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Abstract—Aortic pulse wave velocity (PWV) is a significant and independent predictor of cardiovascular mortality in subjects with essential hypertension and in patients with end-stage renal disease. Its contribution to cardiovascular risk in subjects 70 to 100 years old has never been tested. A cohort of 141 subjects (mean±SD age, 87.1±6.6 years) was studied in 3 geriatrics departments in a Paris suburb. Together with sphygmomanometric blood pressure measurements, aortic PWV was measured with a validated automatic device. During the 30-month follow-up, 56 patients died (27 from cardiovascular events). Logistic regressions indicated that age ($P=0.005$) and a loss of autonomy ($P=0.01$) were the best predictors of overall mortality. For cardiovascular mortality, aortic PWV was the major risk predictor ($P=0.016$). The odds ratio was 1.19 (95% confidence interval, 1.03 to 1.37). Antihypertensive drug treatment and blood pressure, including systolic and pulse pressure, had no additive role. In subjects 70 to 100 years old, aortic PWV is a strong, independent predictor of cardiovascular death, whereas systolic or pulse pressure was not. This prospective result will need to be confirmed in an intervention trial. **(*Arterioscler Thromb Vasc Biol*. 2001;21:2046-2050.)**

Key Words: very old (>70 years) subjects ■ aortic pulse wave velocity ■ cardiovascular mortality ■ drug treatment of hypertension ■ pulse pressure

With increasing age, there is a gradual shift from diastolic blood pressure (DBP) to systolic blood pressure (SBP) and then to pulse pressure (PP) as predictors of cardiovascular (CV) risk, mainly from coronary heart disease. In patients <50 years of age, DBP is the strongest CV predictor. The age range of 50 to 59 years is a transition period when all 3 BP indexes are comparable predictors, and, from 60 years of age, PP becomes superior to both SBP and DBP to predict myocardial infarction.[1–3] In addition, because for a given ventricular ejection aortic stiffness is the major determinant of PP, increased aortic pulse wave velocity (PWV), a classic marker of arterial rigidity, has also been identified as an independent predictor of CV risk in subjects with hypertension, whether in the presence of end-stage renal disease or with preserved renal function.[4–6] However, these epidemiological findings are limited to cohorts between 50 and 75 years of age.

BP increases with age. However, this influence of age differs markedly for SBP and DBP.[7,8] Whereas SBP increases substantially with age, particularly in women after menopause, the increase of DBP with age is less pronounced. Indeed, DBP even tends to fall after 55 years of age. In the elderly, the hemodynamic pattern associating an increase in SBP and a low DBP is a characteristic feature, usually attributed to an age-related increase of arterial stiffness.[7] In elderly populations, SBP and PP are usually considered the major markers of CV risk.[1] However, there is no study in subjects >70 years old that would indicate whether an increase in PWV could be, in place of SBP and PP, the best independent predictor of CV mortality.

A cohort of elderly subjects recruited from 3 geriatrics departments has been investigated since 1998 to determine whether BP and PWV are significant markers of CV morbidity and mortality after 70 years of age.[9] The main objective of the present study was to determine whether brachial SBP or PP and/or aortic PWV could be considered valid markers for CV death after a 30-month follow-up.

Methods

Study Cohort

From June 1998 to March 2001, 182 consecutive patients were hospitalized in 3 geriatrics departments of a Paris suburb. These patients entered the hospital for rehabilitation after infectious disease, congestive heart failure, recent orthopedic or nonorthopedic surgery, recent stroke, or end-stage Parkinson's disease.

Of the 182 subjects, only 164 agreed to participate in the study, and 23 were excluded later for technical reasons (see below). Thus, 141 subjects (103 women, 38 men) were included. Their mean age (±SD) was 87.1±6.6 years. Ninety subjects (63.8%) showed signs of dementia, most commonly caused by Alzheimer's disease or vascular dementia involving multiple infarcts within the brain.[10] The remaining causes did not exceed 5% of demented subjects.

Eighty-one subjects were considered to have normal BP, with an SBP <140 mm Hg and a DBP <90 mm Hg. Among them, 43 were

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receiving antihypertensive drug therapy (ADT). Sixty subjects were considered to have a high BP, defined as an SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg. Among these 60 hypertensive subjects, 32 were receiving ADT. Finally, the 141 subjects could be divided into 4 subgroups defined by their "BP status," according to the presence or absence of high BP and/or ADT: no high BP and no ADT (n=38) (27%); no high BP and ADT (n=43) (30.5%); high BP and no ADT (n=28) (19.9%); high BP and ADT (n=32 (22.7%) Among the 75 subjects receiving ADT, the drug used were calcium antagonists (n=14), β-blockers (n=7), diuretics (n=31), angiotensin-converting enzyme inhibitors (n=34), or miscellaneous drugs (n=5), either alone or in combination. Nitrates were being given to 92 subjects for various CV disorders, including coronary heart diseases (see below). Drug treatment was prescribed to 12 patients for dyslipidemia (drugs including statins or fibrates), and 11 patients were being medically treated for diabetes mellitus (drugs including insulin or sulfamides). Each subject or his/her family (in cases of dementia) provided written consent to participate in the study, which was approved by our institutional review board.

The Mini-Mental State Examination was used by the participating physicians to screen the patients for the presence of cognitive impairments.[11] Information compiled from the questionnaire filled out at inclusion included sex, age, weight, height, body mass index, personal history of diabetes mellitus and/or of dyslipidemia, smoking habits, and use of ADT. In all cases, this information was in accord with that give by relatives and/or included in the most recent (<1 month) previous hospitalization. Causes of death (World Health Organization International Classification of Disease, ninth revision) were obtained from death certificates, hospital record forms, and autopsy data reviewed by the authors. Sudden death was defined as a witnessed death that occurred within 1 hour after the onset of acute symptoms, with no evidence that violence or accident played any role in the fatal outcome. During the follow-up period, 56 deaths were recorded, including 27 fatal CV events.

Fifty-nine patients (42%) had a past and/or present history of CV diseases (CVDs) involving atrial fibrillation (n=14), coronary heart disease (n=17), peripheral vascular disease (n=23), and cerebrovascular disease (n=29). The mean number of CVDs per patient in this population was 0.59±0.78, with 37 patients (26%) with 1 CVD, 20 (14%) with 2, and 2 (1%) with 3.

Measurements

The determinations were made at 10 AM, with each patient in a supine position. Room temperature was between 21°C and 23°C. Brachial BP was measured by using a semiautomatic BP device, the Dinamap apparatus (model 845, Criticon), after a 15-minute rest period. Five measurements, each 2 minutes long, were averaged, enabling a determination of SBP, DBP, mean blood pressure (MBP), and heart rate. After BP was measured, PWV was determined with an automatic device, the Complior (Colson), which obtained an online pulse wave recording with 2 transducers, 1 positioned at the base of the neck for the common carotid artery and the other over the femoral artery, thereby enabling automatic calculation of PWV as previously described.[12,13] The validation of this automatic method and its reproducibility were reported previously.[12,13] We verified in 25 subjects >70 years of age that reproducibility was 8±1%. Among the 164 patients who consented to participate in the study, 23 were excluded for technical reasons, including wandering and agitation (n=11), intensive tremor (n=5), obesity (n=3), hyperreflexia of trachea and cough (n=2), and hypertonia of the neck muscles (n=2).

Venous blood samples were obtained from the subjects after an overnight fast. Plasma was separated without delay at 4°C in a refrigerated centrifuge and stored at 4°C (for routine biochemistry analyses by standard laboratory methods) until use. Total cholesterol was determined with a Technicon Chem assay (Technicon Instruments), and HDL cholesterol was measured in the supernatant after precipitation of apolipoprotein B–containing lipoproteins with heparin-$MnCl_2$. LDL cholesterol was calculated as previously described.[5] Plasma glucose, creatinine, and albumin were measured according to standard techniques. Creatinine clearance was calculated from the Cockroft formula.

Statistical Analyses

Continuous data are expressed as mean±1 SD, and a general linear model ANOVA was used, thereby permitting adjustment according to sex to compare principal parameter means within different categories. Differences in frequency were tested by χ^2 analysis. Explicative variables of mortality were tested first by logistic regression with adjustment on age and sex. Those that were significant ($P \leq 0.20$) were included in the final stepwise logistic regression. Survival analysis with an actuarial method was used to describe CV mortality according to classes of PWV [cut point at 17.7 m/s according to the upper decile and 20 m/s (5% of the population)] and adjusted on pertinent parameters.[4,5] Delay of death in months was computed from the date at which the patients had undergone PWV determination to the date of death or the date of the last measurement (right censored). Analyses were performed with SAS software, version 6.7, under Windows NT 98. A value of $P=0.05$ was considered significant in double-sided tests.

Results

Classification of Subjects According to CV and Overall Mortality

The demographic, clinical, and biochemical characteristics of the study cohort are reported in Table 1. Subjects who died of any cause during the study period (overall mortality) were characterized by a higher age ($P=0.003$), a higher incidence of a past history of myocardial infarction ($P=0.005$), lower creatinine clearance ($P=0.08$), a lower mental score ($P=0.02$), and loss of autonomy ($P=0.01$). Regarding CV mortality, subjects were characterized by a higher incidence of a past history of myocardial infarction ($P=0.001$); a lower creatinine clearance ($P=0.06$); a higher SBP ($P=0.03$), DBP ($P=0.06$), and MBP ($P=0.01$); a higher aortic PWV ($P=0.02$); and a loss in autonomy of movement ($P=0.08$).

Logistic Stepwise Regression of CV and Overall Mortality

For total mortality, age ($P=0.005$) and a loss of autonomy ($P=0.01$) were the 2 variables to consider. Hypoalbuminemia and high C-reactive protein had no significant role in overall mortality. For CV mortality, univariate logistic analysis (Table 2) showed that only MBP ($P=0.01$), SBP ($P=0.02$), a past history of CVD ($P=0.026$), creatinine clearance ($P=0.056$), and autonomy in movement ($P=0.06$) had a significant link with CV mortality. When PWV was added in the final model, the role of these factors disappeared in favor of PWV (Table 3). A 1 m/s increase in PWV increased CV mortality ≈19% (3% to 37%). During this study, adjustment according to ADT and/or nitrates did not modify the results. BP and, in particular, SBP and PP had no additive role, whether it was studied as a quantitative or a qualitative (BP status) variable.

Regarding survival probabilities (the Figure), a high PWV (>17.7 m/s and 20 m/s) was significantly ($P=0.0007$, 0.0008) correlated with CV mortality. For a PWV <17 m/s, the significance disappeared (data not shown).

Discussion

In this study involving 141 patients >70 years of age, we showed that aortic PWV was a major independent predictor of CV mortality and that this marker was extremely powerful, with an adjusted odd ratio of 4.60 (95% confidence interval, 1.4 to 15.7) when PWV was >17.7 m/s (Table 3). BP and, in particular, SBP and PP did not predict CV mortality in this

TABLE 1. Characteristics of the Total Population and Mean Values According to CV and Overall Mortality (Adjusted on Sex)

	Entire	No Death	Overall Death	*P*	No CV Death	CV Death	*P*
n, %	141	48%	52%		79%	21%	
Age, y	87.1±6.6	85.4±7.4	88.7±5.2	0.003	86.7±6.8	88.4±5.6	0.200
Sex, men:women	27:73	20:80	30:70	0.23	21:79	30:70	0.44
Body mass index, kg/m^2	22.03±3.97	21.8±4.0	22.1±3.8	0.640	21.9±3.7	21.8±3.5	0.790
Mental score AU	13.87±8.11	15.3±7.8	11.8±7.7	0.020	14.0±8.0	12.3±7.8	0.330
Dementia, no:yes*	36:64	38.5:61.5	33:67	0.59	35:65	41:59	0.65
Autonomy in movements, no:yes*	54:46	43:57	66:34	0.01	51:49	70:30	0.08
Tobacco consumption, no:yes*	94:6	95:5	96:4	0.93	95:5	96:4	1
Rythmic disorders, no:yes*	90:10	92:8	87:13	0.33	91:9	85:15	0.47
Atherosclerosis of the lower limbs, no:yes*	84:16	88:12	81:19	0.32	86:14	78:22	0.37
Past history of stroke, no:yes*	79:21	79:21	80:20	0.84	82:18	70:30	0.29
Past history of myocardial infarction, no:yes*	88:12	97:7	81:19	0.005	93:7	70:30	0.001
SBP, mm Hg	137.4±17.2	136.6±18.3	138.3±16.3	0.290	135.3±16.3	142.3±17.9	0.030
DBP, mm Hg	74.2±11.5	74.1±10.4	74.3±12.8	0.770	72.8±10.1	76.9±14.3	0.060
MBP, mm Hg	95.7±11.9	95.3±11.6	96.5±12.5	0.350	94.1±10.6	99.6±14.2	0.010
PP, mm Hg	63.2±13.2	62.5±14.5	63.9±11.7	0.270	62.5±13.3	65.3±12.0	0.230
Heart rate, bpm	76.0±10.8	75.7±11.5	76.9±9.8	0.310	76.1±10.7	76.8±10.4	0.640
PWV, m/s	14.15±3.11	13.97±3.08	14.43±3.22	0.460	13.7±2.8	15.4±3.4	0.020
C-reactive protein, g/L	13.85±26.3	11.0±29.5	15.4±21.3	0.260	11.9±26.1	18.8±24.8	0.200
Plasma albumin, g/L	31.9±4.9	32.2±4.6	31.2±4.9	0.650	32.1±4.4	30.5±6.1	0.220
Plasma prealbumin, g/L	197.2±54.3	196.7±48.8	194.6±58.2	0.830	197.5±52.6	183.1±54.4	0.250
Plasma total cholesterol, mmol/L	5.05±1.13	5.19±1.07	4.90±1.21	0.530	5.07±1.11	4.91±1.16	0.870
Plasma HDL cholesterol, mmol/L	1.04±0.38	5.65±1.95	5.59±2.28	0.780	5.50±1.68	6.04±3.41	0.170
Plasma glucose, mmol/L	5.61±2.08	1.05±0.39	1.03±0.36	0.790	1.04±0.37	1.01±0.43	0.960
Plasma creatinine, mmol/L	87.64±44.68	82.2±28.1	93.0±56.6	0.320	83.6±32.6	102.1±75.1	0.100
Creatinine clearance, mL/min	40.59±17.35	44.0±19.8	36.9±13.9	0.080	41.9±18.1	34.6±12.4	0.060
Plasma potassium, mmol/L	4.23±0.34	4.24±0.36	4.24±0.33	0.890	4.2±0.3	4.3±0.3	0.600

AU indicates arbitrary unit. See text for explanation of other abbreviations. Values are mean±1 SD.
*Values are in percent.

population. For the study, we used PWV as a marker of aortic stiffness because it is related to the square root of the aortic elasticity modulus and to the thickness-radius ratio.[5,12] The PWV, determined from the foot-to-foot transit time in the aorta, offers a simple, reproducible, and noninvasive evaluation of regional arterial stiffness. This noninvasive superficial measurement merely estimates the distance traveled by the pulse, and accurate measurements of this distance can only be obtained with invasive procedures. Regarding subjects >70 years of age, because arteries become longer and more convoluted, the path lengths determined from superficial linear measurements are obviously underestimated. Furthermore, aortic PWV may be considered a more reliable index than SBP itself, owing to the frequency of "pseudohypertension" in this elderly population.[14] In recent years, repeatability studies, evaluations with the algorithm derived from Bland and Altman diagrams, and modern computer technology[12,13] have made PWV measurements quite feasible for easily investigating aortic stiffness in clinical studies.

In the present investigation, because of the difficulty of obtaining accurate pulse wave tracings in geriatric patients, 23 subjects had to be excluded from the statistical evaluation for methodological reasons. Similarly, although in this study a significant proportion of patients had confirmed CVD, this value was probably underestimated, because "silent" myocardial ischemia or cerebrovascular disease could not be excluded on the basis of the noninvasive methods used. Finally, because age, BP, and the use of vasoactive agents such as nitrates[7] might influence aortic PWV, adjustments to these parameters were widely used during this study.

In a similar population of old subjects, we had previously established on the basis of a cross-sectional design that PWV was not correlated significantly with age, thereby indicating that the PWV-age curve approximated a plateau for those >70 years and that only the classic relation between age and BP remained significant.[9] Another important finding of this previous investigation was that heart rate significantly influenced PWV. Heart rate dependency on aortic stiffness has

TABLE 2. Odds Ratios on CV Mortality (Adjusted on Age and Sex): Main Results of the Univariate Logistic Analysis

		95% Confidence Interval		
	Odds Ratio	Lower Limit	Upper Limit	*P*
MBP, mm Hg	1.05	1.01	1.09	0.010
PWV, m/s	1.19	1.03	1.37	0.018
SBP, mm Hg	1.03	1.00	1.06	0.020
Past history of CVD, no:yes	2.80	1.13	6.95	0.026
Creatinine clearance, mL/min	0.97	0.93	1.00	0.056
Autonomy in movement, no:yes	0.41	0.16	1.04	0.060
Plasma glucose, mmol/L	1.14	0.95	1.37	0.160
Age, y	1.05	0.98	1.13	0.170
Plasma albumin, g/L	0.94	0.85	1.04	0.210
C-reactive protein, g/L	1.01	1	1.02	0.210

See text for explanation of abbreviations.

been noted previously in such populations.[5,15] In the present follow-up, there was no major interference between PWV and heart rate. Furthermore, we did not observe that heart rate significantly influenced overall and CV mortality.[16,17]

The major finding of the present study was that PWV was a strong predictor of CV risk, independent of heart rate, BP, plasma HDL cholesterol, and dementia, even after adjustment for ADT and nitrates. At a PWV >17.7 m/s, the CV death rate was already 50%. Interestingly, in the present elderly population, BP and particularly SBP and PP did not influence CV mortality. This finding raises the question as to whether BP (mainly SBP or PP), aortic stiffness, or even a combination of both might be the best therapeutic target to reduce CV mortality in the elderly.[3,18] In patients with end-stage renal disease undergoing hemodialysis, Guerin et al[19] have shown that for the same MBP reduction under ADT, PWV was reduced in survivors but remained unmodified in deceased patients. It is noteworthy that in such patients, hypertension has the same clinical features as in the elderly, involving increased aortic stiffness and a disproportionate elevation of SBP over DBP.[4]

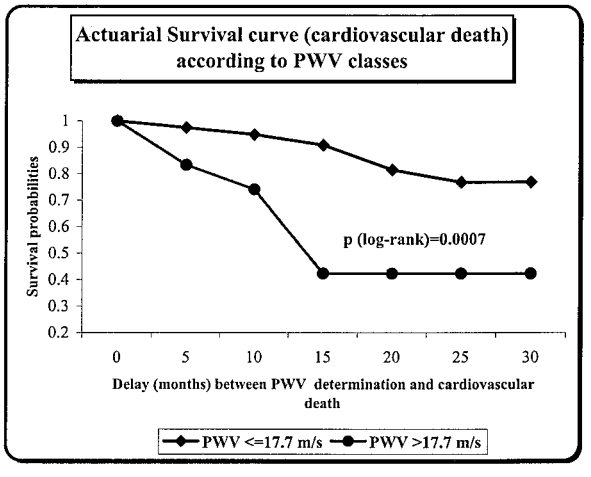
An interesting finding of this follow-up was that low plasma albumin and altered markers of inflammation, such as C-reactive protein, were not significant predictors of overall or CV mortality. Malnutrition and/or C-reactive protein has previously been reported to influence CV risk, particularly in atherosclerotic subjects living in underdeveloped countries and in subjects on chronic hemodialysis.[20–22] Although in a previous cross-sectional study we noted the possible influence of low plasma albumin on the presence of CVD,[9] this finding was not confirmed by the present long-term follow-up. It is noteworthy that loss of autonomy was the main predictor of overall mortality and can mediate the occurrence of poor nutritional status and hypoalbuminemia.

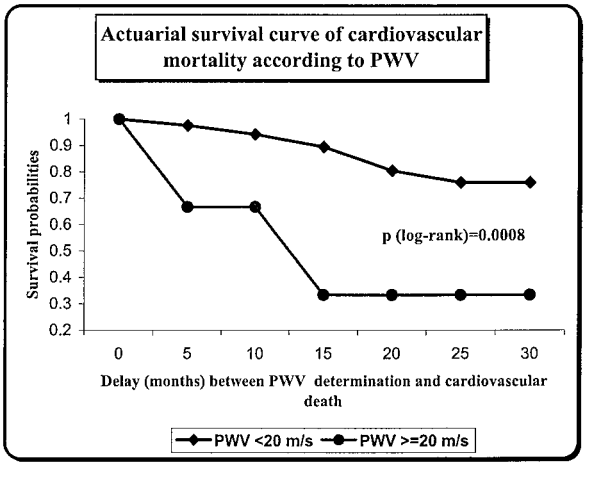
Because the study was conducted in 3 geriatrics departments, several biases may have been introduced into the study population. First, 1 of the main symptoms during hospitalization was the presence of dementia. In a cross-sectional study involving subjects >70 years of age,[9] because PWV was found to be negatively associated with the presence of dementia and in the present investigation, because mental score was negatively correlated with total mortality, the present results were constantly adjusted to this variable. On the other hand, in very old subjects, the diagnosis of hypertension is often difficult to assess because the term "normotensive" may either reflect good health or be considered a symptom of the severity of cancer or congestive heart failure. For this reason, in most statistical evaluations we used BP as both a quantitative and a qualitative variable, thus enabling us to classify our population into 4 different BP status groups

TABLE 3. Stepwise Logistic Procedure of CV Mortality Involving Adjustments on SBP, MBP, Past History of CVD, Creatinine Clearance, Autonomy in Movement, Plasma Glucose, C-Reactive Protein, ADT, and Nitrate Administration

		95% Confidence Interval		
	Odds Ratio	Lower Limit	Upper Limit	*P*
1. Model with PWV in m/s				
PWV m/s	1.19	1.03	1.37	0.016
2. Models with PWV classes				
1. PWV (≤17.7 m/s and >17.7 m/s)	4.6	1.4	15.7	0.01
2. PWV (<20 m/s and ≥20 m/s)	8.8	1.5	50.9	0.02

See text for explanation of abbreviations.





CV mortality: actuarial survival curve according PWV classes.

and to thereby exclude a major role of ADT. Finally, subjects >70 years of age should be considered "survivors," and this particular aspect may have influenced some of our findings. For instance, the lack of contribution of creatinine clearance and blood glucose to overall and CV mortality might suggest that all subjects with diabetes and/or renal insufficiency were already dead. However, in the present population, wide ranges of glycemia and creatinine clearance (Table 1) were observed, suggesting that no major bias was introduced for diabetes and renal insufficiency within the present cohort and that the studied population was indeed valid.

In conclusion, the results of this investigation indicate that the increase in aortic PWV is an independent marker of CV risk in subjects >70 years of age. In this population, arterial stiffness is even a stronger marker than BP itself. Intervention studies are required to assess the validity of this noninvasive, hemodynamic measurement within the framework of CV risk.

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