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Aortic Stiffness Is an Independent Predictor of All-Cause and Cardiovascular Mortality in Hypertensive Patients

Stéphane Laurent, Pierre Boutouyrie, Roland Asmar, Isabelle Gautier, Brigitte Laloux, Louis Guize, Pierre Ducimetiere, Athanase Benetos

Abstract—Although various studies reported that pulse pressure, an indirect index of arterial stiffening, was an independent risk factor for mortality, a direct relationship between arterial stiffness and all-cause and cardiovascular mortality remained to be established in patients with essential hypertension. A cohort of 1980 essential hypertensive patients who attended the outpatient hypertension clinic of Broussais Hospital between 1980 and 1996 and who had a measurement of arterial stiffness was studied. At entry, aortic stiffness was assessed from the measurement of carotid-femoral pulse-wave velocity (PWV). A logistic regression model was used to estimate the relative risk of all-cause and cardiovascular deaths. Selection of classic risk factors for adjustment of PWV was based on their influence on mortality in this cohort in univariate analysis. Mean age at entry was 50 ± 13 years (mean \pm SD). During an average follow-up of 112 ± 53 months, 107 fatal events occurred. Among them, 46 were of cardiovascular origin. PWV was significantly associated with all-cause and cardiovascular mortality in a univariate model of logistic regression analysis (odds ratio for 5 m/s PWV was 2.14 [95% confidence interval, 1.71 to 2.67, $P < 0.0001$] and 2.35 [95% confidence interval, 1.76 to 3.14, $P < 0.0001$], respectively). In multivariate models of logistic regression analysis, PWV was significantly associated with all-cause and cardiovascular mortality, independent of previous cardiovascular diseases, age, and diabetes. By contrast, pulse pressure was not significantly and independently associated to mortality. This study provides the first direct evidence that aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in patients with essential hypertension. (*Hypertension*. 2001;37:1236-1241.)

Key Words: arterial stiffness ■ cardiovascular diseases ■ mortality ■ hypertension, essential ■ pulse wave velocity ■ distensibility

Cardiovascular disease, which remains the leading cause of death in developed countries, is not entirely predicted by classic risk factors. Increased arterial stiffness may increase cardiovascular morbidity and mortality because of an elevation of systolic blood pressure (SBP), which raises left ventricular afterload, and because of a decrease in diastolic blood pressure (DBP), which alters coronary perfusion.^{1,2} Most epidemiological studies have singled out SBP as a stronger risk factor for stroke and coronary heart disease than DBP.³⁻¹⁰ Recent studies have shown that, independent of mean blood pressure (MBP), brachial pulse pressure (PP) was a strong determinant of coronary heart disease,⁵⁻¹⁰ stroke,⁴ and cardiovascular events in hypertensive patients and in a general population.⁵⁻¹⁰ Brachial PP is also a strong independent determinant of recurrent events after myocardial infarction in patients with impaired left ventricular function,¹¹ of risk of heart failure in the elderly,¹² and of all-cause mortality in a general population.^{8-10,13} Furthermore, in a cross-sectional study,¹⁴ aortic pulse-wave velocity (PWV) was shown to be associated with cardiovascular risk, as calculated from the Framingham equations.

Despite these arguments, it remains to be demonstrated whether arterial stiffness, which is a major determinant of PP, has any independent prognostic relevance for all-cause and cardiovascular mortality.¹⁵ To the best of our knowledge, only 3 studies¹⁶⁻¹⁸ have attempted to determine the impact of arterial stiffness on survival. De Simone et al¹⁶ have reported that in 294 hypertensive patients, the stroke volume/PP ratio, an index of total arterial compliance, was an independent predictor of cardiovascular events but not of cardiovascular deaths after adjustment for classic risk factors. Blacher et al¹⁷⁻¹⁸ have observed an independent relationship between arterial stiffness (estimated either from carotid incremental modulus of elasticity or from aortic PWV) and all-cause and cardiovascular mortality in patients with end-stage renal disease. However, the latter studies¹⁷⁻¹⁸ concerned a specific population at high risk of mortality, and a direct relationship between arterial stiffness and all-cause and cardiovascular mortality remained to be determined in hypertensive patients at lower risk.

Arterial stiffness can be assessed noninvasively in large populations by measurement of PWV, a simple and repro-

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ducible method.^{19–22} According to the Moens-Korteweg equation,^{1,19} the PWV, which is related to the square root of the elasticity modulus, rises in stiffer arteries. The elastic properties of the aorta and central arteries are the major determinants of systemic arterial impedance, and the PWV measured along the aortic and aortoiliac pathway is the most clinically relevant. In the present study, we tested the hypothesis that aortic stiffness is a predictor of cardiovascular and all-cause mortality in hypertensive patients after classic cardiovascular risk factors have been controlled.

Methods

Subjects and Study Design

The cohort included the 1980 consecutive patients who attended the outpatient hypertension clinic of Hôpital Broussais between April 1980 and December 1996 and who had a determination of arterial stiffness with PWV. Among them, 483 patients were treated with at least 1 antihypertensive drug at the time of the PWV measurement. The others were referred for clinical and biological investigation before treatment. Demographic data with details of cardiovascular risk factors and previous events were collected on the day when PWV was measured. Diabetes and hypercholesterolemia were indicated by a previous diagnosis or by the use of an oral hypoglycemic agent or a cholesterol-lowering agent. Smoking status was defined as current or past versus never.

A nurse measured supine blood pressure in the right arm with the use of a manual sphygmomanometer. After a 10-minute rest period, pressure was measured 3 times, and the mean of the last 2 measurements was calculated. The first and the fifth Korotkoff's phases were used to define SBP and DBP. Mean BP was calculated as $DBP + [(SBP - DBP)/3]$.

PWV Measurement

PWV was measured along the descending thoracoabdominal aorta using the foot-to-foot velocity method, as previously published and validated.^{20,22} Briefly, waveforms were obtained transcutaneously over the common carotid artery and the right femoral artery, and the time delay (t) was measured between the feet of the 2 waveforms. The distance (D) covered by the waves was assimilated to the distance measured between the 2 recording sites. PWV was calculated as $PWV = D$ (meters)/ t (seconds).^{20,22} Annual mean values of PWV did not change over the study period, which ruled out any major time or population recruitment effect on the obtained values.

Mortality

The follow-up study period ended on December 31, 1996 (mean follow-up, 9.3 years). Deceased subjects were identified from the French mortality records provided by the Institut National de Statistiques et d'Etudes Economiques. A member of the cohort was considered to have died when the individual had the same first name, last name, gender, and date and place of birth as a person recorded in the Institut National d'Etudes Economiques mortality records during the period of follow-up. This was confirmed by the death certificates. Individuals with incomplete matching ($n=42$) were contacted by telephone interview or through their general practitioners, and none of them had died. All other subjects were considered to be alive at the end of the follow-up period. On the basis of this procedure, 107 subjects of our cohort died during the follow-up period. Causes of death were then coded from the death certificates, as provided by INSERM SC8. Causes of death were coded according to the *International Classification of Disease* (ninth revision).

Data Analysis

A logistic regression analysis was used to estimate the relative risk of all-cause and cardiovascular mortality associated with PWV.²³ The adjusted relative risk of experiencing an outcome event during follow-up for an increase in PWV (arbitrarily fixed at 5 m/s) was

TABLE 1. Baseline Characteristics of Patients and Fatal Events

Parameters	Mean \pm SD (Interquartile Range)
Age, y	50 \pm 13 (40–58)
Follow-up duration, mo	112 \pm 53 (77–165)
Gender ratio, men/women	1297/683
BMI, kg \cdot m ⁻²	25 \pm 4 (23–27)
SBP, mm Hg	148 \pm 22 (132–160)
MBP, mm Hg	109 \pm 16 (97–118)
DBP, mm Hg	89 \pm 14 (78–98)
PP, mm Hg	59 \pm 14 (50–66)
HR, bpm	70 \pm 11 (62–76)
PWV, m \cdot s ⁻¹	11.5 \pm 3.4 (9.2–13.1)
CVD risk profile	
Smoking, yes/no	351/1629
Diabetes, yes/no	114/1866
Hypercholesterolemia, yes/no	587/1393
CVD history	
Previous CVD, yes/no	182/1798
Mortality	
All deaths (men/women)	107 (77/30)
Cardiovascular deaths (men/women)	46 (33/13)

BMI indicates body mass index; CVD, cardiovascular disease.

estimated as the odds ratio (OR). Adjusted ORs were calculated as the antilogarithm of the β coefficient of the logistic regression of the outcome events. The 95% confidence interval (CI) around the adjusted OR estimates was obtained with the formula antilogarithm ($\beta \pm 1.96$ SE), in which SE is the standard error of β . Similar calculations of ORs were performed for a 10-year increase in age, a 10 mm Hg increase in blood pressure, and a 10 bpm increase in heart rate (HR). To ensure that any observed association between PWV and a given outcome was not confounded by the presence of classic risk factors, we used a multivariate model of logistic regression that included all cardiovascular risk factors significantly associated with mortality in univariate analysis. Because arterial stiffness is a major determinant of PP (and SBP), we compared a multivariate model that included PWV to models that included either PP or SBP.

Gender (1, male; 2, female), previous history of cardiovascular disease (1, no; 2, yes), diabetes (1, no; 2, yes), hypercholesterolemia (1, no; 2, yes), and smoking status (1, no; 2, yes) were used as dummy variables. All analyses were performed with Statview 6.0 statistical software (Adept Software). Data are expressed as mean \pm SD. A value of $P < 0.05$ was considered significant.

Results

All-Cause Mortality

The characteristics of the population are described in Table 1. In the whole population, 107 fatal events occurred. PWV was significantly associated with all-cause mortality in a univariate model of logistic regression analysis (Table 2). Selection of classic risk factors for adjustment of PWV was based on their influence on all-cause mortality in this cohort with univariate models of logistic regression analysis. Previous cardiovascular disease, age, PP, SBP, HR, and diabetes, were significantly associated with all-cause mortality (Table 2),

TABLE 2. Relative Risk of All-Cause Mortality According to PWV and Cardiovascular Risk Factors: Univariate Analysis

Parameters	OR	Lower 95% CI	Higher 95% CI	P
PWV, 5 m/s	2.14	1.71	2.67	<0.0001
Previous CVD, yes/no	7.27	4.70	11.25	<0.0001
Age, 10 y	2.12	1.78	2.53	<0.0001
PP, 10 mm Hg	1.39	1.24	1.56	<0.0001
SBP, 10 mm Hg	1.17	1.08	1.28	<0.01
HR, 10 bpm	1.24	1.05	1.46	0.01
Diabetes, yes/no	2.19	1.15	4.18	0.01

whereas gender, MBP, DBP, smoking, and hypercholesterolemia were not.

In a multivariate model of logistic regression analysis, PWV was significantly associated with all-cause mortality, independent of previous cardiovascular disease, age, HR, and diabetes (Model 1, Table 3). By contrast, PP (or SBP) was not significantly and independently associated with mortality (Models 2 and 3, Table 3). Similar results were observed when a separate analysis was performed in men only. The analysis was not possible in women because of the low mortality rate.

PWV was significantly higher in patients using antihypertensive drugs at baseline than in untreated patients (11.79 ± 3.64 versus 11.39 ± 3.27 m/s, $P=0.02$). However, this difference was only marginal (+3.5%) and did not affect the relationship between PWV and all-cause mortality. Indeed, when antihypertensive treatment at the original screening (yes/no) was included in a multivariate model of logistic regression analysis, in addition to previous cardiovascular disease, age, and HR, the OR for an increase in PWV of 5 m/s was 1.39 (95% CI, 1.07 to 1.81; $P=0.02$) for all-cause mortality. This value is similar to that in Table 3, which was

obtained without taking into account the administration of antihypertensive drugs.

In the 1798 patients devoid of previous cardiovascular events at entry, PWV significantly predicted all-cause mortality. Indeed, in univariate analysis, the OR for an increase in PWV of 5 m/s was 1.79 (95% CI, 1.45 to 2.14; $P<0.001$) in this subgroup.

Cardiovascular Mortality

Among the 107 fatal events, 46 were of cardiovascular origin, including 19 deaths from coronary heart disease and 17 fatal strokes. The 10 other fatal cardiovascular events were coded as follows in the death certificates: congestive heart failure ($n=3$), pulmonary embolism ($n=2$), hypertension ($n=1$), diabetes with microvascular disease ($n=1$), hypotension ($n=1$), and viral myocarditis ($n=1$).

PWV was significantly associated with cardiovascular mortality in a univariate model of logistic regression analysis (Table 4). Selection of classic risk factors for adjustment of PWV was based on their influence on cardiovascular mortality in this cohort, in univariate models of logistic regression analysis. Previous cardiovascular disease, age, PP, SBP, and

TABLE 3. Relative Risk of All-Cause Mortality According to Cardiovascular Risk Factors in Multivariate Analysis: Various Models Including PWV, PP, or SBP

Parameters	OR	Lower 95% CI	Higher 95% CI	P
Model 1 $\text{CHI}^2=135$				
Previous CVD, yes/no	4.31	2.70	6.88	<0.0001
Age, 10 y	1.78	1.46	2.17	<0.0001
HR, 10 bpm	1.29	1.08	1.55	<0.01
PWV, 5 m/s	1.34	1.04	1.74	0.02
Model 2 $\text{CHI}^2=130$				
Previous CVD, yes/no	4.42	2.78	7.03	<0.0001
Age, 10 y	1.92	1.59	2.31	<0.0001
HR, 10 bpm	1.34	1.13	1.60	<0.001
PP, 10 mm Hg	NS
Model 3 $\text{CHI}^2=132$				
Previous CVD, yes/no	4.34	2.72	6.92	<0.0001
Age, 10 y	1.89	1.56	2.28	<0.0001
HR, 10 bpm	1.31	1.10	1.56	<0.01
SBP, 10 mm Hg	1.06	0.97	1.17	NS

Diabetes (yes/no), included in each of the 3 models, was not significantly associated with all-cause mortality.

TABLE 4. Relative Risk of Cardiovascular Mortality According to PWV and Cardiovascular Risk Factors: Univariate Analysis

Parameters	OR	Lower 95% CI	Higher 95% CI	P
PWV, 5 m/s	2.35	1.76	3.14	<0.0001
Previous CVD, yes/no	14.81	7.98	27.47	<0.0001
Age, 10 y	2.32	1.78	3.01	<0.0001
PP, 10 mm Hg	1.53	1.31	1.80	<0.0001
SBP, 10 mm Hg	1.26	1.12	1.42	<0.001
Diabetes, yes/no	4.23	1.96	9.15	<0.001

diabetes were significantly associated with all-cause mortality (Table 4), whereas gender, MBP, DBP, HR, smoking, and hypercholesterolemia were not.

In a multivariate model of logistic regression analysis, PWV was significantly associated with cardiovascular mortality, independent of previous cardiovascular disease, age, and diabetes (Model 1, Table 5). By contrast, PP was only marginally ($P=0.06$) associated with cardiovascular mortality (Model 2, Table 5). SBP was significantly and independently associated with cardiovascular mortality (Model 3, Table 5). Similar results were observed when a separate analysis was performed in men only. The analysis was not possible in women because of the low mortality rate.

When antihypertensive treatment (yes/no) at the original screening was included in a multivariate model of logistic regression analysis, in addition to previous cardiovascular disease and age, the OR for an increase in PWV of 5 m/s was 1.40 (95% CI, 1.08 to 1.80; $P=0.01$) for cardiovascular mortality. This value is similar to that in Table 5, which was obtained without taking into account the administration of antihypertensive drugs.

In the 1798 patients devoid of previous cardiovascular events at entry, PWV significantly predicted cardiovascular mortality. Indeed, in univariate analysis, the OR for an increase in PWV of 5 m/s was 1.60 (95% CI, 1.12 to 2.13; $P=0.011$).

Discussion

The present study is the first one to provide a direct relationship between aortic stiffness and mortality in a large cohort of hypertensive patients. Indeed, PWV was independently associated with all-cause and cardiovascular mortality after adjustment for previous cardiovascular disease, age, and diabetes.

Our group^{4,8,9} and others^{5-7,10,11} have previously reported the positive independent association between brachial PP, an indirect index of arterial stiffness, and all-cause or cardiovascular mortality. However, these studies provided only indirect arguments for an impact of arterial stiffness on mortality. Indeed, PP was calculated from SBP and DBP, both measured with a sphygmomanometer at the site of the brachial artery. Because of the physiological PP amplification between central and peripheral arteries,^{1,13,24-28} brachial PP may not reflect aortic PP, which influences left ventricular afterload and coronary perfusion. In addition, factors other than arterial stiffness can influence the value of PP, such as HR, cardiac contractility, and venous pressure.^{1,13,26} Thus, brachial PP is only a surrogate index of arterial stiffness.

The international guidelines for the management of hypertension¹⁵ suggested that it would be useful to demonstrate whether arterial stiffness has any independent prognostic relevance for mortality. During the last 20 years, technolog-

TABLE 5. Relative Risk of Cardiovascular Mortality According to Cardiovascular Risk Factors in Multivariate Analysis: Various Models Including PWV, PP, or SBP

Parameters	OR	Lower 95% CI	Higher 95% CI	P
Model 1 $CHI^2=97$				
Previous CVD, yes/no	8.33	4.33	16.02	<0.0001
Age, 10 y	1.69	1.25	2.30	<0.001
PWV, 5 m/s	1.51	1.08	2.11	0.03
Model 2 $CHI^2=95$				
Previous CVD, yes/no	8.09	4.19	15.61	<0.0001
Age, 10 y	1.72	1.27	2.34	<0.0001
PP, 10 mm Hg	1.19	0.99	1.42	0.06
Model 3 $CHI^2=96$				
Previous CVD, yes/no	8.32	4.33	16.02	<0.0001
Age, 10 y	1.82	1.36	2.45	<0.0001
SBP, 10 mm Hg	1.15	1.02	1.30	0.03

Diabetes (yes/no), included in each of the 3 models, was not significantly associated with cardiovascular mortality.

ical progress has allowed arterial stiffness to be determined with simple noninvasive methods and to be used in epidemiological studies. An independent influence of arterial stiffness on survival has recently been demonstrated in patients with end-stage renal disease,^{17,18} a very specific population at high risk of mortality. This has not been shown in hypertensive patients at lower risk,¹⁶ probably because of the small number of patients included in this cohort. Thus, a direct relationship between arterial stiffness and all-cause and cardiovascular mortality remained to be determined in a large population of hypertensive patients.

The present study clearly shows that arterial stiffness may help in the evaluation of the individual risk in hypertensive patients regularly attending the outpatient clinic of a university hospital. Because the population group was only mildly hypertensive at original screening, with the minority on antihypertensive treatment at that time, one might reasonably speculate that the results may apply to the population as a whole. The independent predictability of aortic stiffness can be quantified in the study population: the OR for an increase in PWV of 5 m/s is 1.34 for all-cause mortality (Table 3) and 1.51 for cardiovascular mortality (Table 5). In univariate models of logistic regression analysis, the increased mortality risk because of a 5 m/s increase in PWV is equivalent to that of aging 10 years (Table 2 and 4).

Several mechanisms may explain the association between increased PWV and cardiovascular mortality.¹⁻¹² Arterial stiffness is a cause of premature return of reflected waves in late systole, increasing central pulse pressure and the load on the ventricle, reducing ejection fraction, and increasing myocardial oxygen demand.¹ Arterial stiffness is associated with left ventricular hypertrophy in normotensive and hypertensive patients.^{4,29} Left ventricular hypertrophy is a known risk factor for congestive heart failure and cardiovascular events.³⁰ The elevation of SBP, which raises left ventricular afterload and myocardial work, and the decrease in DBP, which reduces coronary perfusion, result in subendocardial ischemia.^{1,31} Arterial stiffness is correlated with atherosclerosis,^{32,33} probably through the effects of cyclic stress on arterial wall thickening.^{28,34}

Because 483 patients among 1980 were being treated with antihypertensive drugs at the time of PWV measurement, the patients might have lower blood pressure and PWV levels than without treatment. Thus, the predictive value of PWV, observed in the whole population, might not apply to this sub-group. However, when antihypertensive treatment was added to the multivariate model of logistic regression analysis of Table 3, the independent OR for an increase in PWV of 5 m/s remained significant and of similar value than in the original model for both all-cause and cardiovascular mortality.

The subgroup of 182 patients among 1980, who had a history of cardiovascular disease at the baseline PWV examination, might have introduced a bias in the determination of the predictive power of PWV in the whole population, particularly in patients devoid of previous cardiovascular disease at entry, even after adjustment to previous cardiovascular disease in multivariate analysis. Thus, we reanalyzed the subgroup of 1798 patients devoid of previous cardiovas-

cular disease at entry. Univariate analyses in these patients showed that aortic PWV remained significantly predictive of cardiovascular and all-cause deaths.

As expected, we observed significant univariate associations between cardiovascular deaths and either previous cardiovascular disease, age, PP, SBP, and diabetes, with a predominant predictive power for the history of cardiovascular disease.³⁵ The lack of univariate association between MBP and cardiovascular deaths was not unexpected because the present cohort included only patients referred for hypertension, thus reducing the range of MBP values. The lack of prognostic value of DBP on cardiovascular deaths was also not unexpected in the present cohort. Indeed, previous studies^{10,35} reported a positive association between cardiovascular mortality and DBP before 60 years of age and a negative association thereafter. Thus, the findings of the present study underline the predominant role of PP over MBP, as previously published.^{8,9}

In the present cohort, arterial stiffness had an independent predictive power with respect to all-cause and cardiovascular deaths, whereas PP was not significantly and independently associated with all-cause mortality (Table 3) and was only marginally associated with cardiovascular mortality (Table 5). The stronger independent predictive value of PWV may be explained by pathophysiological considerations (PP amplification, multiplicity of PP determinants), as seen above. In addition, the lack of independent predictive value of PP may be due to the smaller size of the present cohort than previously published ones^{4,8-10,36} and/or to the lower mortality rate of our hypertensive population compared with patients with impaired left ventricular function¹¹ or elderly patients.³⁶ Nevertheless, the present study shows that a direct measurement of stiffness may be of greater help than an indirect index (PP) in the evaluation of the individual risk in a cohort of hypertensive patients regularly attending the outpatient clinic of an university hospital.

We conclude that aortic stiffness is significantly associated with the risk of all-cause and cardiovascular mortality in patients with essential hypertension. Measurement of aortic stiffness retains predictive power with respect to all-cause and cardiovascular deaths, even after classic risk factors have been taken into consideration.

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