Arterial Wave Reflections and Survival in End-Stage Renal Failure

Gérard M. London, Jacques Blacher, Bruno Pannier, Alain P. Guérin, Sylvain J. Marchais, Michel E. Safar

Abstract—The increased effect of arterial wave reflections on central arteries like the common carotid artery seen in end-stage renal failure (ESRF) patients favors myocardial hypertrophy and oxygen consumption and alters coronary blood flow distribution. Nevertheless, the impact of wave reflection on the outcome and end points such as mortality remains to be demonstrated. One hundred eighty ESRF patients (age, 54±16 years) were monitored for 52±36 months (mean±SD). Seventy deaths, including 40 cardiovascular (CV) and 30 non-CV events, occurred. At entry, patients, in addition to standard clinical and biochemical analyses, underwent aortic pulse wave velocity measurement and determination of arterial wave reflection by applanation tonometry on the common carotid artery that was expressed as augmentation index. Cox analyses demonstrated that predictors of all-cause and CV mortality were age, aortic pulse wave velocity, low diastolic blood pressure, preexisting CV disease, and increased augmentation index, whereas the prescription of an ACE inhibitor had a favorable effect on survival. After adjustment for all confounding factors, the risk ratio for each 10% increase in augmentation index was 1.51 (95% confidence interval, 1.23 to 1.86; \( P<0.0001 \)) for all-cause mortality and 1.48 (95% confidence interval, 1.16 to 1.90; \( P<0.0001 \)) for CV mortality. These results provide the first direct evidence that in ESRF patients increased effect of arterial wave reflections is an independent predictor of all-cause and CV mortality. (Hypertension. 2001;38:434-438.)

Key Words: end-stage renal failure ■ aortic stiffness ■ mortality ■ arterial wave reflection

The results of several studies support the evidence that pulse pressure (PP) is an independent predictor of cardiovascular (CV) risk in general population.\(^1\)–\(^4\) PP is determined by the interaction of cardiac factors (stroke volume and ejection time) and vascular factors (arterial stiffness and arterial wave reflections).\(^5\)–\(^7\) Epidemiological studies have shown that PP is increased in end-stage renal failure (ESRF) patients in association with increased arterial stiffness of large elastic-type arteries and pronounced effect of arterial wave reflections.\(^7\)–\(^9\) A recent study demonstrated that aortic stiffening, determined by measurement of aortic pulse wave velocity (PWV), was an independent predictor of all-cause and CV mortality of ESRF patients.\(^10\) The impact of wave reflections on the outcome and decisive end points like mortality remains to be demonstrated. The purpose of this prospective study was to analyze the impact of early wave reflection on the outcome of this high-risk population. The results indicate that independent of arterial stiffness, blood pressure (BP), and the usual CV risk factors, a marked effect of wave reflections on central arteries is a significant predictor of ESRF patient mortality.

Methods

Patients

The recruitment period extended from January 1990 to September 1999, and follow-up ended May 31, 2000. Patients were eligible when they had been on hemodialysis (HD) for \(\geq 3\) months and they agreed to participate in the study, which was approved by our institutional board. One hundred eighty patients were included. Patients who underwent renal transplantation and patients who moved were censored on the day of transplantation or departure. All but 17 patients were white, 60% were men, 10% had diabetes mellitus, and 34% had a prior history of CV disease (CVD). During follow-up, all patients were hemodialyzed with the same technique.\(^7\) One hundred thirty-five patients received erythropoietin. At inclusion, 52% of the patients were receiving antihypertensive therapy, which was continued during follow-up. Patients were assigned to receive an ACE inhibitor, calcium antagonists, or a beta-blocker alone or in combination.

Data Collection

Data on mortality were obtained for the entire cohort. Information included personal and family histories, smoking habits, and history of CVD. Blood chemistry analyses were repeated monthly. Heart rate was determined from the ECG. BP was measured with a mercury sphygmomanometer and a cuff of appropriate size. Phases I and V of the Korotkoff sounds were taken as the systolic BP (SBP) and diastolic BP (DBP), respectively. Mean BP (MBP) was calcu-
labeled as follows: MBP = DBP + [(SBP − DBP)/3]. PP was defined as follows: PP = SBP − DBP. Echocardiography (Hewlett-Packard Sonos 100 with a 2.25-MHz probe) was analyzed according to American Society of Echocardiography criteria.11

Aortic PWV (foot-to-foot method) was determined from simultaneous Doppler flow tracings taken from the common carotid artery (CCA) and the femoral artery in the groin.7,8,12 The CCA pressure waveform was recorded noninvasively with a high-fidelity strain-pressure, D.5

The augmented waveform was recorded noninvasively with a high-fidelity strain-doppler flow tracings taken from the common carotid artery (CCA) and the femoral artery in the groin.7,8,12 The CCA pressure waveform was recorded noninvasively with a high-fidelity strain-pressure, D.5

According to the method of Murgo et al13 (Figure 1). The augmented pressure, ΔP, was determined as the height of the late systolic peak (p_2) above the inflection p_1 (ΔP=p_2−p_1) and the ratio of ΔP to PP defines the augmentation index (AIX, in percent). Δ_t represents the travel time (milliseconds) of the pulse wave to peripheral reflecting sites and back. Left ventricular ejection time (LVET) was determined from the foot of the pressure wave to the diastolic incisura. AIX was averaged from 10 to 12 successive waves; its spontaneous variability was 3.1 ± 1%. 

Statistical Analyses

The outcome studied was all-cause and CV mortality. Factors prognostic of survival were identified with the Cox model. The proportional-hazards assumptions were satisfied. Adjusted hazards risk ratios (RRs) were calculated with all the potential prognostic variables. Ninety-five percent confidence intervals (95% CIs) for the RR were obtained as antilogarithm (~e^b). Survival was assessed by the Kaplan-Meier method and the log-rank test. The sensitivities, specificities, and optimal cutoff values for AIX were assessed by the receiver-operator characteristic (ROC) curves.16 Data are expressed as mean ± SD. ANOVA was used to compare normally distributed variables. Frequency differences were tested by the χ^2 test. Gender (0 = male; 1 = female), history of CVD, ACE inhibitor use, β-blocker use, and calcium blocker use were used as dummy variables (0 = no; 1 = yes). Reproducibility of the methods was defined by the British Standards Institution.17

Results

Patient Characteristics

The characteristics of the entire cohort at the time of inclusion are shown in Table 1. The age at inclusion was 54 ± 16 years (range, 14 to 88 years), and patients were on HD for 59 ± 64 months (range, 3 to 260 months). PP was positively correlated with stroke volume, LVET, aortic PWV, and AIX (Table 2). In a multiple regression analysis, AIX was correlated with body height (P = 0.016), LVET (P < 0.0001), aortic PWV (P = 0.038), age (P < 0.01), gender (P = 0.013), and MBP (P < 0.001) (adjusted r^2 = 0.488 for the multiple regression).

Outcome and Prognostic Impact of AIX

The duration of the follow-up was 52 ± 36 months (range, 3 to 122 months). During the follow-up period, 40 CV and 30 non-CV deaths were recorded. According to the Cox analysis using a model including PP, the only independent covariates retained for all-cause mortality were age (P < 0.001) (positive influence) and ACE inhibitor prescription (P < 0.001) (negative influence), whereas PP was not significantly associated (P = 0.0932). According to the Cox analysis using a model including PP, the only independent covariates retained for CV mortality were age (P < 0.001) and PP (P = 0.012) (positive influence) and ACE inhibitor prescription (P < 0.01) (negative influence) (χ^2 for the model 61.9; P < 0.00001; pseudo-R^2 = 0.3716).

Cox analyses in which PP was replaced by its determinants, aortic PWV and AIX, are shown in Table 3. The significant covariates retained by the model for all-cause mortality were age, aortic PWV, and AIX (positive association) and DBP and ACE inhibitor prescription alone or in combination (negative association) (Table 3). The significant covariates retained by the model for CV mortality were AIX, aortic PWV, and history of CVD (positive association) and ACE inhibitor prescription alone or in combination (negative association) (Table 3). The adjusted RR for AIX (10% increase) was 1.51 (95% CI, 1.23 to 1.86) for all-cause mortality and 1.48 (95% CI, 1.16 to 1.90) for CV mortality. Stroke volume was not prognostically associated with outcomes (z value, 0.67; P = 0.504).

Other factors such as gender, heart rate, smoking, duration of HD, and blood chemistry analyses were not significant. Figure 2 shows the probabilities of all-cause and CV survival as a function of the AIX quartiles. Comparisons between survival curves were highly significant. According to the ROC curve analyses for AIX, the best cutoff value of AIX for
all-cause mortality was 24.5%; its sensitivity was 83%, its specificity 67%, and ROC area under the curve (AUC) 0.76, 0.04. The best cutoff value of AIX for CV mortality was 25%; its sensitivity was 80%, its specificity 70%, and AUC 0.74, 0.05. The best cutoff value of PWV was 11.5 m/s for all-cause mortality (specificity, 80%; sensitivity, 74%; AUC, 0.82, 0.03) and 11.3 m/s for CV mortality (specificity, 79%; sensitivity, 64%; AUC, 0.76, 0.04). The ROC AUCs were not statistically different between AIX and PWV.

The data (Table 3) indicate that AIX is an independent determinant of mortality; however, regression analysis showed this factor to be correlated with PWV. Thus, one could wonder what the determination of arterial wave reflection adds to the predictive role of aortic PWV. For this reason, we performed a complementary analysis including only ESRF patients with normal aortic PWV, 11.0 m/s. A previous study has shown that the significant RR for all-cause and CV mortality was associated with aortic PWV, 12 m/s. Of 180 patients, 83 fulfilled this criterion (Table 4). They had been on HD for 56±63 months (range, 3 to 252 months), and the mean follow-up was 56±37 months. Forty-three were men; 40 were women. Twelve patients (14%) had a history of CVD. During follow-up, 10 deaths were recorded, 7 CV and 3 non-CV. According to the Cox analyses, the only significant covariates retained for CV (and all-cause) mortality were age and AIX, with borderline significance for ACE inhibitor prescription (Table 5).

**Discussion**

Arterial disease develops rapidly in ESRF patients and is responsible for the high incidence of CV complications. Large arteries in ESRF patients are characterized by dilation, wall thickening, and a high frequency of calcified atherosclerotic plaques. The principal functional alterations are increased arterial stiffness, incremental elastic modulus, and a marked effect of arterial wave reflections on central arteries such as the CCA. Results of earlier studies showed that increased aortic stiffness and incremental elastic modulus were independent predictors of mortality in ESRF patients undergoing HD. In this study, arterial wave reflections were a major predictor of mortality in ESRF patients on HD. The impact was independent of other factors known to affect the outcome of uremic patients, namely age, prior CVD, anemia, albuminemia, and aortic PWV. The increased effect of wave reflections on the aorta and central arteries causes increased pressure during systole and decreased DBP and/or diastolic tension-time index. These alterations increase LV oxygen requirements and predispose to LV hypertrophy. The reduced DBP contributes to modifications of coronary perfusion with relative subendocardial ischemia. An important result of the present study concerns the fact that the association of mortality with wave reflections was independent of arterial stiffening estimated as aortic PWV.

PP has previously been shown to be an independent CV risk factor. In this study, PP was associated with CV mortality. As shown in Table 2, PP is a surrogate marker that is dependent on cardiac and vascular factors, including stroke volume, LVET, aortic stiffness, and intensity of wave reflections. When the major determinants of PP, mainly aortic PWV and AIX, were included in the Cox models, these factors were predictive of outcome, with a predictive power superior to that of PP alone.

AIX is frequently and simplistically considered to be an index of arterial stiffness. AIX depends on many factors, including age, PWV, traveling distance of pressure waves (body height), LVET, and reflective properties of the arterial system. Arterial stiffening increases PWV and influences the transit time of pressure waves (\(\Delta t_p\) in Figure 1). By increasing PWV, arterial stiffening reduces the \(\Delta t_p\) from the periph-
eral reflection sites toward central arteries, thereby altering the timing of incident and reflected waves. Although arterial stiffening is responsible for the acceleration of the pressure wave transmission, the intensity of wave reflection is dependent on the reflective properties of the vascular tree that could be altered independently of arterial stiffening.25 This independence is shown by the persistent association of wave reflections as a predictor of mortality of patients with normal PWV (Tables 4 and 5). Arterial stiffening, in addition to its own role in CV alterations, enhances the expression of abnormal reflective properties of the vasculature in the aorta and central arteries by favoring an early return of reflected waves.

The peripheral “reflectance” is influenced by physical properties, vasomotor tone, and the number of smaller resistive arteries and branch points.24,25 In this study, we did not evaluate the intensity of wave reflections at their reflective site, but several abnormalities in the microcirculation of ESRF patients have been reported in the literature, including rarefaction of vessels, increased ratios of wall to lumen of small arteries, calcifications of small arterioles, and decreased endothelium-mediated vasodilation.26–28 In ESRF patients, the pathological alterations of these smaller arteries may therefore contribute to increased “reflectance.” Whether the prognosis and outcome associated with the pronounced effect of wave reflection are related to augmentation of late SBP in the central arteries or primarily to alteration of microcirculation remains to be determined.

The results presented here show that prolonged survival was associated with an ACE inhibitor used as an antihypertensive agent. Prescription of β-blocker and/or dihydropyridine calcium blocker had no direct relationship with outcome. The association between survival and ACE inhibitor prescription (Table 3) must be interpreted cautiously, because the study was not designed to compare the effect of different antihypertensive drugs on survival as such and the regimen was influenced by drug tolerance and the optimal effect on BP. Studies on high-risk populations have shown that ACE inhibitors have a favorable prognostic effect, reducing death rates and CV complications.29 The present findings suggest that ACE inhibitors can have a similar favorable effect on ESRF patients, but a specifically designed, prospective, therapeutic trial is needed to confirm this idea.

The ability to generalize the results of this study may be limited because of the characteristics of ESRF patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45±13</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>43/40</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>141±23</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84±15</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>103±16</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>57±15</td>
</tr>
<tr>
<td>Heart period, ms</td>
<td>870±150</td>
</tr>
<tr>
<td>CCA AIX (%)</td>
<td>19±16</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>9.17±1.27</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>85.4±20.4</td>
</tr>
</tbody>
</table>

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<tr>
<th>Variable</th>
<th>RR (95% CI)</th>
<th>z Statistic</th>
<th>P</th>
<th>Pseudo-(r^2)</th>
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<tbody>
<tr>
<td>All cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIX (10%)</td>
<td>1.51 (1.23–1.86)</td>
<td>3.94</td>
<td>0.00008</td>
<td>0.11471</td>
</tr>
<tr>
<td>ACE inhibitor (0=no; 1=yes)</td>
<td>0.30 (0.14–0.66)</td>
<td>−3.00</td>
<td>0.00277</td>
<td>0.06944</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>0.97 (0.96–0.99)</td>
<td>−2.88</td>
<td>0.00401</td>
<td>0.06455</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>1.16 (1.06–1.28)</td>
<td>3.21</td>
<td>0.00131</td>
<td>0.07918</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.03 (1.01–1.05)</td>
<td>1.98</td>
<td>0.04786</td>
<td>0.03159</td>
</tr>
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<td>0.29 (0.12–0.70)</td>
<td>−2.73</td>
<td>0.00641</td>
<td>0.06669</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>1.14 (1.02–1.26)</td>
<td>2.39</td>
<td>0.01689</td>
<td>0.05202</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>3.50 (1.69–7.22)</td>
<td>3.39</td>
<td>0.00071</td>
<td>0.09929</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.84</td>
<td>0.06550</td>
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<td>3.39</td>
<td>0.00071</td>
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Indeed, the CV morbidity and mortality in these patients are much higher than in nonuremic and general populations. The second limitation is that the relationship between mortality and AIX does not imply direct causation. To clarify the causality of the association between wave reflections and mortality or morbidity, the effect of “interventions” aimed at reducing the amplitude of wave reflections will have to be examined.

In conclusion, the results presented herein indicate that an increased effect of wave reflections on central arteries is a strong and independent predictor of mortality of ESRF patients on HD. The effect of wave reflections is dissociated from the changes of aortic stiffness as expressed by PWV, and the significance of wave reflections cannot be confused with that of stiffness. Elucidating the mechanisms at work between arterial wave reflections and mortality in this population necessitates further studies, including direct evaluation of reflective properties of the arterial tree and the alterations responsible for this abnormality.

Acknowledgment

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References

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