Impact of Aortic Stiffness on Survival in End-Stage Renal Disease

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Background—Damage to large arteries is a major factor in the high cardiovascular morbidity and mortality of patients with end-stage renal disease (ESRD). Increased arterial stiffness and intima-media thickness, together with increased pulse pressure, are the principal arterial alterations. Whether increased aortic pulse-wave velocity (PWV), a classic marker of increased arterial stiffness, may predict all-cause and/or cardiovascular mortality has never been investigated.

Methods and Results—A cohort of 241 patients with ESRD undergoing hemodialysis was studied between April 1987 and April 1998. The mean duration of follow-up was 72±41 months (mean±SD). Mean age at entry was 51.5±16.3 years. Seventy-three deaths occurred, including 48 cardiovascular and 25 noncardiovascular fatal events. At entry, together with standard clinical and biochemical analyses, patients underwent echocardiography and aortic PWV measured by Doppler ultrasonography. On the basis of Cox analyses, 2 factors emerged as predictors of all-cause and cardiovascular mortality: age and aortic PWV. Hemoglobin and low diastolic pressure interfered to a smaller extent. After adjustment for all the confounding factors, an OR for PWV 12.0 versus 9.4 m/s was 5.4 (95% CI, 2.4 to 11.9) for all-cause mortality and 5.9 (95% CI, 2.3 to 15.5) for cardiovascular mortality. For each PWV increase of 1 m/s in our study population, all-cause mortality–adjusted OR was 1.39 (95% CI, 1.19 to 1.62).

Conclusions—These results provide the first direct evidence that in patients with ESRD, increased aortic stiffness determined by measurement of aortic PWV is a strong independent predictor of all-cause and mainly cardiovascular mortality. (Circulation. 1999;99:2434-2439.)

Key Words: aorta ■ survival ■ kidney

Patients with end-stage renal disease (ESRD) are at increased risk of cardiovascular disease. Epidemiological and clinical studies have shown that damage of large arteries is a major contributory factor to the high cardiovascular morbidity and mortality of ESRD patients.1 Macrovascular disease develops rapidly in uremic patients and is responsible for the high incidence of ischemic heart disease, left ventricular (LV) hypertrophy, congestive heart failure, sudden death, and stroke.1 Many complications arise in ESRD patients in the absence of clinically significant atherosclerotic disease.2 The principal arterial alteration in this latter situation consists of arterial stiffening associated with arterial enlargement and hypertrophy.3 Arterial stiffening occurs normally with aging4 but also correlates with the prevalence of atherosclerosis. The most obvious consequences of arterial stiffening are higher systolic blood pressure (SBP) and lower diastolic blood pressure (DBP), thereby causing increased LV afterload and altering coronary perfusion.4 The principal outcomes of these changes are LV hypertrophy, aggravation of coronary ischemia, and increased fatigue of arterial wall tissues. Higher SBP and pulse pressure, lower DBP, and LV hypertrophy have been identified as independent factors of cardiovascular morbidity and mortality in the general population5,6 as well as in ESRD patients.7–9

Arterial stiffness can be assessed noninvasively by measurement of pulse-wave velocity (PWV).10,11 According to the Moens-Korteweg equation,4 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 important determinants of cardiovascular coupling, and the PWV measured along the aortic or aortoiliac pathway is the most clinically relevant.4 Nevertheless, whether arterial stiffening is predictive of clinical outcome or death has never been established. To identify the impact of aortic stiffening on cardiovascular and all-cause mortality in hemodialyzed ESRD patients, we conducted a prospective study on a cohort of 241 patients followed up for a period of up to 11 years.

Methods

Patients
This prospective cohort study was started at the F.H. Manhès Hospital, Fleury-Mérogis (in the Paris/Ile de France area), in April 1987. Patients were eligible for entry into the study when (1) they had been on hemodialysis for ≥3 months (48±51 months, (Circulation. 1999;99:2434-2439.)
mean ± SD) and (2) they had no clinical cardiovascular disease during 6 months preceding entry. Patient recruitment was closed in October 1996, and follow-up ended in April 1998. In all, 241 patients fulfilled the entry criteria. Patients who underwent renal transplantation (n = 28) and patients who moved away (n = 7) were censored at transplantation or departure to another unit. All but 6 patients were white. The mean patient follow-up was 72.4 ± 41 months. Data on mortality were obtained for the entire cohort. The mean age of the cohort was 55.2 ± 16.3 years; 61% were male; 7% had insulin-dependent diabetes mellitus; and 48% were treated with different antihypertensive drugs. Of these patients, 126 received recombinant human erythropoietin at some time during follow-up. During the follow-up, all patients were dialyzed by the same unique standardized technique, including synthetic membrane hemodialyzers (AN69 and polysulfone) matched for the subject’s body surface area (1.36 to 2.0 m²), bicarbonate dialysate, and controlled ultrafiltration rate. The duration of dialysis sessions was tailored (4 to 6 hours, 3 times weekly) to achieve a total dialysis dose (Kt/V) ≥ 1.2 (1.38 ± 0.17). Each subject provided informed written consent to participate in the study, which was approved by our institutional review board.

Data Collection
Information compiled from the questionnaire filled out at entry into the study included personal and family histories, smoking habits (126 patients were current or former smokers), and previous history of cardiovascular disease, including coronary artery disease, angina pectoris, cardiac failure, peripheral vascular disease, and cerebrovascular disease. Causes of death (WHO 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 mean follow-up period, we recorded 73 deaths, including 48 fatal cardiovascular events: 15 deaths attributed to coronary heart disease, 12 to cerebrovascular and/or aortic disease, 12 to sudden death, 6 to congestive heart failure, and 3 to pulmonary embolism. The 25 fatal noncardiovascular events were 12 deaths due to cancer, 6 due to infectious disease, 5 by withdrawal from dialysis, and suicide 2. The measurements were performed during the 2 weeks after inclusion, on the morning before the midweek hemodialysis. Blood chemistry was measured at baseline and at monthly intervals. BP was measured with a mercury sphygmomanometer after 15 minutes of rest in the supine position. The mean arterial pressure was calculated as (SBP/3 + DBP)/3. 

Baseline echocardiography was performed with a Hewlett-Packard Sonos 100 device equipped with a 2.25-MHz probe allowing M-mode, 2-dimensional, and pulsed Doppler measurements. Measurements were made according to the recommendations of the American Society of Echocardiography. LV mass was calculated according to the Penn convention. Adequate echocardiographic tracings were obtained for 214 subjects. LV hypertrophy (LV mass index > 132 g/m² in men and > 110 g/m² in women) was present in 81% of the patients.

Baseline aortic PWV was determined from transthecal Doppler flow recordings and the foot-to-foot method. Two simultaneous Doppler flow tracings were taken at the aortic arch and the femoral artery in the groin with a nondirectional Doppler unit (SEGA MB42, 10 MHz) with a handheld probe and recorded on a Gould 8188 recorder (Gould Electronique) at a speed of 100 to 200 mm/s. For aortic flow, the transducer was placed in the suprasternal notch.

When a good-quality high-frequency signal could not be recorded in this location, the transducer was placed laterally at the base of the neck, and the signal from the common carotid artery opposite to the site of arteriovenous fistula was recorded. The time delay (τ) was measured between the bases of the flow waves recorded at these different points and was averaged over 10 beats. The distance (D) traveled by the pulse wave was measured over the body surface as the distance between the 2 recording sites, and when measured from the carotid artery, the distance from the suprasternal notch to the carotid was subtracted. PWV was calculated as PWV = D/τ. All measurements were done by the same observer (G.M.L.), and the intraobserver repeatability of the aortic PWV measurement was 5.8 ± 1.4. The heart period was determined from the 3-lead orthogonal ECG.

Analysis
The outcome events studied were cardiovascular mortality and all-cause mortality. Survival curves were estimated by the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. Prognostic factors of survival were identified by use of logistic regression analysis and the Cox proportional hazards regression model. The assumption of proportional hazards over time was verified before the analyses were performed and was met by all covariates. The assumption concerning linearity of continuous covariates was also verified before analysis. All analyses, including echocardiographic LV mass among the covariates, were limited to the subset with adequate echocardiographic tracings. The cohort was divided into 3 groups (80 or 81 patients per group) according to the PWV < 9.4 m/s in the lower third, between 9.4 and 12.0 in the second third, and > 12.0 in the upper third. Variables were considered to be prognostic if they were found to be significant (P < 0.05) in the logistic regression or the Cox proportional hazards regression models of all-cause or cardiovascular mortality. The adjusted relative risk of experiencing an outcome event during follow-up for the patients in the second or in the upper third of any prognostic variable compared with the risk of the patients in the lower third was estimated as the OR. Adjusted ORs were calculated as the antilogarithm of the β coefficient of the logistic regression of the outcome events with all the prognostic variables, considered as continuous variables in the model (PWV, age, time on dialysis before inclusion, DBP, and hemoglobin). The 95% CIs around the adjusted OR estimates were obtained with the formula antilogarithm(β ± 1.96 SE), where SE is the standard error of β.

Data are expressed as mean ± SD. ANOVA was used for comparison of normally distributed continuous variables. Differences in frequency were tested by χ² analysis. Sex (1, male; 2, female), previous history of cardiovascular disease (1, no; 2, yes), and antihypertensive drug therapy (1, no; 2, yes) were used as dummy variables. Statistical analysis was performed with NCSS 6.0.21 software. Repeatability and reproducibility of the methods were defined as recommended by the British Standards Institution. A value of P < 0.05 was considered significant. All tests were 2-sided.

Results
Patient Characteristics
The characteristics of the cohort at the time of inclusion are shown in Table 1. The characteristics of patients as a function of their PWV values are shown in Table 2. Comparing the different subgroups, age, age at the initiation of dialysis, SBP, mean BP, pulse pressure, LV mass index, tobacco life-long dose, and incidence of diabetes and previous cardiovascular events increased from the lower to the upper third, whereas DBP and serum albumin decreased. Serum albumin levels were negatively associated with age (P < 0.001), and in the subsequent analysis, the role of the albumin level could not be differentiated from the influence of aging.

Outcome and Prognostic Impact of Aortic PWV
During the follow-up period, 73 deaths were recorded. According to the Cox analysis, the significant covariates retained by the model were only age, PWV, and DBP (negative association) (Table 3). Smoking, heart rate, hemoglobin, serum albumin, LV hypertrophy, antihypertensive drug therapy, sex, parathyroid hormone, and previous cardio-
Aortic Stiffness and Mortality

TABLE 1. Characteristics of Patients at Inclusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients (n=241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco lifelong dose, pack·y</td>
<td>9±15</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.2±1.2</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1±0.5</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.4±1.1</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.8±1.1</td>
</tr>
<tr>
<td>Parathyroid hormone, pg/mL</td>
<td>239±240</td>
</tr>
<tr>
<td>Plasma albumin, g/L</td>
<td>39.8±2.4</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>5.8±1.2</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>157±28</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>85±16</td>
</tr>
<tr>
<td>Heart period, ms</td>
<td>830±131</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>11.1±3.1</td>
</tr>
<tr>
<td>Previous cardiovascular events, %</td>
<td>24</td>
</tr>
</tbody>
</table>

vascular events did not reach statistical significance in multivariate analysis. After adjustments for all the prognostic variables (PWV, age, time on dialysis before inclusion, DBP, and hemoglobin), PWV was the strongest predictor of mortality, followed by the duration of hemodialysis before inclusion and the patient’s age at inclusion (Table 4). Duration of hemodialysis before inclusion was inversely correlated with the patient’s age at start of hemodialysis (P<0.001) and at inclusion (P=0.05). Compared with patients in the lower third of PWV, patients in the upper third had a 5.4-fold adjusted risk of all-cause mortality (95% CI, 2.4 to 11.9). For each PWV increase of 1 m/s in our study population, all-cause mortality relative risk was 1.39 (95% CI, 1.19 to 1.62).

Forty-eight cardiovascular deaths were documented during the follow-up period. According to the Cox analysis, the significant covariates entering the model were age, PWV, hemoglobin, and DBP (Table 3). Serum lipids, smoking, heart rate, LV hypertrophy, antihypertensive therapy, sex, and parathyroid hormone did not reach statistical significance in multivariate analysis. After adjustment for all the prognostic variables, PWV was again the strongest predictor of cardiovascular mortality (Table 4). Compared with patients in the lower third of PWV, patients in the upper third had a 5.9-fold adjusted risk of cardiovascular mortality (95% CI, 2.3 to 15.5). Duration of hemodialysis before inclusion predicted cardiovascular mortality but to a lesser degree. The Figure shows the probabilities of all-cause (A) and event-free (B, cardiovascular) survival as a function of PWV values. Comparisons between survival curves were highly significant.

Considering 3 tertile groups according to age at initiation of dialysis, we found that PWV, in univariate analysis, was

TABLE 2. Characteristics of Patients at Inclusion According to Tertiles of PWV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>&lt;9.4 (n=81)</th>
<th>9.4–12.0 (n=80)</th>
<th>&gt;12.0 (n=80)</th>
<th>P ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40.1±14.4</td>
<td>50.2±13.6</td>
<td>64.4±10.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex, M/F ratio</td>
<td>1.4±0.5</td>
<td>1.4±0.5</td>
<td>1.4±0.5</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>2.5</td>
<td>6.3</td>
<td>12.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Time on dialysis before inclusion, mo</td>
<td>50±51</td>
<td>49±50</td>
<td>45±53</td>
<td>...</td>
</tr>
<tr>
<td>Age at initiation of dialysis, y</td>
<td>36±16</td>
<td>46±14</td>
<td>61±12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tobacco lifelong dose, pack·y</td>
<td>4±7</td>
<td>8±11</td>
<td>14±21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.3±1.3</td>
<td>5.2±1.0</td>
<td>5.2±1.2</td>
<td>...</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.4±1.1</td>
<td>3.4±0.9</td>
<td>3.4±1.1</td>
<td>...</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.2±0.4</td>
<td>1.1±0.5</td>
<td>1.1±0.4</td>
<td>...</td>
</tr>
<tr>
<td>Total/HDL cholesterol, ratio</td>
<td>5.0±2.0</td>
<td>5.4±2.0</td>
<td>5.0±2.0</td>
<td>...</td>
</tr>
<tr>
<td>Plasma albumin, g/L</td>
<td>40.4±2.4</td>
<td>39±2.3</td>
<td>38±2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.7±1.0</td>
<td>1.9±1.1</td>
<td>1.8±1.0</td>
<td>...</td>
</tr>
<tr>
<td>Parathyroid hormone, pg/mL</td>
<td>237±246</td>
<td>261±229</td>
<td>221±246</td>
<td>...</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>5.6±1.2</td>
<td>5.9±1.1</td>
<td>5.9±1.2</td>
<td>...</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>141±26</td>
<td>159±24</td>
<td>172±26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>82±17</td>
<td>90±15</td>
<td>84±16</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>101±19</td>
<td>113±16</td>
<td>113±17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>59±17</td>
<td>69±17</td>
<td>88±20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart period, ms</td>
<td>836±141</td>
<td>841±136</td>
<td>811±115</td>
<td>...</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>159±47</td>
<td>167±48</td>
<td>181±47</td>
<td>0.02</td>
</tr>
<tr>
<td>LV hypertrophy, %</td>
<td>76</td>
<td>79</td>
<td>89</td>
<td>...</td>
</tr>
<tr>
<td>Previous cardiovascular events, %</td>
<td>6</td>
<td>19</td>
<td>48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antihypertensive therapy at inclusion, %</td>
<td>42</td>
<td>49</td>
<td>53</td>
<td>...</td>
</tr>
</tbody>
</table>
strongly related to mortality in the 3 subsets (r=0.44, 
\( P < 0.0001 \) for the lower tertile; r=0.40, 
\( P = 0.0016 \) for the second tertile; and 
\( r = 0.47, P < 0.0001 \) for the upper tertile). 
Differences in mortality for the 3 aortic stiffness categories 
persisted after stratification by age and time since initiation of 
dialysis (data not shown).

### Discussion

Arterial stiffness increases with age,\(^4,10\) hypertension,\(^16\) dia-
abetes mellitus,\(^17\) atherosclerosis,\(^18\) and ESRD.\(^3\) In ESRD
patients, the increased arterial stiffness is associated with 
acceleration of the arterial aging process, namely dilatation 
and increased wall thickness of major arteries. In this study, 
we found that arterial stiffness in patients who require 
hemodialysis was a major predictor of all-cause and cardio-
vascular mortality. The role of arterial stiffening was inde-

dependent of other factors known to affect the outcome of 
uremic patients, namely age, overall duration of ESRD, 
preexisting cardiovascular disease, degree of LV hypertro-

### TABLE 3. Proportional Hazards Regression Analysis of Cardiovascular and 
All-Cause Mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression Coefficient</th>
<th>SE</th>
<th>z Value</th>
<th>Pseudo ( R^2 )</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular mortality (yes, no)*</td>
<td>Age, y 0.049</td>
<td>0.016</td>
<td>3.11</td>
<td>0.06</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>PWV, m/s 0.160</td>
<td>0.052</td>
<td>3.09</td>
<td>0.06</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin, mmol/L 0.286</td>
<td>0.124</td>
<td>2.30</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>DBP, mm Hg -0.020</td>
<td>0.010</td>
<td>-1.99</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>All cause mortality (yes, no)†</td>
<td>Age, y 0.049</td>
<td>0.013</td>
<td>3.84</td>
<td>0.08</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>PWV, m/s 0.153</td>
<td>0.044</td>
<td>3.51</td>
<td>0.07</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>DBP, mm Hg -0.021</td>
<td>0.009</td>
<td>-2.43</td>
<td>0.03</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Model pseudo \( R^2 = 0.32; \) model \( \chi^2 = 68.9; \) model \( P < 0.0001. \)
†Model pseudo \( R^2 = 0.36; \) model \( \chi^2 = 93.0; \) model \( P < 0.0001. \)

### TABLE 4. ORs of Mortality (All-Cause and Cardiovascular) According to Prognostic Variables 
Divided into Tertiles

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>No. of Subjects</th>
<th>Deaths, n (%)</th>
<th>Adjusted OR (95% CI)</th>
<th>Deaths, n (%)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV, m/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9.4*</td>
<td>81</td>
<td>6 (7)</td>
<td>1.0</td>
<td>2 (2)</td>
<td>1.0</td>
</tr>
<tr>
<td>9.4–12.0</td>
<td>80</td>
<td>16 (20)</td>
<td>2.5 (0.7–9.1)</td>
<td>12 (15)</td>
<td>4.2 (0.7–24.5)</td>
</tr>
<tr>
<td>&gt;12.0</td>
<td>80</td>
<td>51 (64)</td>
<td>5.4 (2.4–11.9)</td>
<td>34 (42)</td>
<td>5.9 (2.3–15.5)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45*</td>
<td>81</td>
<td>5 (6)</td>
<td>1.0</td>
<td>4 (5)</td>
<td>1.0</td>
</tr>
<tr>
<td>45–60</td>
<td>80</td>
<td>27 (33)</td>
<td>4.4 (1.2–16.1)</td>
<td>16 (20)</td>
<td>2.6 (0.6–10.9)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>80</td>
<td>41 (51)</td>
<td>2.2 (1.1–4.6)</td>
<td>28 (35)</td>
<td>1.5 (0.7–3.0)</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.1*</td>
<td>81</td>
<td>28 (35)</td>
<td>1.0</td>
<td>15 (19)</td>
<td>1.0</td>
</tr>
<tr>
<td>5.1–6.2</td>
<td>80</td>
<td>22 (27)</td>
<td>0.3 (0.1–0.8)</td>
<td>15 (19)</td>
<td>0.7 (0.3–1.8)</td>
</tr>
<tr>
<td>&gt;6.2</td>
<td>80</td>
<td>23 (29)</td>
<td>0.6 (0.4–1.0)</td>
<td>18 (25)</td>
<td>1.0 (0.6–1.6)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;78*</td>
<td>81</td>
<td>30 (37)</td>
<td>1.0</td>
<td>20 (25)</td>
<td>1.0</td>
</tr>
<tr>
<td>78–94</td>
<td>80</td>
<td>23 (29)</td>
<td>0.5 (0.2–1.3)</td>
<td>13 (16)</td>
<td>0.6 (0.2–1.5)</td>
</tr>
<tr>
<td>&gt;94</td>
<td>80</td>
<td>20 (25)</td>
<td>0.6 (0.3–1.0)</td>
<td>15 (19)</td>
<td>0.9 (0.5–1.5)</td>
</tr>
<tr>
<td>Time on dialysis before inclusion, mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12*</td>
<td>81</td>
<td>16 (20)</td>
<td>1.0</td>
<td>10 (12)</td>
<td>1.0</td>
</tr>
<tr>
<td>12–50</td>
<td>80</td>
<td>23 (29)</td>
<td>1.1 (0.5–2.9)</td>
<td>15 (19)</td>
<td>1.1 (0.4–2.8)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>80</td>
<td>34 (43)</td>
<td>2.8 (1.7–4.7)</td>
<td>23 (29)</td>
<td>2.2 (1.3–3.6)</td>
</tr>
</tbody>
</table>

Adjustments were made on all the prognostic variables in this table.
*Patients in this category served as the reference group.
Aortic Stiffness and Mortality

Whether enhanced arterial stiffness is a risk factor contributing to the development of cardiovascular disease or is a marker of established cardiovascular disease is a matter of debate. A study in Chinese and Australians has suggested that morphological and structural alterations of the aorta may be influenced by both environmental and mostly genetic factors, suggesting that changes of biomechanical properties of major arteries may precede the development of clinically overt disease. Although data reported in the literature indicate that LV hypertrophy is an independent factor of overall mortality in ESRD, we did not find an independent association between LV hypertrophy and death. As a determinant of pressure load, arterial stiffness correlates with LV mass and ratio of LV wall thickness to radius in ESRD patients as well as in those with essential hypertension. The collinearity between aortic stiffness and LV hypertrophy in the present study is the most probable cause for the absence of independent association between mortality and LV mass.

Arterial stiffness is associated with increased SBP and decreased DBP. In ESRD patients, enhanced SBP has been shown to be associated with the development of ischemic heart disease, and a relationship between low DBP and mortality was found in these patients as well as in the general population. Contrary to the observation made by Charra et al but in agreement with others, we did not find an independent relationship between hypertension and patient survival. Confirming data reported in the literature, the present study indicates that other factors associated with survival are patient age and the number of years on dialysis. However, in the present population, PWV measurement persisted as a strong predictor of mortality whatever the age of the patient and even if this measurement was made (long) after the initiation of dialysis.

In the present study, there was a weak inverse relationship between the hemoglobin level and cardiovascular mortality. In the general population, an association between increased risks of all-cause and cardiovascular mortality and higher hematocrit values was observed. In ESRD, anemia is considered an independent risk factor for cardiovascular disease and mortality. Data by Besarab et al show that in ESRD, the normalization of hemoglobin level in patients with compromised cardiovascular function was not associated with favorable improvement in survival. The possibility that excessive correction of anemia and increased blood viscosity is deleterious for microcirculation in patients with damaged arterial function cannot be ruled out and was also suggested by Iseki et al.

The ability to generalize the results of the present study may be limited because the demographics and characteristics of the ESRD patients reported were significantly different from those of ESRD patients in North America and in northern Europe. The proportion of diabetics among ESRD patients, while steadily increasing in France, remains low; diabetic patients represented 6.9% of ESRD patients in 1989. Survival on hemodialysis is superior in France and southern Europe to that in northern Europe or North America, the salient difference being the death rate due to myocardial ischemia and infarction, which is greater in northern Europe. The overall annual mortality rate in ESRD patients in France was 13.3% in 1995 and 6% in the Paris area and the Ile de France. Therefore, the impact of aortic PWV on mortality in the present relatively “low-risk” population

PWV measurement offers a simple, reproducible, indirect, and noninvasive evaluation of regional arterial stiffness. The PWV determined from foot-to-foot transit time in the aorta eliminates the influence of wave reflections and is close to the characteristic PWV determined from phase velocities. The critical factors are the precise measurements of this transit time and the length of the vascular segments. Transcutaneous determination of the vessel length is an approximation that might underestimate the vascular length, an error that might arise especially in elderly patients with unfolded tortuous aorta. Despite these limitations, measurement of PWV is strongly correlated to direct measurements of arterial distensibility and can be considered a good surrogate to evaluation of arterial stiffness by phase-locked echo-tracking systems. Several clinical cross-sectional studies have found an association between atherosclerosis and abnormal arterial stiffness, especially an association between aortic stiffness and coronary artery disease. Studies in ESRD patients have shown that arterial stiffness is enhanced independently of age and BP, making these patients an appropriate test population to analyze the impact of arterial stiffness on mortality.

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of ESRD patients possibly underlines the pathological role of aortic stiffening. In addition, it is important to consider 2 other influences that the relatively lower mortality rates might have on our final results. First, the substantially lower cardiovascular mortality rates might result in an underestimate of the true impact of aortic stiffness on overall mortality in ESRD populations in North America and Europe. Second, in populations with much higher undifferentiated mortality rates, the predictive value of aortic PWV might be altered substantially.

To qualify as a risk factor, increased aortic stiffness must raise the probability of an adverse outcome. The results of the present analysis suggest that this is indeed the case. Although correlation does not imply causation, aortic PWV is a strong independent predictor of cardiovascular and all-cause mortality in patients with ESRD on hemodialysis. In addition, aortic stiffness measurements could serve as an important tool in identifying patients at risk of cardiovascular disease. The ability to identify these patients would lead to better risk stratification and earlier and more cost-effective preventive therapy.

Acknowledgments

This work was supported by the Société Française d’Hypertension Artérielle, the Groupe d’Etude de Pathophysiologie de l’Insuffisance Rénale, Daniel Brun for Organica Association, the Groupe de Pharmacologie et d’Hémodynamique Cardio-vasculaire, and the Union des Mutuelles de l’Ile de France.

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Circulation. 1999;99:2434-2439
doi: 10.1161/01.CIR.99.18.2434
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
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