Aortic Stiffness Is an Independent Predictor of Primary Coronary Events in Hypertensive Patients

A Longitudinal Study

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Abstract—Arterial stiffness may predict coronary heart disease beyond classic risk factors. In a longitudinal study, we assessed the predictive value of arterial stiffness on coronary heart disease in patients with essential hypertension and without known clinical cardiovascular disease. Aortic stiffness was determined from carotid-femoral pulse wave velocity at baseline in 1045 hypertensives. The risk assessment of coronary heart disease was made by calculating the Framingham risk score according to the categories of gender, age, blood pressure, cholesterol, diabetes, and smoking. Mean age at entry was 51 years, and mean follow-up was 5.7 years. Coronary events (fatal and nonfatal myocardial infarction, coronary revascularization, and angina pectoris) and all cardiovascular events served as outcome variables in Cox proportional-hazard regression models. Fifty-three coronary events and 97 total cardiovascular events occurred. In univariate analysis, the relative risk of follow-up coronary event or any cardiovascular event increased with increasing level of pulse wave velocity; for 1 SD, ie, 3.5 m/s, relatives risks were 1.42 (95% confidence interval [CI], 1.10 to 1.82; $P<0.01$) and 1.41 (95% CI, 1.17 to 1.70; $P<0.001$), respectively. Framingham score significantly predicted the occurrence of coronary and all cardiovascular events in this population ($P<0.01$ and $P<0.0001$, respectively). In multivariate analysis, pulse wave velocity remained significantly associated with the occurrence of coronary event after adjustment either of Framingham score (for 3.5 m/s: relative risk, 1.34; 95% CI, 1.01 to 1.79; $P=0.039$) or classic risk factors (for 3.5 m/s: relative risk, 1.39; 95% CI, 1.08 to 1.79; $P=0.01$). Parallel results were observed for all cardiovascular events. This study provides the first direct evidence in a longitudinal study that aortic stiffness is an independent predictor of primary coronary events in patients with essential hypertension. (***Hypertension*. 2002;39:10-15.)**

Key Words: arterial stiffness ■ cardiovascular morbidity ■ cardiovascular mortality ■ coronary heart disease

Although coronary heart disease (CHD) has declined in the United States and in most European countries,[1,2] its prevention is a major goal. Aggressive medical therapy substantially reduces the likelihood of recurrent major coronary syndromes in patients with established CHD, and similar potential exists for risk reduction in patients without established CHD (ie, primary prevention). Identification of primary CHD risk, commonly performed by use of published algorithms, is mandatory to adapt the intensity of interventions.

Despite the recognized advantages of global risk assessment, important limitations have been noticed.[2] Among them, newly individualized risk factors are not taken into account. Few epidemiological studies focused on arterial stiffness, which may represent a valuable predictor of cardiovascular (CV) risk in essential hypertensives. Brachial pulse pressure (PP), which has been repeatedly reported as an independent risk factor for CHD,[3,4] is only an indirect estimate of arterial stiffness.[5] Because of the physiological PP amplification between central and peripheral arteries, brachial PP may not reflect aortic PP, which influences left ventricular afterload and coronary perfusion.[5,6] In addition, factors other than arterial stiffness such as heart rate (HR), cardiac contractility, and venous pressure can influence the value of PP. Arterial stiffness may predict CHD events to a larger extent than PP, because it directly influences left ventricular afterload and coronary perfusion and because it may partially parallel the extent of coronary atherosclerosis.[4–6]

Arterial stiffness can be assessed noninvasively by measurement of pulse wave velocity (PWV), a simple and reproducible method.[7,8] PWV measured along the aortic and aortoiliac pathways is the most clinically relevant because the aorta and its first branches are responsible for most of the pathophysiological effects of arterial stiffness. An indirect

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argument for an influence of PWV on CV risk comes from a cross-sectional study showing that PWV and Framingham risk score (FRS) were correlated in a composite population of patients with and without atherosclerosis manifestations.[9] Most important, recent longitudinal studies directly demonstrated that arterial stiffness, measured through PWV,[10,11] carotid elastic modulus,[12] or ratio of stroke volume to PP,[13] was an independent predictor of all-cause and CV mortality in patients with end-stage renal disease[11,12] and in essential hypertensives.[10,13] However, to the best of our knowledge, the predictive value of aortic stiffness on primary CHD events has never been established in patients with essential hypertension in a longitudinal study.

Thus, the aims of the present study were (1) to establish the relationship between aortic stiffness measured through PWV and primary CHD events in hypertensive patients and (2) to show that PWV retains its predictive value independently of classic risk factors assessed either through a Framingham algorithm or a multivariate Cox model.

Methods

Subjects and Study Design

The cohort included 1045 essential hypertensive patients with no overt CV disease or symptoms who attended the outpatient hypertension clinic of Hôpital Broussais between April 1980 and December 1996 and had a baseline measurement of arterial stiffness. None of these patients were referred for typical symptoms of CHD or other CV disease. Demographic data with details of CV risk factors were collected on the day when PWV was measured. Diabetes (yes/no) and hypercholesterolemia (yes/no) were indicated by a previous diagnosis or the use of an oral hypoglycemic agent or a cholesterol-lowering agent. Smoking status (yes/no) was defined as current use. The procedures followed were in accordance with institutional guidelines.

Blood pressure was measured as previously published.[10] PWV, a classic index of arterial stiffness,[7,8] was measured along the descending thoracoabdominal aorta with the foot-to-foot velocity method as previously published and validated.[8–10]

A coronary disease prediction algorithm based on the FRS was calculated for each patient.[1] Gender-specific prediction equations were formulated to predict CHD risk according to age, diabetes, smoking, Joint National Committee blood pressure categories, and National Cholesterol Education Program total, LDL, and HDL cholesterol categories.[1]

Events

The follow-up period ended on December 31, 1996. Patients in whom the first event was death were identified as previously described,[3,10] as well as causes of death. CHD was defined as fatal and nonfatal myocardial infarction, sudden death, coronary revascularization, and documented angina pectoris. Other CV events in our cohort included strokes, newly discovered abdominal aortic aneurysm, new onset of peripheral arterial disease (defined as new onset of intermittent claudication confirmed by angiography), hypertension-related nephroangiosclerosis (with biopsy diagnosis), and heart failure. Follow-up time was defined from the date of the baseline examination to the date of the first CV event or to the date of last contact free of CV disease.

Statistical Analysis

The primary end point of this study was the first fatal or nonfatal CHD event during follow-up. A secondary end point was the occurrence of any fatal and nonfatal primary CV events. The effects of classic risk factors on PWV were analyzed with a multivariate regression analysis. We used Cox regression analysis[14] to calculate the unadjusted and adjusted relative risks (RRs) and 95% confidence intervals (CIs) for CHD and all CV events in relation to FRS and PWV levels (per 1-SD increment of FRS and/or PWV). To identify independent predictors of CHD and all CV events, we used multivariate Cox regression analyses with stepwise selection. Variables included in multivariate models were PWV and FRS or classic CV risk factors. Classic CV risk factors were age, gender, blood pressure, HR, hypercholesterolemia, diabetes, smoking, and previous antihypertensive treatment. For each analysis, blood pressure parameters included either systolic (SBP) and diastolic blood pressure (DBP) or mean blood pressure (MBP) and PP. The hazard ratio and 95% CI were calculated as appropriate. All calculations were performed with the NCSS 2000 statistical package (J.L. Hintze, Kaysville, Utah).

An expanded Methods section can be found in an online data supplement available at http//www.hypertension.aha.org.

TABLE 1. Baseline Characteristics of Patients

Parameters	Patients With CV Event (n=97)	Patients Without CV Event (n=948)	P
Age, y	56±13	50±12	<0.0001
Follow-up duration, mo	79±50	71±67	NS
Gender ratio, men/women	74/23	607/341	<0.01
BMI, kg/m^2	25.9±3.1	25.4±3.6	NS
SBP, mm Hg	156±25	150±19	<0.01
MBP, mm Hg	114±18	110±14	<0.01
DBP, mm Hg	93±16	90±14	NS
PP, mm Hg	62±17	59±13	<0.01
HR, bpm	71±12	71±11	NS
Smoking, yes/no	23/74	208/740	NS
Diabetes, yes/no	13/84	52/896	<0.001
Previous antihypertensive treatment, yes/no	52/45	303/645	<0.0001
Hypercholesterolemia, yes/no	26/71	277/659	NS
Total cholesterol, mg/dL	235±46	226±43	<0.05
LDL cholesterol, mg/dL	157±40	147±37	<0.05
HDL cholesterol, mg/dL	49±13	54±15	<0.01
PWV, m/s	12.8±3.2	11.4±3.1	<0.0001
FRS	7.4±3.3	5.8±3.8	<0.0001

BMI indicates body mass index. Values are mean±SD. See text for details.

Results

Demographic and Clinical Characteristics

The baseline characteristics of the 1045 study participants are given in Table 1. The sample comprised 674 men and 371 women. The mean age of participants at entry was 51 years. The mean follow-up time was 5.7 years, during which 53 subjects developed CHD (45 nonfatal, 8 fatal). A total of 97 fatal and nonfatal CV events were observed. Of the initial 53 CHD events, 33 were coronary revascularization or documented angina pectoris, 12 were myocardial infarction with survival beyond 1 day, and 8 were CHD deaths. Other CV events were stroke (n=19), newly discovered abdominal aortic aneurysm (n=7), new onset of peripheral arterial disease (n=10), hypertension-related nephroangiosclerosis (n=6), and heart failure (n=2).

Compared with subjects who did not experience CHD events, subjects who developed CHD events were mostly

TABLE 2. RR of Primary CHD and CV Events According to PWV, FRS, and Classic CV Risk Factors: Univariate Analysis

Parameters	RR	Lower 95% CI	Higher 95% CI	*P*
CHD events				
PWV (3.5 m/s)	1.42	1.10	1.82	<0.01
FRS (4 points)	1.51	1.10	2.05	<0.01
Age (10 y)	1.42	1.12	1.81	<0.01
Hypercholesterolemia (yes/no)	2.49	1.38	4.48	<0.01
Sex (M/F)	2.32	1.14	4.76	<0.02
All CV events				
PWV (3.5 m/s)	1.41	1.17	1.70	<0.001
FRS (4 points)	1.57	1.25	1.98	<0.0001
Age (10 y)	1.47	1.23	1.76	<0.0001
SBP (10 mm Hg)	1.12	1.02	1.22	0.015
PP (10 mm Hg)	1.16	1.02	1.32	0.019
Hypercholesterolemia (yes/no)	1.73	1.09	2.76	0.017
Diabetes (yes/no)	2.16	1.21	3.84	<0.01
Gender (M/F)	1.64	1.02	2.62	0.036

men, were 4.5 years older, and had a higher PWV (12.8±3.3 versus 11.5±3.1, respectively; $P<0.001$) and FRS (7.1±2.8 versus 5.9±3.9, respectively; $P<0.001$). Blood pressure was not significantly different. Compared with subjects who did not experience CV events, subjects who developed CV events were mostly men and were older. They had a higher PWV and FRS (Table 1), and their SBP, MBP, PP, total cholesterol, and LDL cholesterol were higher. They more frequently had diabetes and treated hypertension.

In multivariate analysis, the significant independent determinants of PWV were age ($P<0.0001$), SBP ($P<0.0001$) [or MBP ($P<0.0001$) and PP ($P<0.0001$) in a second model], hypercholesterolemia ($P<0.0001$), and diabetes ($P<0.02$), whereas gender, DBP (in the first model), HR, weight, height, smoking, and previous antihypertensive treatment were not significantly and independently related to PWV.

CHD Events

Unadjusted RR

Using PWV as a continuous variable in Cox proportional-hazard models showed strong associations with the occurrence of CHD (Table 2). In univariate analysis, the RR of developing CHD predicted by 1 SD of PWV (3.5 m/s) was 1.42 ($P<0.01$). FRS significantly predicted CHD events (Table 2), and each SD of FRS (4 points) was associated with an RR of 1.51 ($P<0.01$). Figure 1 shows that the observed incidence of CHD events parallels the incidence of CHD, which has been predicted from the Framingham equation, except in the highest values of FRS. Age, gender, and hypercholesterolemia were significantly associated with CHD events (Table 2), whereas SBP, DBP (or MBP and PP), HR, smoking, previous antihypertensive treatment, and diabetes were not.

Multivariate Analysis for Prediction of CHD Risk

In multivariate analysis, when both FRS and PWV were used as continuous variables in the same model, PWV remained significantly associated with the occurrence of CHD, whereas FRS was not. After adjustment for FRS, 1 SD of PWV was associated with a 34% increase in risk (RR, 1.34; 95% CI, 1.01 to 1.79; $P=0.039$). As an alternative to FRS adjustment, the predictive value of PWV for CHD was tested after adjustment for classic risk factors in a "free-coefficient" Cox model. Under these conditions, 1 SD of PWV was associated with a 39% increase in risk (RR, 1.39; 95% CI, 1.08 to 1.79; $P=0.01$) independently of hypercholesterolemia, age, gender, SBP, DBP, HR, diabetes, smoking, and previous antihypertensive treatment. Including MBP and PP in the model instead of SBP and DBP did not change the results.

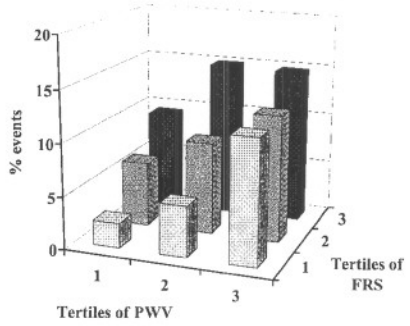

Figure 1. Observed incidence of fatal or nonfatal CHD in patients free of overt CHD at entry vs the predicted incidence of CHD calculated with the Framingham equation.

The risk of developing a CHD event rose with each tertile of PWV (Table 3) and remained significant after adjustment for FRS or all CV risk factors (Table 3). The increase in risk of CHD events with tertiles of PWV was particularly steep for patients considered at low risk, ie, belonging in the first and second tertiles of FRS. Indeed, in this subpopulation, the RRs of developing CHD were 2.37 ($P<0.001$) and 5.60 ($P<0.001$) for the second and third tertiles of PWV, respectively. Accordingly, the area under the receiver-operating characteristic curve of PWV decreased from the lowest to the highest tertile of FRS (area under the receiver-operating characteristic curve: from 0.71±0.09 to 0.53±0.07; $P<0.01$).

All CV Events

Unadjusted RR

Similar patterns were observed for all CV events (Tables 2 and 3). Using PWV as a continuous variable in a Cox proportional-hazard model also showed strong associations with the occurrence of all CV events (Table 2). In univariate analysis, the RR of developing any CV event predicted by 1 SD of PWV (3.5 m/s) was 1.41 ($P<0.001$). FRS was also a significant predictor of all CV events (for 1 SD of FRS, ie 4 points: RR, 1.57; $P<0.0001$). Age, SBP (and PP in a second model), hypercholesterolemia, diabetes, and gender were significantly associated with all CV events (Table 2), whereas DBP (and MBP in a second model), HR, previous antihypertensive treatment, and smoking were not.

Multivariate Analysis for Prediction of CV Risk

In multivariate analysis, when both FRS and PWV were used as continuous variables in the same model, PWV remained significantly associated with the occurrence of all CV events. After

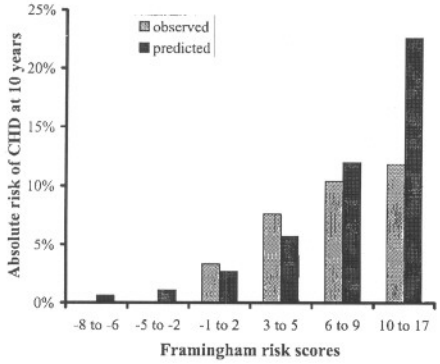

Figure 2. Rate of all CV events according to increasing tertiles of PWV and FRS.

adjustment for FRS, 1 SD of PWV remained associated with a 24% increase in risk (RR, 1.24; 95% CI, 1.17 to 1.68; $P=0.038$). In contrast, there was only a trend ($P=0.064$) for a predictive value of PWV for all CV events after adjustment for classic risk factors in a free-coefficient Cox model, including age, gender, BP (either SBP and DBP in a first model or MBP and PP in a second model), HR, hypercholesterolemia, diabetes, smoking, and previous antihypertensive treatment. In comparison, PP and SBP were significantly associated with the occurrence of all CV events (for 10 mm Hg: RR=1.16, $P=0.019$, and RR=1.12, $P=0.015$, respectively) in univariate analysis but not after adjustment for other classic risk factors or FRS.

The frequency of all CV events rose with increasing tertiles of PWV within each tertile of FRS (Figure 2). The RR of presenting any CV event was 1.59 ($P<0.001$) for the second tertile of PWV and 2.53 ($P<0.001$) for the third tertile compared with the first tertile (Table 3). The RR of presenting any CV event associated with PWV remained significant after adjustment for FRS but was no more significant after full adjustment for all CV risk factors (Table 3). The increase in CV risk with tertiles of PWV was steeper for patients belonging to the first and second tertiles of FRS but to a smaller extent than for CHD. Accordingly, the area under the receiver-operating characteristic curve of PWV decreased from the lowest to the highest tertile of FRS (area under the receiver-operating characteristic curve: from 0.65±0.07 to 0.53±0.04; $P<0.01$). In addition, PWV significantly ($P=0.002$) predicted all CV events in patients considered at low risk, ie, belonging to the first and second tertiles of the FRS, even after full adjustment for all CV risk factors (Table 3).

Discussion

The main result of the present study is that in a population of essential hypertensive patients with no overt CV disease or symptoms at baseline, arterial stiffness measured through PWV predicted the occurrence of CHD beyond the prediction provided by classic risk factors assessed through either a Framingham algorithm or a multivariate Cox model.

TABLE 3. Rates and RRs of CHD and All CV Events as a Function of PWV Expressed as Tertiles

	Events, n (%)	Unadjusted (95% CI)	Adjusted for FRS (95% CI)	Adjusted for Age, Sex, BP, and Other CV Risk Factors (95% CI)
All patients				
CHD events				
PWV, m/s				
<10.0 m/s	10/348 (2.9)	1.00	1.00	1.00
10.0–12.3 m/s	14/349 (4.0)	1.67 (1.16–2.42)	1.67 (1.16–2.42)	1.63 (1.13–2.36)
>12.3	29/348 (8.3)	2.80 (1.33–5.87)	2.80 (1.33–5.87)	2.66 (1.27–5.56)
CV events				
PWV				
<10.0 m/s	17/348 (4.9)	1.00	1.00	1.00
10.0–12.3 m/s	38/349 (10.9)	1.59 (1.21–2.08)	1.38 (1.03–1.84)	1.22 (0.91–1.65)
>12.3	54/348 (15.5)	2.53 (1.47–4.34)	1.90 (1.07–3.39)	1.49 (0.82–2.71)
Patients at low risk*				
CHD events				
PWV				
<10.0 m/s	5/289 (1.7)	1.00	1.00	1.00
10.0–12.3 m/s	10/242 (4.1)	2.37 (1.45–3.86)	2.37 (1.45–3.86)	2.43 (1.49–3.96)
>12.3	17/166 (10.2)	5.60 (2.10–14.93)	5.60 (2.10–14.93)	5.90 (2.22–15.68)
CV events				
PWV				
<10.0 m/s	10/289 (3.5)	1.00	1.00	1.00
10.0–12.3 m/s	23/242 (9.5)	1.85 (1.28–2.69)	1.85 (1.28–2.69)	1.82 (1.25–2.65)
>12.3	24/166 (14.5)	3.44 (1.65–7.25)	3.44 (1.63–7.25)	3.31 (1.56–7.05)

*Patients belonging to the first and second FRS tertiles.

Clinical Implications

Recent longitudinal studies directly demonstrated that arterial stiffness measured through PWV,[10,11] carotid elastic modulus,[12] or ratio of stroke volume to PP[13] was an independent predictor of all-cause and CV mortality in patients with end-stage renal disease[11,12] and in essential hypertensive patients.[10,13] However, to the best of our knowledge, the predictive value of aortic stiffness on primary CHD events has not previously been established in patients with essential hypertension in a longitudinal study.

Several mechanisms may explain the association between increased PWV and CHD events. Arterial stiffness is a cause of premature return of reflected waves in late systole, increasing central PP and the load on the ventricle, reducing ejection fraction, and increasing myocardial oxygen demand.[5] Arterial stiffness is associated with left ventricular hypertrophy, a known risk factor for coronary events, in normotensive and hypertensive patients. 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.[5] Arterial stiffness is correlated with atherosclerosis, probably through the effects of cyclic stress on arterial wall thickening.[15] Aortic stiffening accompanying age and CV risk factors is caused by various phenomena, including fibrosis, breaks in elastin fibers, calcifications, and diffusion of macromolecules within the arterial wall. The measurement of aortic stiffness, which integrates these alterations, may also reflect parallel lesions present at the site of proximal coronary vasculature.

Elevated PP, which is usually regarded as a manifestation of increased arterial stiffness, and SBP are both independent risk factors for CHD.[3,4] Although in the present study PP and SBP predicted all CV events in univariate analysis, they lost their predictive value after adjustment for PWV. The stronger independent predictive value of PWV over brachial PP may be explained by pathophysiological considerations (PP amplification, multiple determinants of aortic PP) but also by other factors: the smaller size of the present cohort than previously published ones,[3,4] the low event rate of our hypertensive population, or the insufficient precision of the sphygmomanometer compared with ambulatory blood pressure monitoring.[16] 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 CHD risk in a cohort of hypertensive patients regularly attending the outpatient clinic of an university hospital.

Study Strengths and Limitations

The present study of a subset of a previously published cohort[10] related to the determination of all-cause and CV mortality. Because our objective was to focus on primary CHD events, we excluded patients without medical follow-up, and among the remaining 1214 medical records, we excluded 169 patients who had CV disease at baseline.

Because most of the determinants of PWV, like age and hypercholesterolemia, are also risk factors for CHD, it was mandatory to verify that the predictive value of PWV on CHD events remained significant after adjustment for these risk factors. This was done by adjusting the predictive value of PWV to that of a global coronary risk assessment determined 2 ways: through a Framingham algorithm (FRS) and through a multivariate Cox model including classic CV risk factors. PWV remained an independent predictor of CHD and CV events after adjustment for CHD risk factors in each of these models.

The FRS was established in a white population from North America studied during the 1970s. Its use in clinical assessment of risk, however, is recommended even in non-American populations, and the FRS is widely used in practice.[2] We confirmed that FRS significantly predicted the occurrence of CHD in the study sample (Figure 2). Interestingly, the predictive value of PWV for primary CHD events was more marked for patients considered at low risk, ie, belonging to the first and second FRS tertiles (Figure 1 and Table 3), than for patients at high risk, ie, belonging to the third FRS tertile, indicating that this low- to intermediate-risk population benefited the most from risk assessment with PWV.

In addition, to take into account the specificity of this French population and the fact that FRS did not fully predict the occurrence of CHD in patients with the highest FRS (Figure 2), we also used a multivariate Cox model including in a free-coefficient manner all risk factors taken into account in the calculation of FRS and previous antihypertensive treatment. This model did not alter the independent predictive value of PWV on CHD events.

Because one third of the patients had already been treated for hypertension at baseline, the predictive value of PWV observed in the whole population might not apply to this subgroup. However, in a multivariate Cox model including previous antihypertensive treatment (yes/no) among other classic risk factors (see the Results section), the predictive value of PWV remained significantly and independently associated with an increased risk of CHD.

In conclusion, this study provides the first direct evidence in a longitudinal study that aortic stiffness is an independent predictor of primary CHD in patients with essential hypertension. Our results show that measuring aortic stiffness helps to identify patients at high risk of CHD who may benefit from more aggressive management.

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