Intraaortic Pulse Pressure Amplification in Subjects at High Coronary Risk

Mohamed Temmar, Piotr Jankowski, Marcel Peltier, Vincent Mouquet, Dorota Dębicka-Dąbrowska, Farah Hamida, Kalina Kawecka-Jaszcz, Michel E. Safar

Abstract—Peripheral (brachial) pulse pressure normally exceeds central (aortic) pulse pressure but is a less powerful predictor of cardiovascular risk. The difference between the 2 variables, called pulse pressure amplification, has never been specifically studied between the proximal and distal aorta in coronary patients. Our goal was to determine aortic pulse pressure amplification in subjects at high coronary risk, with emphasis on associated renal and inflammatory factors. Blood pressure was measured invasively in the ascending aorta, abdominal aorta (at the level of kidneys), and iliac artery in 101 subjects (mean age, 63±11 years; 61 men) undergoing coronary angiography. Independently of age, sex, and the presence of coronary stenosis, the increase of pulse pressure between the ascending and terminal aorta was over 10 mm Hg (P<0.001), whereas mean blood pressure remained unchanged. Pulse pressure amplification did not differ significantly between patients with and without coronary artery stenosis. Irrespective of confounding variables, high pulse pressure measured in the ascending aorta and at the level of renal arteries (but not in the iliac artery) was independently related to proteinuria. The increase in pulse pressure from the ascending aorta to the renal level was negatively associated with leukocyte count, even after multivariate adjustment (β coefficient, −0.19; 95% CI, −0.39 to 0.0; P<0.05). Increased plasma creatinine and aortic pulse wave velocity were independently and positively correlated (β coefficient, 0.36; CI, 0.18 to 0.54; P<0.001). Independently of coronary atherosclerosis, aortic pulse pressure integrates the predictive value of aortic, inflammatory, and renal factors. (Hypertension. 2010;55:327-332.)

Key Words: central pulse pressure ■ pulse pressure amplification ■ coronary artery disease ■ chronic kidney disease ■ blood pressure

Peripheral (brachial) pulse pressure (PP) constantly exceeds central (aortic) PP but is a less powerful predictor of cardiovascular (CV) risk.1,2 Several factors are involved in the development of this difference.1,3 Among them, 3 factors can be considered to have major importance for the higher predictive value of central PP compared with brachial PP: the presence of aortic PP amplification, anomalies of kidney structure and function, and inflammatory factors.4

It has been shown that systolic blood pressure (SBP) and PP are physiologically higher in peripheral than in central arteries.1,4–6 In contrast, peripheral diastolic blood pressure (DBP) is slightly lower compared with central DBP.1,4–6 Finally, nearly identical values are observed regarding mean blood pressure (MBP). This well-established behavior of the different blood pressure (BP) components is known to protect the heart against pressure integrates the predictive value of aortic, inflammatory, and renal factors.

Just in the middle of the abdominal aorta is the kidney, an important organ to consider. In subjects with hypertension or chronic renal disease, increased aortic stiffness or indices of pulsatility are frequently associated with proteinuria or reduced renal function, a situation favoring the development of CV events.8 However, measurements of intraaortic PP at the level of kidneys, particularly in patients at high coronary risk, have been poorly studied previously. The difference in BP between ascending aorta and renal arteries has never been investigated. Finally, inflammatory factors that play a key role in the development of atherosclerosis and its complications8,9 are frequently associated with increased central PP.1,5

Our working hypothesis was that aortic, renal, and inflammatory factors all together influence central PP. Thus, the aim of the present study was to determine PP amplification along the aorta in patients at high coronary risk and to correlate this...
hemodynamic parameter with renal and inflammatory factors that can influence CV risk.

Methods

Study Population
Consecutive patients suspected of coronary artery disease undergoing nonemergency coronary angiography in the Hospital-University Center of Amiens, Picardie, France, and in the I Department of Cardiology and Hypertension, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland, were eligible for the study. We excluded from the analysis all patients with acute coronary syndrome, significant valvular disease, heart failure, impaired left ventricular systolic function (ejection fraction <50%), atrial fibrillation, aortic aneurysm or aorto-arterial prosthesis, C-reactive protein level >10 mg/L, recent infectious or inflammatory disease, or treatment with nonsteroidal antiinflammatory drugs, steroids, or antibiotics in the preceding 2 weeks. Twenty subjects were recruited in the Polish center and 81 in the French center, so the study population consisted of 101 patients. All subjects underwent coronary angiography through the femoral artery access. The study procedures were in accordance with institutional guidelines, and all participants gave informed consent.

BP Measurements

Invasive BP measurements were obtained in the supine position. BP was measured using a low-compliance fluid-filled system after verification of the system frequency (around 18 Hz) and the damping coefficient (around 35) as previously described.6,8 The transducer was localized on the level of the aortic valve. BP was measured sequentially at 3 different sites: in the ascending aorta at the level of coronary arteries, in the abdominal aorta at the level of the origin of renal arteries, and in the iliac artery. MBP was obtained by direct integration of the BP curve. PP was calculated as the difference between SBP and DBP. PP amplification was calculated as the difference between PP measured at the above-mentioned 3 sites and expressed in absolute values (mm Hg). In addition, PP augmentation in the ascending aorta, abdominal aorta, and iliac artery was calculated only in the Polish center. Hard copies were made of the pressure tracings using a chart recorder at a speed of 25 mm/s. PP augmentation was calculated off-line as the difference between the top of the primary wave and the top of the reflected wave (5 wave measurements were averaged in every case) and expressed in mm Hg. In 4 subjects, it was not possible to find the inflection point on the pulse wave curve because of almost ideal overlapping of the ascending arms of the primary and reflected pressure waves.

Noninvasive brachial BP was measured before femoral puncture using a mercury sphygmomanometer with cuff size adapted to the patient’s arm circumference. The mean of 3 measurements was used in the study. Noninvasive aortic pulse wave velocity (PWV) was determined in the French center using the foot-to-foot method as described previously10 (Complior, Colson). The superficial distance covered by the pulse wave was measured directly from the carotid to the femoral artery. This method for distance assessment may overestimate PWV by ~2 to 3 m/s on average.10

Coronary Artery Stenosis Determination

Cardiac catheterization was performed according to a standard technique. Coronary atherosclerosis was evaluated by a number of diseased coronary arteries. The 3 major coronary vessels (left anterior descending artery, circumflex artery and right coronary artery) and their branches were evaluated for the extent of coronary atherosclerosis. A diseased artery was defined as >50% stenosis in at least 1 of its segments. Significant left main artery stenosis was coded as 2-vessel disease.

Other Variables

Fasting blood samples were taken before coronary angiography for blood cell count, as well as for the analysis of plasma cholesterol, triglycerides, glucose, and creatinine levels.9 Diabetes was defined as a fasting blood glucose level of 7.0 mmol/L or more or the use of an antidiabetic drug. Participants with total cholesterol levels ≥5.2 mmol/L or being prescribed a lipid-lowering drug were considered to have hypercholesterolemia. Current smokers were defined as those who had smoked any tobacco in the previous month. In addition, high-sensitivity C-reactive protein level and 24-hour proteinuria were measured in the French center according to standard methods.8 All CV drugs taken within 24 hours before catheterization were analyzed. The following medication classes were considered in the analysis: β-blockers, renin-angiotensin system inhibitors (angiotensin-converting-enzyme inhibitors and AT1 receptor antagonists), calcium antagonists, diuretics, lipid-lowering drugs, and antidiabetic agents.

Statistical Analysis

Statistical analysis was performed using SAS statistical software (SAS Institute Inc., Cary, NC) and STATISTICA 6.0 software (StatSoft, Inc., Tulsa, OK). Categorical variables are reported as percentages and continuous variables as mean±SD. Because age and sex are reported as major PP determinants,1,3,5 all comparisons were systematically adjusted for these parameters. We used a general linear model as implemented in the STATISTICA 6.0 package for comparisons between independent and dependent samples. Multivariate regression analysis was used to assess the independent relationship between PP and proteinuria or creatinine level. Regression coefficients were compared using the method described by Cohen and Cohen.11 We used stepwise multivariate regression analysis to find the best models when PP amplification or PWV served as the dependent variable. Mallows’ Cp statistic was used as a criterion of the best model. Only subjects from the French center (n=81) were included in the analysis whenever proteinuria, PWV, or C-reactive protein was analyzed. Two-sided P values <0.05 were considered statistically significant.

Results

We recruited 61 men and 40 women. The mean age of participants was 62.9±10.8 years. Fifty-three (52.5%) subjects were diagnosed as having at least 1 significant coronary artery stenosis (CAS). Among them, 23 (43.4%) had 1-vessel disease, 18 (34.0%) had 2-vessel disease, and 12 (22.6%) had 3-vessel disease. The clinical characteristics of the study population according to the presence of CAS are shown in Table 1. The main difference was in the rate of lipid lowering drugs use, which was higher in subjects with CAS.

Table 2 shows the intraaortic BP values in the 2 groups of subjects. After adjustment for age and sex, patients with CAS had significantly higher ascending aortic PP, as well as abdominal aortic SBP and PP. These findings persisted after further adjustments for a number of variables, including height and BP-lowering drugs (data not shown). No significant difference was found in mean values of PP amplification between patients with and without CAS.

The changes in BP values along the aorta are shown in Table 3. Although SBP amplification was significant in univariate analysis (P<0.0001), the significance disappeared after adjustment for age, sex, and CAS. On the other hand, the PP amplification was highly significant both in univariate analysis (P<0.0001) and after adjustment. DBP was significantly lower in the iliac artery compared with the ascending aorta. MBP did not differ between the various arterial sites. The BP curve of a 62-year-old woman is shown in Figure 1 as an example. Mean values of PP augmentation measured in the ascending aorta, in the abdominal aorta at the level of renal arteries, and in the iliac artery are presented in Figure 2. The difference in PP augmentation between the ascending aorta and the level of renal arteries was significant (P<0.01), whereas the difference between the
abdominal aorta and the iliac artery did not reach significance (Figure 2). Similar results were obtained when the augmentation index (in percent) was calculated or adjustment for heart rate was performed (data not shown).

Table 4 shows the results of multivariate regression analysis with intraaortic PP as a dependent variable. Plasma creatinine was significantly related to PP in the ascending and abdominal aorta in models 1 and 2, but not after full adjustment (model 3). The relationship between iliac PP and creatinine did not reach significance in any of the constructed models. Moreover, the \( \beta \) coefficient for the association between abdominal PP and plasma creatinine was significantly higher compared with iliac PP–creatinine association in model 1, although this difference did not persist after further adjustments. In contrast to plasma creatinine, proteinuria was significantly related to the ascending aortic and abdominal PP in all statistical models. Plasma creatinine and proteinuria did not correlate with MBP.

The independent factors related to PP amplification from the ascending aorta to the level of renal arteries were MBP, heart rate, high-density lipoprotein cholesterol level, age, and leukocyte count (Table 5). When we expressed PP amplification as a ratio, results did not change significantly (data not shown). Aortic PWV was independently predicted by plasma creatinine level, irrespective of age, MBP, renin-angiotensin system inhibitor prescription, total cholesterol level, and diabetes (Table 6).
The relationship between PWV and renin-angiotensin system inhibitors was negative.

Discussion

Recently, more and more attention has been given to the ascending aortic BP measurements. Central PP was shown to be related to the risk of death in patients with renal insufficiency, but no such association could be shown for peripheral pressure. Roman et al studied patients with risk factors but without symptoms of coronary artery disease and concluded that central aortic pressure better predicts incident CV disease than brachial pressure. Similar findings were reported by Pini et al in an older population. Finally, in patients undergoing coronary angiography, central but not brachial PP predicted event-free survival.

This study showed, in subjects at high coronary risk, a progressive increase in aortic PP from the proximal to the distal aorta without any change in MBP. The major augmentation was observed between the ascending aorta and the level of renal arteries. This augmentation was higher in patients with a high level of high-density lipoprotein cholesterol and low leukocyte count, independent of age, MBP, and heart rate. Plasma creatinine level and proteinuria were related to PP in the ascending and abdominal aorta but not in the more distal site. Results were independent of age and a number of other factors, but they were more obvious for proteinuria than for plasma creatinine. Aortic PWV and creatinine level were significantly and positively associated, independently of age and MBP. PWV was negatively associated with the use of renin-angiotensin system inhibitors. Taken together, the results point to the major importance of renal and inflammatory factors associated with the disturbed aortic function in subjects with high coronary risk.

To the best of our knowledge, this study is the first to explore the relationship between intraaortic BP and renal function.

Table 4. The Relationship Between Invasively Measured Aortic PP in the Ascending Aorta, in the Abdominal Aorta on the Level of Renal Arteries, and in the Iliac Artery, and Proteinuria and Plasma Creatinine Levels (n=81)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ Coef.</td>
<td>$P$</td>
<td>$\beta$ Coef.</td>
<td>$P$</td>
<td>$\beta$ Coef.</td>
<td>$P$</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>Creatinine 0.354</td>
<td>0.028</td>
<td>0.267</td>
<td>0.040</td>
<td>0.281</td>
<td>0.157</td>
</tr>
<tr>
<td></td>
<td>Proteinuria 0.405</td>
<td>0.003</td>
<td>0.309</td>
<td>0.006</td>
<td>0.353</td>
<td>0.031</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>Creatinine 0.388*</td>
<td>0.017</td>
<td>0.268</td>
<td>0.048</td>
<td>0.305</td>
<td>0.138</td>
</tr>
<tr>
<td></td>
<td>Proteinuria 0.430</td>
<td>0.002</td>
<td>0.314</td>
<td>0.007</td>
<td>0.374†</td>
<td>0.028</td>
</tr>
<tr>
<td>Iliac artery</td>
<td>Creatinine 0.279</td>
<td>0.093</td>
<td>0.191</td>
<td>0.147</td>
<td>0.243</td>
<td>0.241</td>
</tr>
<tr>
<td></td>
<td>Proteinuria 0.389</td>
<td>0.006</td>
<td>0.282</td>
<td>0.013</td>
<td>0.299</td>
<td>0.079</td>
</tr>
</tbody>
</table>

Model 1: age and sex are included. Model 2: age, sex, MBP, and CAS are included. Model 3: age, sex, MBP, CAS, height, weight, waist, heart rate, smoking, diabetes, hypercholesterolemia, potassium, C-reactive protein, leukocyte count, PWV, and treatment are included. MBP was measured in the ascending aorta, in the abdominal aorta on the level of renal artery origin, and in the iliac artery when ascending aortic, abdominal, and iliac PP was a dependent variable, respectively.

* $P<0.05$ vs creatinine-iliac artery PP $\beta$ coefficient.
† $P=0.08$ vs proteinuria-iliac artery PP $\beta$ coefficient.
The presence of aortic SBP and PP amplification has been well tentatively lowered DBP, which was around a value of 70 mm Hg. renal arteries. PP amplification was mainly due to a slight wave reflections (Figures 1 and 2) and to the possibility of their diameter below the renal artery level and also to the presence of evaluation may correspond to the physiological reduction of aortic aorta, the amplification was considerably attenuated. This attenuation to the level of renal arteries. In the distal part of the SBP and PP amplification, was similar in subjects with and even in subjects after kidney transplantation.22 These results of a positive relationship between aortic PP and proteinuria in atherosclerotic subjects. Wang et al found a relationship between central or brachial PP and glomerular filtration rate in a relatively healthy population.21 We clearly showed an independent relationship between intraaortic pressure and kidney function in high-risk patients. Our findings concerning the relationships between aortic PP, proteinuria, and renal function are important to consider but difficult to interpret. Physiologically, renal blood flow is maintained constant, despite changes in systemic MBP, through modification in vascular smooth muscle cell tone that leads to changes in preglomerular resistance. Under these conditions, it is difficult to understand the positive association between proteinuria and aortic PP (and not MBP), which supposes a loss in renal autoregulation. However, histomorphometric studies have shown that in severe or accelerated hypertension in humans, preglomerular arterioles are consistently dilated.17 It has been observed in subjects with systolic hypertension that increased PP (and not MBP) was associated with reduced renal blood flow and glomerular filtration rate. This finding has been observed in both cross-sectional and longitudinal investigations.18,19 Finally, urinary albumin excretion was shown to be independently associated with an elevated arterial stiffness.20 These findings agree with our results of a positive relationship between aortic PP and proteinuria in atherosclerotic subjects.

Table 5. The Independent Factors Related to PP Amplification From the Ascending Aorta to the Level of Renal Arteries (n=101)

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>95% CI</th>
<th>Partial $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP</td>
<td>−0.30</td>
<td>−0.50 to −0.10</td>
<td>0.18</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.27</td>
<td>0.08 to 0.48</td>
<td>0.12</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>0.25</td>
<td>0.06 to 0.43</td>
<td>0.07</td>
</tr>
<tr>
<td>Age</td>
<td>−0.20</td>
<td>−0.39 to −0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>−0.19</td>
<td>−0.39 to −0.00</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Table 6. The Independent Factors Related to the Aortic PWV (n=81)

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>95% CI</th>
<th>Partial $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine</td>
<td>0.36</td>
<td>0.18 to 0.54</td>
<td>0.14</td>
</tr>
<tr>
<td>Age</td>
<td>0.36</td>
<td>0.17 to 0.54</td>
<td>0.15</td>
</tr>
<tr>
<td>MBP</td>
<td>0.20</td>
<td>0.02 to 0.38</td>
<td>0.07</td>
</tr>
<tr>
<td>RAS inhibitors</td>
<td>−0.20</td>
<td>−0.38 to −0.02</td>
<td>0.13</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>−0.20</td>
<td>−0.38 to −0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>Diabetes (yes, 1; no, 0)</td>
<td>0.17</td>
<td>0.00 to 0.35</td>
<td>0.07</td>
</tr>
</tbody>
</table>

RAS denotes renin-angiotensin system.
as these patients were excluded from our study. As we examined a limited number of subjects, it is still possible that the results might have differed if a larger group had been analyzed. Although the carotid-femoral distance used in our study for PWV estimation was shown to somewhat overestimate the PWV evaluated from the subtraction procedure, the 2 methods provide highly correlated results that can be deduced from each other (personal data). A fluid-filled system was used to record the intraaortic pressure. Although the use of a high-fidelity pressure transducer would increase the accuracy of the recorded pressure waveform, it was shown that the difference between the methods is small, and therefore the use of the latter method would not change the results significantly. Finally, it should be emphasized that we were unable to demonstrate any cause-and-effect relationship because of the cross-sectional nature of our study. Further longitudinal research is needed.

Perspectives
This study showed close association between intraaortic PP and renal function in patients at high coronary risk, as well as an independent relationship between leukocyte count and PP amplification. Our findings suggest that assessment of aortic PP during coronary angiography could help to identify those who are at especially high risk. Central PP is more powerful than brachial PP in the prediction of CV risk because this parameter integrates not only the role of the heart and aorta but also the role of the kidneys, as well as inflammatory factors. According to the international recommendations, the drug dosage should be adapted to the brachial BP. The present data showed that the aortic-brachial and the aortic-renal amplifications are similar and approximate to 8 to 9 mm Hg. This simple observation facilitates drug dosage in high-risk subjects.

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Disclosures
None.

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