if the relation between central and brachial blood pressures was unequivocal. However, this is not the case: pressure amplification is determined by wave travel and reflection phenomena, and these change not only from one subject to another but also with (patho)physiological changes within the individuals10–12 and with administration of drugs affecting the heart rate.11 In recent work, McEnery et al10 have shown that pressure amplification is directly related to heart rate and height (the taller and the higher the heart rate, the higher the amplification) and inversely related to age and a number of cardiovascular risk factors. The aim of this study was to assess the magnitude and correlates of central-to-peripheral amplification in the upper limb in the Asklepios Study cohort of healthy, middle-aged men and women.12

Materials and Methods
The total Asklepios Study cohort consists of 2524 volunteers (age between 35 and 55 years), and carotid artery (CA), BA, and radial artery (RA) pressure waveforms were acquired noninvasively using applanation tonometry in 1873 subjects (895 women). The study was approved by the local ethics committee, and written, informed consent was obtained from all of the subjects. Details on the study design and methodology can be found elsewhere.12

Subjects were allowed 10 to 15 minutes of rest in a temperature-controlled environment before the examinations. First, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the supine position with a validated oscillometric blood pressure monitor, the Omron HEM-907 (Omron Matsuoka Co Ltd), followed by brachial, radial, and carotid tonometry. These measurements were done using a previously described custom-built acquisition system consisting of a pen tonometer (SPT 301, Millar Instruments) and dedicated software developed in Matlab (The MathWorks).13 Each recording consisted of a 20-second window of raw data, and an averaged waveform was constructed from ≥10 cardiac cycles.

To quantify the shape of the averaged carotid, brachial, and radial waveforms, the form factor14 (FF) was calculated as follows:

\[ FF = \frac{\text{mean}(P_{wf}) - \text{min}(P_{wf})}{\text{max}(P_{wf}) - \text{min}(P_{wf})} \]

where \( P_{wf} \) is the measured pressure waveform. For a triangular waveform, the FF value is 0.5, whereas it tends toward 1 for more rectangular-shaped waveforms. It is the percentage of the amplitude of the waveform to be added to the minimal value (\( \min(P_{wf}) \)) to obtain the mean value (\( \text{mean}(P_{wf}) \)). As such, when applying the one-third rule used to estimate mean arterial blood pressure (MAP) from DBP and SBP, one assumes a FF of 33%.

For the calibration of the tonometer waveforms, we applied the previously described calibration scheme.15–16 The BA waveforms were first calibrated using DBPBA and SBPBA measured at the BA, and MAP was estimated as the mean value of this calibrated waveform. The radial and CA waveforms were subsequently calibrated on the basis of DBPBA and MAP estimated as the mean value of this calibrated waveform. Pulse pressure (PP) was defined as the amplitude of these calibrated waveforms and derived at the CA (PPCA), BA (PPBA), and RA (PPRA). As described by Segers et al17 for details on how these parameters were determined. All of the analyses were performed using SPSS 15 (SPSS Inc).

Results
General clinical characteristics of the population, stratified for men and women and as a function of age and sex, are provided in Table 1.

Waveform Characteristics: The Form Factor
In both men and women, the form factor was highest at the CA (population mean: 44.0±3.2%), and decreased toward the BA (42.4±3.3%) and RA (38.0±3.3%). The difference in the form factor (Table 2 and Figure 1) between men and women is smallest at the level of the CA, with a mean value of 44.2±3.3% in women and 43.9±3.1% in men (\( P=0.096 \)). At this site, it decreases with age in women, whereas the trend to decrease with age in men was less strong. At the BA, the form factor was higher in women (43.7±3.1%) than in men (41.2±3.0%; \( P<0.001 \)). It increased with age in men (\( P<0.001 \)), whereas there was no effect of age in women (\( P=0.362 \)). The difference in the form factor between men and women is also present at the level of the RA (39.5±2.9% versus 36.7±3.1%; \( P<0.001 \)), with an increase with age in both men and women (\( P<0.001 \)).

Carotid-to-Radial Amplification
With subjects classified per semidecade of age, carotid-to-radial amplification varied from ≈25% in the youngest men to 8% in the oldest women. Amplification was higher in men (20±14%) than in women (13±12%; \( P<0.001 \)) and decreased with age (\( P<0.001 \)) in both (Table 2 and Figure 2). The difference between sexes was such that, over the studied age range, the amplification in the oldest men (age 50 to 55 years) was of the same magnitude as in the youngest women (age 35 to 40 years), ie, ≈17%. The amplification over the brachial-to-radial path contributed substantially to the total amplification, explaining most of the amplification in men and practically all of the amplification in women. In absolute values, the average difference between carotid and radial PPs was 8.3±6.6 mm Hg in our population, varying from 12.7±6.8 mm Hg in the youngest men to 4.5±5.7 mm Hg in the oldest women category.

Correlates and Determinants of Carotid-to-Radial Amplification
In what follows, all of the reported correlation coefficients have \( P \) values of <0.001. Carotid-to-radial amplification was...
associated with age (correlation coefficient: −0.26 in women and −0.24 in men, respectively), heart rate (0.25/0.22), mean blood pressure (−0.24/−0.23), height (0.12/0.18), weight (0.12/0.14), total arterial compliance (0.24/0.24), vascular resistance (−0.30/−0.31), reflection magnitude (−0.26/−0.27), and carotid-femoral pulse wave velocity (−0.19/−0.15). The strongest correlation in univariate analysis, however, was found with the AIx (−0.51 in women; −0.47 in men; see also Figure 3). In a multiple linear regression model with carotid-to-radial amplification as the dependent variable, AIx, total arterial compliance, and heart rate were identified as the 3 major determinants of upper limb amplification, entering the model in that order. The total variance ($R^2$) explained by the model was 0.30 in men and 0.31 in women.

### Table 1. Basic Clinical Data and Parameters of Large Artery Stiffness and Wave Reflection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age Categories, y</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35 to 40</td>
<td>41 to 45</td>
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<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (N=895)</td>
<td>247</td>
<td>231</td>
</tr>
<tr>
<td>M (N=978)</td>
<td>236</td>
<td>257</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>64.0±10.1</td>
<td>64.3±11.9</td>
</tr>
<tr>
<td>M</td>
<td>79.6±11.4</td>
<td>79.7±11.3</td>
</tr>
<tr>
<td>Height, cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>165.1±5.9</td>
<td>163.9±6.0</td>
</tr>
<tr>
<td>M</td>
<td>177.4±6.4</td>
<td>175.9±6.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>23.4±3.5</td>
<td>23.9±4.1</td>
</tr>
<tr>
<td>M</td>
<td>25.2±3.3</td>
<td>25.7±3.2</td>
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<tr>
<td>Brachial SBP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>123.8±14.3</td>
<td>125.8±14.5</td>
</tr>
<tr>
<td>M</td>
<td>130.4±10.5</td>
<td>133.0±12.7</td>
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<tr>
<td>HR, bpm</td>
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<td></td>
</tr>
<tr>
<td>F</td>
<td>65.1±9.2</td>
<td>65.4±8.3</td>
</tr>
<tr>
<td>M</td>
<td>60.4±8.5</td>
<td>60.8±8.9</td>
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<tr>
<td>PWV, m/s</td>
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<tr>
<td>F</td>
<td>5.92±1.08</td>
<td>6.17±1.23</td>
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<tr>
<td>M</td>
<td>5.89±0.89</td>
<td>6.31±1.07</td>
</tr>
<tr>
<td>Ctot, mL/mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>0.97±0.25</td>
<td>0.93±0.24</td>
</tr>
<tr>
<td>M</td>
<td>1.19±0.34</td>
<td>1.19±0.33</td>
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<tr>
<td>Pb/Pf, —</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>0.46±0.08</td>
<td>0.48±0.09</td>
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<tr>
<td>M</td>
<td>0.44±0.08</td>
<td>0.48±0.09</td>
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<tr>
<td>AIx, %</td>
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<td></td>
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<tr>
<td>F</td>
<td>14.63±12.46</td>
<td>18.98±10.84</td>
</tr>
<tr>
<td>M</td>
<td>0.90±13.29</td>
<td>8.95±13.69</td>
</tr>
<tr>
<td>SVR mm Hg/mL per s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>1.29±0.30</td>
<td>1.31±0.29</td>
</tr>
<tr>
<td>M</td>
<td>1.15±0.24</td>
<td>1.19±0.29</td>
</tr>
</tbody>
</table>

$F$ indicates female; $M$, male; PWV, carotid-femoral pulse wave velocity; Ctot, total arterial compliance; Pb/Pf, reflection magnitude; SVR, systemic vascular resistance; BMI, body mass index. $P$ value for age follows from a model including age and sex and applies to both. It was, however, verified that the significance of the relation with age persisted in subgroup analysis.
with the major part explained by AIX ($R^2$ 0.22 in men and 0.26 in women), whereas both total arterial compliance and heart rate each equally explained the remaining variance. Pooling data of men and women, total $R^2$ was 0.36, with 29% of the variance explained by AIX, whereas both total arterial compliance and heart rate each explained an additional 3%.

### Discussion

It is beyond any doubt that the pressure pulse is amplified from the central aorta toward the RA. Subjects of debate are, however, the absolute value (in millimeters of mercury) of this amplification and how the amplification is distributed over the aorta-brachial-radial pathway. Assuming CA pressure to be a surrogate for central aortic pressure, and (the difference between) mean and DBP to remain constant, our data allow us to answer some of these questions and to speculate on others.

As illustrated in Figure 2 (right), the relative increase in PP from the CA to the RA is highest (25%) in the youngest men and lowest (8%) in the oldest women categories. In both men and women, it decreases with age. The carotid-to-radial amplification that we found is lower than the values reported recently by McEniery et al,9 who found central-to-brachial amplifications of 44% in healthy subjects (mean age: 45 years) and up to 54% in a subgroup of (young) smokers. Assuming a constant difference between MAP and DBP throughout the large arteries, it is easily demonstrated that $\text{PP}_{\text{BA}}/\text{PP}_{\text{Central}} = \text{FF}_{\text{Central}}/\text{FF}_{\text{BA}}$. Assuming an average form factor of the central pressure wave of 45%,14 a central-to-brachial amplification of 44% would imply a brachial form factor of 31%. This is a very low value, indicative for highly peaked waveforms. This value is substantially lower than the form factor of 40% from an invasive study19 and lower than the values at the RA in the present study, where we found the waveform to be sharper than at the BA. The somewhat higher
resting heart rates may contribute to this difference, but we speculate that also the calibration procedure followed by McEniery et al.⁹ (who did not account for any brachial-to-radial pressure amplification on calibration of the RA pressure waveforms) explains at least part of the discrepancy. When the unamplified RA tonometer waveforms are subsequently used to estimate central blood pressure using a transfer function, the estimated central blood pressure will, artificially, be too low, resulting in an apparently high central-to-brachial amplification.²⁰

The absolute amplification from the carotid-to-radial pathway was ≈13 mm Hg in the youngest men group and decreased to ≈5 mm Hg in the oldest women. Overall, the average difference between central and radial PPs was 8.3±6.6 mm Hg. With the knowledge that carotid pressure is ≈2 mm Hg higher than central aortic pressure, we estimate the average aorta-to-radial amplification in our population in the order of 10 mm Hg. This is (somewhat) lower than the value of 12 mm Hg found by McEniery et al.⁹ in healthy subjects (mean age: 45 years). The major difference between our study and the work of McEniery et al.⁹ (based on the SphygmoCor device) is that they ascribe this amplification entirely to central-to-brachial amplification, without any further amplification toward the RA. This is in contrast with our data, because we found an important contribution to the amplification along the brachial-to-radial pathway (see Figure 2), confirming previous findings.²¹

Our data confirm that pressure amplification depends on many factors. In agreement with data reported previously, we found pressure amplification to decrease with age and increase with heart rate and height.⁹ The strongest (negative) association, however, was found with the carotid AIx, confirming previous findings.¹⁰ This is not surprising, because AIx quantifies SBP augmentation attributed to wave reflection and depends on magnitude and timing of reflected waves. These are the same factors affecting pressure augmentation. In a multiple linear regression model, AIx alone explained ≈30% of the variance in carotid-to-radial amplification, which is virtually the same number as reported by Protogerou et al.¹⁰ Other factors contributing to some extent were total arterial compliance and heart rate, explaining another 6% of the variance. Nevertheless, the fact that only ≈36% of the variance in amplification can be explained indicates that it is a complex multifactorial phenomenon. We repeated the multiple linear regression model (with the relative carotid-to-radial amplification as the independent variable) adding glucose levels, high-density lipoprotein and total cholesterol levels, body mass index or waist circumference, nicotine exposure, and calculated 10-year Framingham risk score as independent variables, but none of these parameters entered the model and significantly improved the $R^2$ value. This may be attributable to the fact that the middle-aged Asklepios population is a low-risk population with a narrow age range. McEniery et al.⁹ found risk factors (hypertension, cardiovascular disease, smoking, hypercholesterolemia, and diabetes mellitus) to each explain ≈1% of the variance in the amplification ratio.

Our findings depend, in part, on brachial pressure waveforms obtained via tonometry, which is still subject to

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**Figure 2.** Absolute (left) and relative (right) amplifications of the pressure pulse from the CA to the BA (filled bars), and from the BA to RA (hatched bars). The relative amplification was calculated with carotid PP as the reference.

**Figure 3.** Relation between carotid AIx and relative carotid-to-radial amplification in men and women. Solid line is the regression line in women ($R^2=0.26$) and the dashed line is the regression line in men ($R^2=0.22$).
The procedure is not feasible in all subjects (it is more difficult in obese subjects), requires a highly skilled and trained operator, and the local anatomy of the BA may be not as well suited for applanation tonometry as the RA. In our Asklepios population, we could not record BA pressure waveforms with satisfactory quality within a reasonable time frame in 417 subjects (~18% of the population). However, when feasible, the recording of the waveforms was qualitatively judged as reliable as on the CA or RA by the operator. The values that we found for the form factor at the BA (Table 2 and Figure 1) are, as one might expect, in between the value at the CA and RA and close to the value of 40% reported recently by Bos et al (based on invasive data). Nevertheless, the values that we found are somewhat higher, leading to a more pronounced brachial-to-radial contribution to the total amplification than one would find when using a value of 40%. Note, however, that the reported values of relative carotid-to-radial-amplification (Figure 2, right) are independent of the brachial tonometer measurements; these only interfere when assessing the carotid-to-brachial and brachial-to-radial contributions.

The form factor quantifies the shape of the wave, but it also expresses the percentage of PP to add to DBP to estimate mean blood pressure. When using the widely applied rule of thumb to estimate mean blood pressure, a form factor of one third (33%) is assumed. It is clear from our data that this value is too low and that the one-third rule to estimate MAP should be reconsidered, especially when using MAP for tonometer calibration purposes. Anyhow, given the strong dependence of the brachial pressure wave shape and amplitude on all factors impacting pressure amplification, one fixed formula to estimate MAP from DBP and SBP is doomed to show some flaws.

The further away from the heart, the more important the difference in form factor becomes between men and women. At the BA, the form factor is ~2% lower in men, and this difference increases to ~3% at the level of the RA. It is also observed that the carotid and brachial form factors are close in women, resulting in very little difference between carotid and brachial PPs. We speculate that this is related to the different body proportions in men and women, with the difference between the aorta-carotid and the aorta-brachial distances being larger in men than in women. Although we did not measure detailed anthropometric data, the distance between the suprasternal notch and the CA was only 0.4 cm less in women, whereas the difference in the distance between the suprasternal notch and RA was >6 cm in our population, which supports this view.

It is clear that our study is not free from limitations, the most important ones being the relatively narrow age range of our study and obviously the absence of invasive data. Nevertheless, it is clear that population data can only be acquired with noninvasive means, especially in young to middle-aged apparently healthy subjects as in the Asklepios population, where pressure amplification is most obvious. Also, although the validity of BA applanation tonometry is still debated, we have clearly demonstrated carotid-to-radial amplification independent of this measurement making use of the (ratio of the) carotid and radial form factors.

**Perspectives**

Because of the amplification of the pressure pulse along the BA and RA of the upper limb, peripheral blood pressure does not accurately reflect central blood pressure. A major inconvenience is the highly variable nature of the magnitude of this amplification. It is lower in women than in men, decreases with age, and is inversely related to heart rate. In our middle-aged population of apparently healthy men and women, we found carotid AIx to be the best predictor of the magnitude of the amplification, with an inverse relation between both. Whether quantification of the magnitude of amplification (or, rather, the lack of pressure amplification) would be useful in the assessment of cardiovascular risk remains to be demonstrated. Given that amplification diminishes with age and with a strong negative association with carotid AIx, its additional discriminative power might be low in older populations at high cardiovascular risk. It is also noteworthy that the observed magnitude of amplification depends on the method used to assess the central blood pressure, with the calibration of the noninvasively measured waveforms being a determining factor.

In conclusion, the central-to-radial amplification of the pressure pulse is substantial in healthy middle-aged subjects. The amplification is higher in men than in women, decreases with age, and is primarily negatively associated with the carotid AIx.

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**Disclosures**

None.

**References**


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