Stiffness of Capacitive and Conduit Arteries
Prognostic Significance for End-Stage Renal Disease Patients
Bruno Pannier, Alain P. Guérin, Sylvain J. Marchais, Michel E. Safar, Gérard M. London

Abstract—The aorta is the principal capacitive element of the arterial tree and its increased stiffness, determined by measurement of aortic pulse wave velocity (PWV), is a strong independent predictor of cardiovascular mortality in the general population and end-stage renal disease (ESRD) patients. Whether stiffness of ESRD patients’ peripheral arteries has the same prognostic value has never been investigated. A cohort of 305 ESRD patients was followed for 70±49 months (mean±SD). Ninety-six deaths of cardiovascular origin occurred. At entry into the study, together with standard clinical and biochemical analyses, patients’ aortic, brachial artery, and femorotibial PWV were determined. Based on Kaplan–Meier survival curve analyses and Cox proportional hazards analyses, adjusted for age, pulse pressure, and clinical data, aortic PWV was a significant and independent predictor of outcome. Neither brachial artery nor femorotibial artery stiffness was able to predict cardiovascular outcome. Receiver operating characteristic curve analysis of aortic PWV indicated the cutoff value of 10.75 m/s, with 84% sensitivity, 73% specificity, 87% negative predictive value, and 72% positive predictive value. These results provide evidence that, in ESRD, increased stiffness of capacitive arteries, like the aorta, is an independent strong predictor of cardiovascular mortality, whereas stiffness of peripheral conduit arteries had no prognostic value. (Hypertension. 2005;45:592-596.)

Key Words: arteries ■ mortality ■ renal disease

Patients with end-stage renal disease (ESRD) are at very high risk for cardiovascular (CV) complications.1 In ESRD patients, arterial stiffness is increased and is associated with acceleration of the arterial aging process, namely dilation and increased wall thickness of major arteries.2 Recent studies have established that aortic stiffness, as evaluated by pulse wave velocity (PWV), is an independent predictor of all-cause and CV mortality in high-risk ESRD patients,3-5 and also as in essential hypertension, type 2 diabetes, and the elderly.6-9 Aortic PWV was also shown to predict primary coronary events and fatal stroke.10,11 Aortic PWV has also emerged as a potential target for intervention, because a therapeutic trial showed that decreasing aortic stiffness improves prognosis and patient outcome.12 The function and structure of the arterial system is heterogeneous and differs markedly between central elastic large arteries (aorta and major branches), representing the principal capacitive system, and stiffer peripheral muscular arteries with predominantly conduit function.13 All the studies that found a relationship between arterial stiffness and fatal outcome concerned aortic PWV, but the predictive value of PWV measured in peripheral arteries has not yet been examined. The purpose of the present study was to determine the predictive value of regional arterial stiffness, including carotid–femoral arteries (aortic) PWV, carotid–radial artery (brachial) PWV, and femoral–posterior tibial artery (femorotibial) PWV, for CV mortality in ESRD patients on hemodialysis.

Patients and Methods
The cohort included 305 patients (189 men, 116 women) who were admitted to our hemodialysis unit between January 1, 1987 and September 1, 2003. Patients were enrolled if they: (1) had been on hemodialysis for at least 3 months; (2) agreed to participate in the study, which was approved by our institutional review board; (3) were free of any CV complication during the 6 months preceding entry into the study; and (4) had no hemodynamically significant lower limb arteries occlusive lesions. Their mean follow-up was 70±49 months (range, 3 to 204 months). Patients who underwent renal transplantation and patients who moved were censored on the day of transplantation or departure. The causes of ESRD were 30% primary or secondary glomerulonephritis, 20% interstitial nephritis, 13% polycystic kidney disease, 10% had diabetes mellitus, 22% hypertensive nephropathy, and 6% ESRD of unknown origin. History of CV disease (CVD) was reported in 89 (29.2%) of patients. During follow-up, all patients underwent hemodialysis using the same technique.2 At inclusion, 52% of patients received antihypertensive therapy with angiotensin-converting enzyme inhibitors, β-blockers, or dihydropyridine calcium channel blockers given in monotherapy or in associations. The antihypertensive treatment was continued during follow-up.

Data Collection
All clinical, hemodynamic, and blood chemistry data reported are those obtained at the inclusion. Information compiled from the questionnaire completed at entry included personal and family histories, smoking habits, and previous history of CVD, including coronary artery disease, congestive heart failure, peripheral vascular disease, and cerebrovascular disease. During follow-up, we recorded 96 fatal CV events attributed to coronary artery disease, mesenteric infarction, sudden death, congestive heart failure, or stroke. Causes
of death (WHO International Classification of Disease, 9th revision) were obtained from death certificates, hospital records, 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 had played any role in the fatal outcome.

Cardiovascular Measurements
All determinations were made during the 2 weeks after inclusion on the morning before the midweek hemodialysis. Blood pressure (BP) was measured with a mercury sphygmomanometer after 15 minutes of recumbency. Phases I and V of the Korotkoff sounds were taken, respectively, as systolic BP (SBP) and diastolic BP (DBP) thresholds. Five measurements taken at 2-minute intervals were averaged. Blood lipids and serum albumin were determined by automated methods. Pulse pressure (PP) was measured as SBP – DBP. At each examination, arm BPs and bilateral ankle BP (posterior tibial artery or dorsalis pedis artery), measured by handheld 8-MHz Doppler (M942 SEGA), were taken with the subject supine. Each measurement was taken twice. The means of the 2 measurements for each leg and for the arm were used to calculate ankle–brachial pressure index. Normal ankle–brachial pressure index was defined as >0.90 and <1.40.

Arterial PWV was determined by the foot-to-foot method as previously described and validated. Simultaneously, recorded pulse waveforms were obtained transcutaneously over the common carotid and femoral arteries in the groin (aortic PWV), over the carotid and radial arteries (brachial PWV), and over the femoral and posterior tibial arteries (femorotibial PWV). PWV was calculated as the distance between recording sites measured over the surface of the body, divided by the time interval between the feet of the flow waves. This interval was averaged over 10 to 15 cardiac cycles. Aortic PWV was determined in all 305 patients. Brachial PWV was determined on the arm not bearing the arterio-venous shunt and could be determined in 258 patients (47 patients had or have had arterio-venous shunts in both arms). Femoral PWV was obtained in 247 patients with normal ankle–brachial pressure index (1.14±0.09).

Analysis
The primary outcome event studied was CV mortality. Data are expressed as means±SD unless otherwise specified. Sex (0, man; 1, woman), diabetes (0, no; 1, yes), and prescription of antihypertensive drugs (0, no; 1, yes) were used as categorical variables. The Kaplan–Meier method was applied to estimate survival probabilities, and the log-rank test was used to determine their significance. For Kaplan–Meier analysis, the cohort was divided into tertiles. The primary analyses used the unadjusted Cox proportional hazards analysis to evaluate the risk ratios of CV risk factors. Multivariate Cox proportional hazards analysis was then applied to determine the independence of the relationships of all unadjusted significant covariates of CV mortality (P<0.05). The following covariates were considered: age, sex, smoking, diabetes, blood lipids, systolic BP, diastolic BP, PP, time on hemodialysis, and PWVs. Variable significance was defined as P<0.05 adjusted for all variables in the final model. To determine whether PWV might be variables, receiver operating characteristic curves were plotted, and we calculated sensitivity, specificity, positive predictive value, negative predictive values, and cutoff values. ANOVA and Bonferroni multiple comparison tests were applied to analyze aortic PWV differences according to the causes of ESRD. All tests were performed using NCSS 2000 software (J. Hintze; Kaysville, Utah).

Results
Patients Characteristics
Parameters concerning traditional risk factors and arterial parameters are reported in Table 1. The population was principally characterized by an isolated increase of SBP and normal DBP. In addition to anemia, which is characteristic of ESRD patients, the only abnormality was moderately increased triglycerides also typical for these patients. The values of aortic PWV according the different causes of ESRD are shown in Figure 1. PWV was significantly lower in patients with interstitial nephritis (ANOVA P<0.0001; F= 7.37) and nonsignificantly different in the remaining groups. According to the multivariable regression analysis, aortic PWV was positively associated with age (P<0.00001), PP (P<0.00001), smoking (P<0.00001), diabetes (P=0.007), and low-density lipoprotein cholesterol (P=0.015). Brachial and femorotibial PWVs were associated only with PP (P=0.00001) than the association between PP and aortic PWV was much stronger (R²=0.302; P<0.00001) than the association between PP and brachial PWV (R²=0.102; P<0.00001) or femoral PWV (R²=0.056; P=0.0002).

![Figure 1. Distribution of aortic pulse wave velocity (PWV) according to causes of end-stage renal disease (ESRD). DM indicates diabetes mellitus; GN, glomerulonephritis; IN, interstitial nephritis; PKD, polycystic kidney disease; hypertension, hypertensive nephropathy. ***P<0.0001 NI different from the other groups.](image-url)
Outcome and Prognostic Impact of Arterial Stiffness

During the follow-up period, 96 patients died of CV disease: 41 myocardial infarctions, 28 congestive heart failures, 14 sudden deaths, and 13 strokes (75 patients died among those 258 patients with brachial PWV measurement, and 72 patients died among those 247 patients with femorotibial PWV measurements). The probability of CV survival is shown in Figure 2. Only aortic PWV was associated with CV mortality, and the differences between the tertiles was highly significant. Our unadjusted Cox analysis identified (Table 2) age, smoking, history of CVD, diabetes, SBP, PP, and aortic PWV as being significantly associated with CV mortality. In the entire population, the prescription of antihypertensive treatment was not significantly associated with the outcome (risk ratio, 0.81; 95% confidence interval, 0.51 to 1.30; \( P = 0.379 \)) (Table 2). When the univariate Cox analysis was restricted to the group of patients using antihypertensive treatment, the prescription of angiotensin-converting enzyme inhibitors was associated with risk reduction (risk ratio, 0.34; 95% confidence interval, 0.19 to 0.60; \( P = 0.001 \)). Because of the tight relationship between aortic PWV and PP, 2 multivariable Cox models were tested (Table 3). The first model (\( R^2 = 0.294 \)) included age (\( P = 0.0001 \)), history of CVD (\( P = 0.0013 \)), diabetes mellitus (\( P = 0.0633 \)), smoking (\( P = 0.0807 \)), and PPs (\( P = 0.0063 \)). Once this base model had been determined, aortic PWV was added, with the following results: (\( R^2 = 0.325 \)), age (\( P = 0.0026 \)), history of CVD (\( P = 0.0035 \)), diabetes mellitus (\( P = 0.2204 \)), smoking (\( P = 0.5604 \)), PP (\( P = 0.1995 \)), and aortic PWV (\( P = 0.0059 \)) (Table 3). Only age, history of CVD, and aortic PWV had significant prognostic variables for CV mortality. Brachial and femoral PWV were not significant predictors. Figure 3 shows the receiver operating characteristic curves and the areas under the curves for the different regional PWVs.

Discussion

In agreement with previous studies on ESRD patients,3–5 patients with essential hypertension and diabetes,6–11 our present findings indicate that aortic PWV is a strong and independent predictor of CV mortality. In contrast, the PWVs...
of peripheral conduit arteries, for both upper and lower limbs, has no prognostic value for CV mortality in ESRD patients. This observation confirms that PWV measured along the aortic and aorto-iliac pathway is the most clinically relevant, because the aorta and its major large branches are physiologically the principal arterial capacitive element.13

The arterial system is heterogeneous, and the processes of structural and functional changes differ markedly in central capacitive arteries and more peripheral conduit arteries.13 Whereas in younger populations the aortic PWV is lower than brachial or femoral PWV, the effect of aging on PWV is more pronounced in the aorta, and in older populations aortic and peripheral limb PWV are almost similar.14 The accelerated stiffening of central over peripheral arteries was also observed in ESRD patients,17 and in patients with impaired glucose metabolism17 or type 2 diabetes.18 As shown herein, aortic PWV is independent of age and systolic BP or PP associated with several risk factors, whereas arm and leg PWV are principally dependent on operating BP, principally PP.

Aorta is a major capacitive element of the arterial tree and, as such, is a major determinant of the amplitude of the incident/forward pressure wave.13,19,20 Aortic PWV also influences the time of return of wave reflections and timing of incident and reflected pressure waves.19,20 As such, aortic stiffness is an important determinant of PP and has a marked impact on left ventricular afterload, myocardial oxygen consumption, and coronary perfusion.13,19–22 Aortic stiffening occurs before the onset of clinical disease17,23 and is a prognostic indicator of risk of CV complications.24 The reliability of aortic PWV as a guide to therapeutic efficacy in ESRD was previously demonstrated.12 In younger and middle-aged populations, the peripheral limb arteries are stiffer than the aorta,13,14 and they primarily have a conduit function.25 Furthermore, the morbidity associated with peripheral arteries is more influenced by caliber reduction and the presence of stenotic lesions. The presence of hemodynamically significant stenotic lesions in the limb induces poststenotic BP decrease. In light of the BP dependency of arterial stiffness, in the presence of hemodynamically relevant lower limb artery stenosis, the measure of PWV loses its significance as a measure of stiffness.26 In this present study, as normally observed, limb PWV was higher than aortic PWV, and inclusion criteria required the absence of hemodynamically significant lower limb occlusive lesions.

Stiffening of the aorta and large conduit arteries increases SBP and decreases DBP, thereby increasing PP,13 hence, PP could be used as a crude guide to stiffness.24 However, a number of other factors, including left ventricular function and the intensity of wave reflection depending on the properties of distal vasculature (arterial reflectance), also influence PP.19,20,25 As shown herein, PP is strongly associated with aortic PWV and loses its significance when direct measurement of stiffness with PWV is used in the models (Table 3). PWV measurements offer a simple and reproducible evaluation of regional arterial stiffness. According to the Moens–Korteweg formula, PWV depends on intrinsic elastic properties of the arterial wall (elastic modulus), arterial wall thickness, and diameter.13 As such, PWV integrates functional and structural elements and can be considered an integrated index of vascular function. The limitation of PWV measurements is their inability to directly differentiate between functional and structural factors contributing to stiffening. Moreover, because of the BP dependency of the parameter, an adjustment for BP must always be made.

The ability to generalize the present results may be limited because the demographics and characteristics of the ESRD patients reported were different from those in North America and elsewhere. This concerns principally the proportion of diabetic subjects, which, although steadily increasing in France, remains lower. Nevertheless, as shown by Shoji et al4 in ESRD diabetic patients, aortic PWV was an independent predictor of all-cause and CV outcome.

### Table 3. Adjusted Cox Proportional Hazards Analysis Reports

<table>
<thead>
<tr>
<th>Variables</th>
<th>Report 1</th>
<th>Report 2</th>
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</thead>
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<td>Wald Z</td>
<td>P Value</td>
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<td>Age, y</td>
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<td>0.0001</td>
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<td>History CVD (1 yes; 0 no)</td>
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<td>Smoking, pack/y</td>
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<tr>
<td>Diabetes (1 yes; 0 no)</td>
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<tr>
<td>Pulse Pressure, mm Hg</td>
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<td>0.0063</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
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<td>...</td>
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</tbody>
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R = 0.294
R = 0.325

**Figure 3.** Receiver operating characteristics curves for pulse pressure, aortic PWV, brachial PWV, and femoral PWV in ESRD patients.
In summary, several reports, including the present one, indicate that aortic PWV is a risk marker of CV disease and an independent predictor of CV mortality in ESRD patients and the general population. In contrast to aortic PWV peripheral arteries, PWV had no prognostic value in ESRD patients. Whether a similar absence of a relationship between CV mortality is present in the general population remains to be established.

Perspectives
Aortic PWV has emerged as an important surrogate risk marker and independent predictor of CV events in essential hypertension, elderly subjects, diabetic patients, and patients with ESRD. A previous study also showed that changes of aortic PWV are a reliable guide to therapeutic efficacy. The methods used to measure surrogate markers should be non-invasive, rapid, inexpensive, reproducible with high sensitivity and specificity, and easily accessible. Measurement of aortic PWV satisfies these requirements. Aortic PWV can be determined using automatic devices, which have been validated and have proven good reproducibility and repeatability coefficients. Taking aortic stiffness into consideration might provide a more accurate individual risk assessment, resulting in earlier and more effective preventive therapy.

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References
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