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-Jaszc, Michel E. Safar

Abstract—Peripheral (brachial) pulse pressure normally exceeds central (aortic) pulse pressure but is a less powerful predictor of cardiovascular (CV) risk.1, 2 Several factors are involved in the development of this difference.3–5 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 an increase in afterload, but it tends to lessen with age.5, 7

Increased arterial stiffness and alterations in the transit of wave reflections are major determinants of SBP and PP amplification.3 Pressure amplification between the carotid and brachial arteries has been widely studied in the literature, but amplification between the proximal and distal aorta has never been investigated in subjects with coronary atherosclerosis.1, 5

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 complications6,9 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

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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 previously11 (Compiloir, 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. 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
C-reactive protein, mg/L§ 2.63 (2.61) 3.09 (2.90) 0.24
Potassium, mmol/L 4.09 (0.38) 4.05 (0.31) 0.80

Renal factors
Creatinine, μmol/L 86.3 (26.6) 85.0 (22.5) 0.34
Proteinuria, mg/24 hours§ 242.2 (657.2) 298.3 (819.0) 0.76

Hemodynamic measurements
Brachial SBP, mm Hg 133.8 (17.0) 137.4 (21.0) 0.62
Brachial DBP, mm Hg 79.0 (11.0) 79.2 (9.4) 0.92
Brachial PP, mm Hg 54.8 (15.1) 58.2 (17.7) 0.59
Heart rate, bpm 67.3 (12.0) 69.1 (14.5) 0.23
Aortic PWV, m/s§ 12.2 (3.6) 12.6 (3.1) 0.74

Medications, n (%)
β-Blockers 23 (47.9) 37 (69.8) 0.02
RAS inhibitors 25 (52.1) 31 (58.5) 0.33
Calcium antagonists 12 (25.0) 16 (30.2) 0.47
Diuretics 16 (33.3) 21 (39.6) 0.66
Lipid-lowering drugs 25 (52.1) 42 (79.2) <0.01
Antidiabetic agents 14 (29.2) 23 (43.4) 0.17

French and Polish data did not differ statistically and were analyzed together.

*R Adjusted for age, sex, and CAS.
† Adjusted only for sex.
‡ Adjusted only for age.
§ Measured in 42 subjects with CAS and in 39 subjects without it.

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 β 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.

![Figure 1](image1.png)

**Figure 1.** An example of BP curve measured in the ascending aorta on the level of coronary arteries (A), in the abdominal aorta on the level of renal arteries (B), and in the iliac artery (C) in a 62-year-old woman.

![Figure 2](image2.png)

**Figure 2.** The mean systolic pressure augmentation (mm Hg) measured in the ascending aorta, in the abdominal aorta on the level of renal artery origin, and in the iliac artery (n=16). Markers denote mean value, and whiskers denote standard error.

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<tbody>
<tr>
<td></td>
<td>β Coefficient</td>
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<td>Ascending aorta</td>
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<td>Iliac artery</td>
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</tr>
<tr>
<td>Proteinuria</td>
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<td>0.006</td>
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</tbody>
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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 β coefficient.
†P<0.05 vs proteinuria-iliac artery PP β coefficient.
damage, as well as inflammatory factors, using an invasive approach that enhances the robustness of the results. The study design was strong enough to establish consistent results regarding SBP, PP, and mostly PP amplification under these routine conditions.

Aortic PP Amplification

The major hemodynamic finding of our study was that in patients with CAS, PP was markedly increased not only in the ascending aorta but also in the abdominal aorta at the level of renal arteries. PP amplification was mainly due to a slight increase in SBP along the aorta, in association with a consistently lowered DBP, which was around a value of 70 mm Hg. The presence of aortic SBP and PP amplification has been well established in the literature, as has its significant attenuation with age. In the present study, we observed that the increase of SBP and PP from the thoracic aorta to the femoral artery, ie, the SBP and PP amplification, was similar in subjects with and without CAS and was approximately 8 mm Hg from the ascending aorta to the level of renal arteries. In the distal part of the aorta, the amplification was considerably attenuated. This attenuation may correspond to the physiological reduction of aortic diameter below the renal artery level and also to the presence of specific reflection sites at the level of the renal artery or its branches. Taken together, all these findings point to the role of wave reflections (Figures 1 and 2) and to the possibility of their pharmacological modifications.

Aortic PP, Proteinuria, and Renal Function

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. 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. Finally, urinary albumin excretion was shown to be independently associated with an elevated arterial stiffness. These findings agree with our 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. We clearly showed an independent relationship between intraaortic pressure and kidney function in high-risk patients.

In our study, aortic stiffness, measured by noninvasive aortic PWV, was significantly and positively linked to plasma creatinine, independently of age and MBP. This result has already been shown in the literature in many other situations involving chronic kidney disease with or without high BP, and even in subjects after kidney transplantation. These observations suggest the presence of a common factor that might associate increased arterial stiffness, SBP, and reduced renal function. Both BP and progression of chronic kidney disease may be decreased by angiotensin blockade.

Aortic PP and Leukocyte Count

Numerous cross-sectional studies have suggested the role of vascular wall inflammation in hypertensive subjects. This was suggested on the basis of positive associations between C-reactive protein and BP (mainly PP) levels, as well as significant associations of BP with the presence of intercellular adhesion molecule-1, leukocyte count, or fibrinogen in various populations. There is convincing evidence, dating back to 1974, for the predictive value of leukocyte count in subjects with atherosclerosis. Low PP amplification predicts mortality in high-risk subjects with end stage renal disease. Our results may suggest that PP amplification may partly contribute to the predictive value of inflammatory factors.

PP is a complex parameter depending mainly on left ventricular stroke volume, arterial stiffness, height, and aortic wave reflections. Given that arteriolar bifurcations are the major wave reflections sites in the vascular tree, the role of the microvasculature on aortic PP needs to be particularly emphasized. Impairment of microvessels, and hence peripheral resistance, by deteriorating blood cell rheology may influence PP via the magnitude of the resulting wave reflections. Importantly, a relatively small number of leukocytes (5000 cells/mm³, or <0.1% of blood volume) can increase vascular resistance by 25% and favor the presence of low PP amplification and high aortic PP.

Finally, it is important to note that these results were observed in a selected sample of patients at coronary risk undergoing standard coronary angiography using intraarterial BP measurement under drug treatment. Our findings should not be generalized to patients with acute coronary syndrome.
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 the drug dosage in high-risk subjects.

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Disclosures
None.

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