Aortic Pulse Wave Velocity as a Marker of Cardiovascular Risk in Hypertensive Patients

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Abstract—Large artery damage is a major contributory factor to cardiovascular morbidity and mortality of patients with hypertension. Pulse wave velocity (PWV), a classic evaluation of arterial distensibility, has never been ascertained as a cardiovascular risk marker. To determine the factors influencing aortic PWV and the potential predictor role of this measurement, we studied a cohort of 710 patients with essential hypertension. Atherosclerosis alterations (AA) were defined on the basis of clinical events. Calculation of cardiovascular risks, by use of Framingham equations, was performed in subjects without AA. PWV was higher in the presence of AA (14.9±4.0 versus 12.4±2.6 m/s, $P<0.0001$), even after adjustments on confounding factors and was the first determinant ($P<0.0001$) of the extent of atherosclerosis assessed as the sum of the atherosclerotic sites. In patients without AA, all cardiovascular risks increased constantly with PWV. Furthermore, at a given age, aortic PWV was the best predictor of cardiovascular mortality. The odds ratio of being in a high cardiovascular mortality risk group (>5% for 10 years) for patients in the upper quartile of PWV was 7.1 (95% confidence intervals 4.5 to 11.3). The presence of a PWV >13 m/s, taken alone, appeared as a strong predictor of cardiovascular mortality with high performance values. This study shows that aortic PWV is strongly associated with the presence and extent of atherosclerosis and constitutes a forceful marker and predictor of cardiovascular risk in hypertensive patients. (***Hypertension*. 1999;33:1111-1117.**)

Key Words: atherosclerosis ■ hypertension, essential ■ aortic stiffness ■ cardiovascular risk

Hypertension is a well-recognized cardiovascular risk factor.[1] Interventional studies in hypertensive populations have demonstrated the significant decrease in cardiovascular events obtained by antihypertensive drug treatment.[2] Nevertheless, in these studies, the number of patients needed to be treated in order to avoid 1 cardiovascular event remains high, particularly in the younger population. Clearly, the consideration of the other cardiovascular risk factors associated with hypertension would enable a more accurate evaluation of individual risk, risk stratification, and cost-effective preventive therapy.[3] From the Framingham population, evaluations have been proposed, taking into account simultaneously the contribution of blood pressure (BP), tobacco consumption, gender, lipid profile, diabetes mellitus, and ECG left ventricular hypertrophy.[4] However, an appropriate and simple evaluation of individual risk, based on a single measurement, is still lacking.

Arterial stiffness increases with age[5] and hypertension[6] and is also enhanced in subjects with diabetes mellitus,[7] atherosclerosis,[8] and end-stage renal disease.[9] The most obvious consequences of arterial stiffening are increased pulsatile BP caused by higher systolic BP (SBP) and lower diastolic BP (DBP), thereby causing increased left ventricular afterload and altering coronary perfusion.[6,9] High SBP and pulse pressure, low DBP, and left ventricular hypertrophy have been identified as independent factors of cardiovascular morbidity and mortality in the general population.[1,10–12] Arterial stiffness can be assessed noninvasively with the use of pulse wave velocity (PWV) measurement, that is, the velocity of the pulse wave to travel a given distance between 2 sites of the arterial system. Nevertheless, whether aortic stiffening is predictive of clinical outcome and/or mortality needs to be established.

The goal of the present study was (1) to test the ability for aortic PWV to act as a marker of individual cardiovascular risk, integrating the atherosclerotic vascular damages caused by the most common cardiovascular risk factors, and (2) to identify high-risk patients from a hypertensive population never treated or even treated medically by antihypertensive agents. To determine (1) the factors influencing aortic stiffness (estimated by measuring the carotid-femoral PWV), and (2) the potential predictor role of this measurement on cardiovascular risk assessed by a scale, we conducted this cross-sectional study on a cohort of 710 patients with essential hypertension. The results indicate (1) that aortic PWV determined from a single measurement is strongly associated with the presence and extent of atherosclerosis, (2) and that this measurement is highly related to cardiovascular risk as assessed by the standard Framingham equations.[4]

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Methods

Study Cohort

From January 1996 to June 1997, ≈1500 patients entered the Department of Internal Medicine of Broussais Hospital for a cardiovascular check-up ordered by their general practitioner or their cardiologist because of the presence of 1 or several cardiovascular risk factors involving high BP, smoking, dyslipidemia, diabetes mellitus, and/or family history of premature cardiovascular disease (CVD), with or without previously identified atherosclerotic alterations (AA). From those 1500 patients, only subjects with essential hypertension were selected. In never-treated hypertensive subjects (n=105), high BP was defined as an SBP >140 mm Hg and/or a DBP >90 mm Hg, measured by sphygmomanometry, in the supine position with a minimum of 3 casual measurements during the last month. In treated hypertensive subjects (n=605), patients were included regardless of whether BP was well controlled (SBP <140 mm Hg and DBP <90 mm Hg). Patients with all forms of secondary hypertension, on the basis of classic laboratory and radiology tests, were not included. Patients with cancer (other than basal cell carcinoma), with insulin-dependent diabetes, or with severe renal insufficiency (creatinine >300 μmol/L) were not included in the study. The study cohort was then composed of 710 hypertensive consecutive patients (412 men, 298 women) with mean age (±SD) of 60±13 years. From the 710 patients, 605 (85%) were treated with antihypertensive therapy at inclusion; the mean number of antihypertensive drugs was 1.48±1.01 per patient. The antihypertensive drugs included calcium antagonists (323 patients), β-blockers (225 patients), diuretics (212 patients), angiotensin-converting enzyme inhibitors (195 patients), central-acting agents (68 patients), angiotensin II antagonists (17 patients), and α-blockers (11 patients), either alone or in combination. One hundred eight (15%) patients were medically treated for dyslipidemia (drugs including statins or fibrates). Sixty-six (9%) patients were medically treated for diabetes mellitus (drugs including sulfamids and/or biguanids). Each subject provided informed consent for the study, which was approved by our institutional review board.

Information compiled from the questionnaire filled out at inclusion included gender, age, weight and height, body mass index, family (first-degree relatives) history of premature cardiovascular events (<55 years old in men and <60 in women), personal history of diabetes mellitus, personal history of dyslipidemia, smoking habits, previous diseases, and use of medications including antihypertensive drugs. From the clinical questionnaire and the findings of the check-up during hospitalization, AA was present in 180 patients and absent in 530 patients. For a description of AA in hypertensive patients, the usual criteria were used according to the International Classification of Diseases (9th revision) for coronary heart disease (CHD), cerebrovascular disease, peripheral vascular disease, and abdominal aortic aneurysm. Dyslipidemia was defined as a total/high-density (HDL) cholesterol ratio >5 or the presence of a hypocholesterolemic drug (statins or fibrates). Diabetes mellitus was defined as a fast glycemia >7.8 mmol/L or the presence of hypoglycemic agents (sulfamids and/or biguanids).

One hundred eighty patients had AA involving ≥1 vascular site, including CHD (106 patients), peripheral vascular disease (58 patients), cerebrovascular disease (56 patients), and abdominal aorta aneurysm (37 patients). The mean number of vascular sites involved by AA in the population of the 180 patients was 1.43±0.65 per patient. Extent of atherosclerosis was assessed as the number of vascular sites involved by AA: 0 (530 patients), 1 (119 patients), 2 (45 patients), or 3 (16 patients).

Methods

The measurements were performed in the morning after an overnight fast, each patient being in supine position. Brachial BP was measured with a mercury sphygmomanometer after 15 minutes of rest. Phases I and V of the Korotkoff sounds were considered respectively as SBP and DBP. The mean BP (MBP) was calculated as MBP=DBP+(SBP−DBP/3). Five measurements 2 minutes apart were averaged.

After BP determination, the PWV measurement was performed before the 3-lead orthogonal ECG and blood sample in a controlled environment at 22±2°C. PWV was determined with the use of an automatic device: the Complior (Colson), which allowed an online pulse wave recording and automatic calculation of PWV with 2 transducers, 1 positioned at the base of the neck for the common carotid artery and the other over the femoral artery, as previously described.[13] The validation of this automatic method and its reproducibility have been previously described, with an intraobserver repeatability coefficient of 0.935 and an interobserver reproducibility coefficient of 0.890.[13]

Heart period was determined from the 3-lead orthogonal ECG. On the basis of the 8-second recording, the average heart rate was calculated (in beats per minute) during that period. ECG left ventricular hypertrophy was defined as a Sokolow index superior to 35 mm. Waist circumference midway between the lowest rib and the iliac crest and hip circumference at the level of the great trochanters were measured with flexible tape. Venous blood samples were obtained in subjects after an overnight fast. Plasma was separated without delay at 4°C in a refrigerated centrifuge and stored at 4°C (for the determination of routine chemistry profile by standard methods) until analysis. Total cholesterol and triglycerides were determined with the use of a Technicon Chem assay (Technicon Instruments), and HDL cholesterol was measured in the supernatant after precipitation of apolipoprotein B–containing lipoproteins with heparin-manganese chloride. Low-density lipoprotein cholesterol was calculated by the formula of Friedewald et al[14] for patients with serum triglyceride concentrations <4.0 mmol/L.

Statistical Analysis

Overall Population (n=710)

Data are expressed as mean±SD. Student's *t* test was used for comparison of normally distributed continuous variables. Differences in frequency were tested by χ^2 analysis. Gender was used as a dummy variable (1, male; 2, female). Statistical analysis was performed on NCSS 6.0.21 software.[15] A value of $P<0.05$ was considered significant. All testing was double-sided. Multiple regression analysis was performed to assess linear associations between aortic pulse wave velocity, extent of atherosclerosis, and determinants of clinical, biochemical, and cardiovascular parameters. Logistic regression analysis was used to assess the correlations between the presence of AA (1=yes, 0=no) and determinants of clinical, biochemical, and cardiovascular parameters. Prognostic variables for the presence of AA, determined from the logistic regression analysis, were divided into 2, 3, or 4 clinically pertinent subgroups. The relative risk of AA in each group of any prognostic variable compared with the reference group was estimated as the crude odds ratio. Confidence limits of crude odds ratios were calculated according to Woolf's method.[16] The adjusted relative risk of AA in each group compared with the reference group was estimated as the adjusted odds ratio. Adjusted odds ratios were calculated as the antilogarithm of the β-coefficient of the logistic regression of AA with all the prognostic variables divided into 2, 3, or 4 groups (plasma creatinine, tobacco life-long dose, age, PWV, DBP, and diabetes mellitus). Ninety-five percent confidence intervals (CI) around the adjusted odds ratios estimated were obtained from the formula antilogarithm ($\beta \pm 1.96 \times SE\beta$), where $SE\beta$ is the standard error of β.

Population Without AA

Of the 530 patients without AA, age range was from 30 to 74 years in 462 patients. In this group corresponding to the age range of the Framingham cohorts, before the 12 years of follow-up, 10-year different cardiovascular risks were calculated on the basis of the equations derived from the Framingham Heart Study and from the Framingham Offspring Study.[4] Calculations were made for the following outcomes: myocardial infarction (MI) (including silent and unrecognized MI); death from CHD (sudden or nonsudden); CHD (consisting of MI, angina pectoris, coronary insufficiency and CHD death); stroke, including transient ischemia; CVD (including

TABLE 1. Characteristics of Patients According to Presence or Absence of Atherosclerotic Alterations

Parameter	Atherosclerotic Alterations n=180	No Atherosclerotic Alterations (n=530	P
Age, y	67±12	57±13	<0.0001
Gender, M/F	129/51	284/246	<0.0001
SBP, mm Hg	149±22	144±20	0.003
DBP, mm Hg	80±12	84±12	0.0004
Mean BP, mm Hg	103±13	104±13	...
Pulse pressure, mm Hg	69±19	60±17	<0.0001
Heart rate, bpm	67±10	69±10	0.03
Diabetes mellitus, ratio	0.2±0.4	0.1±0.3	0.0002
Current smoker, ratio	0.3±0.5	0.2±0.4	<0.0001
Tobacco life-long dose, pack-years	20±21	9±16	<0.0001
Duration of antihypertensive therapy, y	13±9	9±9	<0.0001
Dyslipidemia, ratio	0.5±0.5	0.4±0.5	0.0001
Body mass index, kg/m^2	26±4	27±4	0.002
Waist-to-hip ratio	0.96±0.09	0.94±0.08	0.02
Total/HDL cholesterol, ratio	4.8±1.6	4.5±1.4	0.016
Plasma glucose, mmol/L	6.2±1.8	6.1±1.6	...
Plasma creatinine, μmol/L	107±35	88±24	<0.0001
ECG left ventricular hypertrophy, ratio	0.1±0.3	0.1±0.3	...
Pulse wave velocity, m/s	14.9±4.0	12.4±2.6	<0.0001

Continuous variables are expressed as mean±SD.

all the above plus congestive heart failure and peripheral vascular disease); and death from CVD.

In this population of 462 patients, PWV was divided into 4 quartiles of 115 or 116 patients. A 10-year absolute MI risk >5%, a 10-year absolute CHD risk >15%, a 10-year absolute CHD mortality risk >5%, a 10-year absolute stroke risk >5%, a 10-year absolute CVD risk >20%, and a 10-year cardiovascular mortality risk >5% were defined as high risks. The relative risk of being in the high-risk group according to the presence versus absence of cardiovascular risk factors was calculated as the crude odds ratio.

PWV as a Diagnostic Test

To assess the performance of PWV considered as a diagnostic test, with the use of receiver operating characteristic (ROC) curves, we calculated sensitivities, specificities, positive predictive values, and negative predictive values of PWV at different cutoff values, first to detect the presence of AA in the overall population and second to detect patients with high 10-year cardiovascular mortality risk in the subgroup of 462 patients without AA with age range from 30 to 74 years. Optimal cutoff values of PWV were defined as the maximization of the sum of sensitivity and specificity.

Results

Overall Population

Table 1 shows the characteristics of the patients according to the presence or absence of AA. Mean (±SD) PWV was 14.9±4.0 m/s in the group of patients with AA and 12.4±2.6 m/s for the patients without AA ($P<0.0001$).

Age ($P<0.0001$), SBP ($P<0.0001$), plasma glucose ($P<0.0001$), the presence of AA ($P<0.0001$), plasma creatinine ($P=0.0001$), and gender ($P=0.03$) were the only independent factors modulating PWV. Lipids, smoking, duration of antihypertensive therapy, and the presence of any antihypertensive drug did not significantly enter the multiple regression analysis.

The only independent factors modulating the presence of AA were plasma creatinine ($P<0.0001$), tobacco life-long dose ($P<0.0001$), age ($P=0.0001$), PWV ($P=0.0004$), DBP ($P=0.03$), and the presence of diabetes mellitus ($P=0.06$). When the extent of atherosclerosis was considered as the independent variable, only PWV ($P<0.0001$), tobacco life-long dose ($P<0.0001$), plasma creatinine ($P<0.0001$), body mass index ($P=0.002$), DBP ($P=0.003$), the presence of dyslipidemia ($P=0.007$), and age ($P=0.008$) entered the multiple regression analysis. Considering the presence of AA or extent of atherosclerosis as the dependent variable in multivariate analysis, SBP did not significantly persist in the model, probably because of the strong colinearity between SBP and PWV ($r=0.354$, $P<0.0001$) and, to a lesser extent, between SBP and age ($r=0.155$, $P<0.0001$).

Table 2 shows the odds ratios of AA according to prognostic variables (defined by the logistic regression). Adjustments were made on all the prognostic variables in this table. Patients with PWV >15 m/s, with creatinine >110 μmol/L, >70 years old or those who smoked >20 pack-years had an increased adjusted risk of AA, whereas those whose DBP was >110 mm Hg had a decreased adjusted risk of AA.

Population Without AA: PWV as a Predictor of Cardiovascular Risks According to the Framingham Equations

We observed a constant increase for all the risks (MI, CHD, death from CHD, stroke, CVD, and death from CVD) with

TABLE 2. Odds Ratios of Atherosclerotic Alterations According to Prognostic Variables

Prognostic Variable	No. of Subjects	Atherosclerosis, n (%)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Plasma creatinine, μmol/L				
<70*	124	13 (10)	1.00	1.00
70–90	263	53 (20)	1.92 (1.01–3.65)	1.80 (0.89–3.63)
90–110	194	48 (25)	2.36 (1.23–4.53)	1.42 (0.99–2.04)
>110	129	66 (51)	4.88 (2.56–9.29)	1.70 (1.31–2.21)
Tobacco life-long dose, pack-years				
0*	409	71 (17)	1.00	1.00
0–20	128	29 (23)	1.31 (0.81–2.11)	1.54 (0.89–2.66)
>20	173	80 (46)	2.66 (1.85–3.83)	1.93 (1.54–2.42)
Age, y				
<50*	162	15 (9)	1.00	1.00
50–60	201	34 (17)	1.83 (0.96–3.48)	1.50 (0.75–3.05)
60–70	181	54 (30)	3.22 (1.75–5.93)	1.49 (1.01–2.18)
>70	166	77 (46)	5.01 (2.77–9.07)	1.57 (1.20–2.06)
Pulse wave velocity, m/s				
<10.5*	145	18 (12)	1.00	1.00
10.5–12	173	28 (16)	1.30 (0.69–2.45)	1.14 (0.57–2.26)
12–15	230	57 (25)	2.00 (1.13–3.53)	1.08 (0.76–1.24)
>15	158	75 (47)	3.82 (2.18–6.70)	1.34 (1.03–1.76)
DBP, mm Hg				
<70*	198	63 (32)	1.00	1.00
70–90	285	74 (26)	0.82 (0.56–1.20)	0.69 (0.43–1.11)
90–110	146	31 (21)	0.67 (0.41–1.08)	0.83 (0.62–1.12)
>110	81	12 (15)	0.47 (0.24–0.92)	0.75 (0.56–0.98)
Diabetes mellitus, yes-no				
No*	605	138 (23)	1.00	1.00
Yes	105	42 (40)	1.75 (1.17–2.62)	1.62 (0.98–2.68)

Adjustments were made on all prognostic variables in this table.
*Patients in this category served as reference group.

the increase of PWV. Figure 1 shows the relation between PWV and 10-year CVD risk (r=0.495; P<0.0001). The relations between PWV and the other risks (MI, CHD, death from CHD, stroke and death from CVD) had the same levels of statistical significance, with correlation coefficients ranging between 0.44 and 0.50 (data not shown).

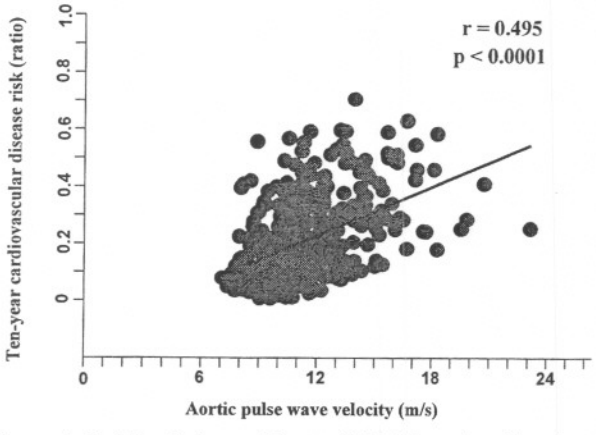

Figure 1. Relation between 10-year CVD risk and aortic pulse wave velocity.

Table 3 shows the odds ratios of being in a high-risk group according to the presence versus absence of a cardiovascular risk factor. Aortic PWV appeared (1) as a stronger predictor than plasma creatinine, left ventricular hypertrophy, and total/HDL cholesterol for any type of cardiovascular risks, (2) as a stronger predictor than smoking for all risks but MI, and (3) as a stronger predictor than hypertension for all risks but stroke. Furthermore, at a given age, PWV appeared as the strongest predictor of cardiovascular mortality. The odds ratio of being in the high-risk cardiovascular mortality group for patients with PWV >13.5 m/s was 7.1 (95% CI 4.5 to 11.3).

PWV as a Diagnostic Test

In the overall population, optimal cutoff value of PWV to detect the presence of AA was 13 m/s with the following performance: 62% sensitivity, 67% specificity, 39% positive predictive value, and 84% negative predictive value (area under ROC curve=0.69±0.07, data not shown)

In the subgroup of 462 patients without AA with age range from 30 to 74 years, optimal cutoff value of PWV to

TABLE 3. Odds Ratio of Being in High-Risk Group According to Presence Versus Absence of Cardiovascular Risk Factor

	Odds Ratio of Being in High-Risk Group (95% CI)					
Parameter	MI	CHD	CHD Mortality	Stroke	CVD	Cardiovascular Mortality
Pulse wave velocity, >13.5 m/s	3.5	4.6	4.9	6.1	5.3	7.1
	(2.3–5.5)	(2.9–7.2)	(3.1–7.8)	(3.8–9.6)	(3.4–8.4)	(4.5–11.3)
Gender, male	6.6	7.1	7.3	2.0	3.8	2.9
	(4.4–9.9)	(4.5–11.2)	(4.3–12.7)	(1.3–3.1)	(2.6–5.7)	(1.9–4.3)
Age, >60 y	3.0	3.9	7.3	11.1	6.1	12.9
	(2.0–4.4)	(2.6–5.9)	(4.5–11.9)	(6.7–18.2)	(4.0–9.2)	(8.1–20.5)
Plasma glucose, >7.0 mmol/L	8.1	5.9	5.5	7.1	8.4	4.7
	(4.0–16.3)	(3.3–10.1)	(3.2–9.7)	(4.0–12.5)	(4.3–16.4)	(2.6–8.2)
Hypertension, >160/90 mm Hg	2.8	3.4	3.2	6.8	3.6	2.8
	(1.8–4.2)	(2.2–5.2)	(2.0–5.0)	(4.3–10.8)	(2.3–5.4)	(1.9–4.3)
Current smoker, yes-no	9.0	3.7	2.6	1.9	3.8	2.2
	(4.8–16.8)	(2.3–6.0)	(1.6–4.3)	(1.2–3.2)	(2.3–6.3)	(1.4–3.6)
Tobacco life-long dose, >20 pack-years	4.4	2.0	1.9	1.7	2.6	1.7
	(2.6–7.2)	(1.3–3.2)	(1.2–3.2)	(1.1–2.8)	(1.6–4.1)	(1.1–2.8)
Total/HDL cholesterol, ratio >5	3.7	3.9	3.6	1.5	3.6	2.8
	(2.5–5.5)	(2.6–5.9)	(2.3–5.7)	(1.0–2.3)	(2.3–5.4)	(1.9–4.3)
Left ventricular hypertrophy, yes-no	2.2	11.2	3.0	2.2	4.9	4.5
	(1.2–4.1)	(5.3–23.8)	(1.6–5.6)	(1.2–4.0)	(2.5–9.5)	(2.4–8.4)
Plasma creatinine, >100 μmol/L	1.8	2.5	2.7	1.7	1.8	1.8
	(1.1–2.7)	(1.6–3.9)	(1.7–4.3)	(1.1–2.8)	(1.2–2.8)	(1.2–2.8)

Ten-year absolute MI risk >5%, 10-year absolute CHD risk >15%, 10-year absolute CHD mortality risk >5%, 10-year absolute stroke risk >5%, 10-year absolute CVD risk >20%, and 10-year cardiovascular mortality risk >5% were considered high.

detect patients with high 10-year cardiovascular mortality risk was 13 m/s with the following performance: 60% sensitivity, 84% specificity, 67% positive predictive value, and 80% negative predictive value (area under ROC curve=0.78±0.07, Figure 2).

Discussion

The salient findings of this study were that in a population of treated or untreated subjects with essential hypertension, aortic PWV was strongly related to the presence and extent of AA, including CHD, peripheral vascular disease, cerebrovascular disease, and abdominal aorta aneurysm and that PWV was a strong predictor of cardiovascular risks as determined by the Framingham equations. Furthermore, the presence of a PWV >13 m/s, taken alone, appeared as a strong predictor of cardiovascular mortality with high performance values.

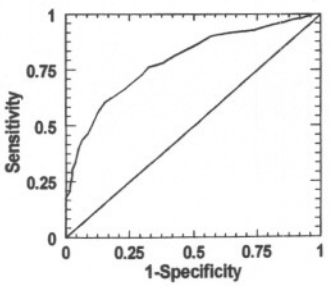

Figure 2. ROC curve: Aortic pulse wave velocity in detection of patients with high 10-year cardiovascular mortality (area under curve=0.78±0.07).

In the present study, we used PWV, which is as a marker of aortic stiffness, since it is related to the square root of the elasticity modulus and to the thickness/radius ratio.[6] The PWV determined from foot-to-foot transit time in the aorta offers a simple, reproducible, and noninvasive evaluation of regional aortic stiffness.[17,18] This noninvasive superficial measurement allows only an estimate of the distance traveled by the pulse, and accurate measurements of this distance are obtained only with invasive procedures. In this regard, some authors suggested a possible correction based on anatomic dimensions of the body,[19] whereas others recommended subtracting the distance between the suprasternal notch to the carotid location from the total distance when the carotid pulse is recorded instead of the aortic arch pulse, because the pulse traveling is in the opposite direction.[6] In fact, because arteries become longer and tortuous with age, the path lengths determined from superficial linear measurements are underestimated. Repeatability studies, checks made with Bland and Altman diagrams,[20] and modern computer technology[13] now made it quite feasible to simply investigate aortic stiffness in cardiovascular epidemiologic studies. Since the principal factors modulating the level of PWV are age and BP,[5,6] epidemiologic studies involving PWV should be adjusted to these 2 parameters. The studied population was composed of patients entering the Department of Internal Medicine of

Broussais Hospital for a cardiovascular check-up, thus very close to clinical practice, and including young and old hypertensive subjects, with and without hypertensive drug treatment. Moreover, it should be noted that although a significant proportion of patients (25%) had confirmed AA, this proportion was probably underestimated, including unrecognized silent myocardial ischemia or cerebrovascular disease, since invasive explorations were not systematically performed.

In the totality of the present population, the presence of AA influenced the level of PWV independent of age and BP. Most of the studies relating PWV to cholesterol and/or dyslipidemia found minimal or inconsistent correlations.[9,21] As suggested by others,[22–24] the present correlation between PWV and AA points to the presence of diffuse and calcified atherosclerotic plaques in association with the development of extracellular matrix, mainly collagen tissue. Our finding that PWV was strongly related to the number of atherosclerotic sites confirms this interpretation. The presence of a negative correlation between DBP and the presence and extent of atherosclerosis has been previously reported.[6,11] Indeed, the consequences of arterial stiffening on BP are not only increased SBP and pulse pressure but also decreased DBP at any given mean BP value. In fact increased pulse pressure, decreased DBP, and increased PWV are related to the same common denominator, namely increased aortic stiffness, a parameter that is associated with increased cardiovascular risk.[25] Finally, we found that PWV was strongly associated with diabetes and renal insufficiency, 2 conditions in which AA and hypertension are commonly present, and increased arterial stiffness has been previously noted.[7,9,26]

An important result of the present study was that in the population of hypertensive subjects without AA, increased aortic PWV might be a significant predictor of cardiovascular events. The presence of a PWV >13 m/s, taken alone, appeared as a strong predictor of cardiovascular mortality with high performance values. In recent longitudinal studies, we and others have shown that increased pulse pressure, the major hemodynamic consequence of increased aortic PWV, was a strong independent predictor of cardiac mortality, mainly MI, in populations of normotensive and hypertensive subjects.[10–12] The present study is somewhat different in nature because only cross-sectional data are presented. However, the use of the Framingham equation–based cardiovascular scale as comparator is important to consider because the evaluation of cardiovascular risks with this scale results from large (>5000 persons) and long-term (≥12 years) longitudinal studies with the use of a multifactorial approach, with none lost to follow-up. Using this scale, we showed that aortic PWV is, for a given age, the strongest predictor of cardiovascular mortality and mostly that this single measurement gives an individual evaluation of all cardiovascular risks very close to the level calculated by the multiple risk factors involved in the equations. Because cardiovascular risks according to Framingham equations are calculated on the basis of instant levels of major cardiovascular risk factors, PWV depends on the level of present and past exposure to vascular damage factors and therefore is more closely related to individual cardiovascular risk than any risk scale giving more of a population risk level than an individual risk level. Furthermore, because our population included both treated and untreated hypertensive subjects, the predictive value of PWV was adequate even in the presence of antihypertensive drug treatment. The same observation has been made for pulse pressure measurements that are predictive of MI even in treated hypertensive subjects.[12]

There are several methodological limitations involved with the cardiovascular risk scales. First, cardiovascular risk is lower in France than in the United States and has also shown a decline over the past few decades. Second, cardiovascular risk may differ significantly from one individual to the next, which has an impact on calculations based on part of the cardiovascular risk factors only. Third, the Framingham equations have been modeled on the basis of an asymptomatic population, consisting in a majority of normotensive subjects. These equations should probably be corrected for their application to hypertensive populations such as our study population. Finally, we have furthermore hypothesized for the risk calculation that regardless of whether drugs were involved, for the same blood pressure there was the same risk. Of course, given that our study is cross-sectional, we cannot project any hypothesis regarding the extent of antihypertensive drug–related benefit on cardiovascular risk assessment for the future. From a methodological point of view, therefore, the relation between PWV, atherosclerosis, and cardiovascular risk cannot be directly extended to include normotensive populations.

In conclusion, the present study has shown, in a cohort of untreated and treated hypertensive subjects, that increased aortic PWV was strongly associated with the presence of AA and was even a strong predictor of cardiovascular risk. These results could have important clinical implications in risk assessment strategies. Whether increased aortic PWV constitutes a trigger mechanism or rather a marker of morbid events cannot be evaluated from the present study. The longitudinal investigation of a large unselected population is required to evaluate the independent contribution of PWV to the individual cardiovascular risk.

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