Scientific Contributions

Central Pulse Pressure and Mortality in End-Stage Renal Disease

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Abstract—Damage of large arteries is a major factor in the high cardiovascular morbidity and mortality of patients with end-stage renal disease (ESRD). Increased aortic pulse wave velocity (PWV) and brachial pulse pressure (PP) are the principal arterial markers of cardiovascular mortality described in these patients. Whether central (carotid) PP and brachial-carotid PP amplification may predict all-cause (including cardiovascular) mortality has never been investigated. A cohort of 180 patients with ESRD who were undergoing hemodialysis was studied between January 1990 and March 2000. The mean duration of follow-up was 52 ± 36 months (mean$\pm$SD). Mean age at entry was 51.5 ± 16.3 years. Seventy deaths occurred, including both cardiovascular and noncardiovascular fatal events. At entry, patients underwent carotid PP measurements (pulse wave analysis), echocardiography, and aortic PWV (Doppler ultrasonography), together with standard clinical and biochemical analyses. On the basis of Cox analyses, after adjustment of age, time on dialysis before inclusion, and previous cardiovascular events, 3 factors emerged as predictors of all-cause mortality: carotid PP, brachial/carotid PP, and aortic PWV. Adjusted hazard ratios for 1-SD increments were 1.4 (1.1 to 1.8) for carotid PP, 0.5 (0.3 to 0.8) for brachial/carotid PP, and 1.3 (1.0 to 1.7) for PWV. Brachial blood pressure, including PP, had no predictive value for mortality after adjustment. These results provide the first direct evidence that in patients with ESRD, the carotid PP level and, mostly, the disappearance of PP amplification are strong independent predictors of all-cause (including cardiovascular) mortality. (*Hypertension*. 2002;39:735-738.)

Key Words: renal disease ■ blood pressure ■ pulse ■ aorta ■ mortality

A number of clinical studies have recently shown that pulse pressure (PP) is an independent predictor of cardiovascular (CV) and all-cause mortality.[1] Whether PP may be considered as a specific mechanical CV risk factor or as the surrogate of an underlying vascular disease remains unknown. However, only brachial PP has been considered as a CV risk factor in the different prediction models involving hypertension, end-stage renal disease (ESRD), and various CV diseases.[1] From a pathophysiological viewpoint, it is the aortic and not the brachial artery blood pressure (BP) that is "seen" by the heart and the coronary and carotid arteries, the 3 specific sites where main clinical events occur. In subjects with ESRD, a population in which CV mortality is substantially increased, it is aortic pulse wave velocity (PWV), the major determinant of central PP, rather than brachial PP that may be considered as a specific independent CV risk factor.[2] Thus, it is important to determine the predictive value, in terms of CV and all-cause mortality, of aortic PP compared with brachial PP.

Studies of pulsatile arterial hemodynamics have shown that although mean arterial pressure remains nearly constant along the arterial tree, PP increases markedly from central (thoracic aorta and carotid artery) to peripheral (brachial) arteries.[3] This increase is caused by the propagation of the pressure wave along arterial vessels, with a progressive decline in artery diameter and increase in arterial stiffness. This alteration modifies the summation of wave reflections at each particular point of the arterial tree, making aortic PP physiologically lower than brachial PP and thus leading physiologically to PP amplification. Furthermore, when conduit arteries become stiffer, as in elderly subjects or subjects with hypertension and/or ESRD, the reflected waves occur earlier in the thoracic aorta and thus are noticed within the systolic portion of the BP curve, favoring a supplementary increase of systolic peak. Finally, with aging, PP increases more rapidly in the thoracic aorta than in peripheral arteries, thus producing an attenuation of the physiological increase in PP from central to peripheral arteries. Whether the attenuation of PP amplification from the carotid to the brachial artery may be a marker of CV and overall mortality has never been investigated.

The purpose of the present study was to evaluate the comparative values of brachial PP, carotid PP, and carotid-brachial PP amplification in the prediction of all-cause

mortality in patients with ESRD, independently of the usual CV risk factors observed in this population, such as age, previous CV events, or left ventricular (LV) hypertrophy.

Methods

Patients

This prospective cohort study was started at the F.H. Manhès Hospital, Fleury-Mérogis (in the Paris–Ile de France area), in January 1990.[1] Patients were eligible for entry into the study when (1) they had been on hemodialysis for ≥3 months (59±64 months, mean±SD), and (2) they had had no clinical CV disease during the 6 months preceding study entry. Patient recruitment was closed in 1999, and follow-up ended in March 2000. One hundred eighty patients fulfilled the entry criteria. Patients who underwent renal transplantation and patients who moved away were censored on the day of transplantation or departure to another unit. All but 12 patients were white. The mean patient follow-up was 52±36 months. Data on mortality were obtained for the entire cohort. The mean age of the cohort was 54±16 years (range, 14 to 88 years); 59% were male; and 8% had insulin-dependent diabetes mellitus. One hundred seven patients received recombinant human erythropoietin at some time during follow-up. During the follow-up, all patients were dialyzed using the same unique standardized technique, including synthetic membranes hemodialyzers (AN69 and polysulfone) matched for the subject's body surface area (1.36 to 2.1 m²), bicarbonate dialysate, and controlled ultrafiltration rate. The duration of dialysis sessions was tailored (4 to 6 hours, thrice weekly) to achieve a Kt/V ≥1.2. Each subject provided informed consent to participate in the study, which was approved by our institutional review board.

Data Collection

Information compiled from the questionnaire filled out at inclusion included personal and family histories, smoking habits (89 patients were current or former smokers), and previous history of CV disease, including coronary artery disease, angina pectoris, cardiac failure, peripheral vascular disease, and cerebrovascular disease. During the mean follow-up period, we recorded 70 deaths.

Noninvasive Measurements

The measurements were performed during the 2 weeks after study inclusion, on the morning before the midweek hemodialysis. Blood chemistry was measured at baseline and monthly intervals. BP was measured with a mercury sphygmomanometer after 15 minutes of recumbency. Phases I and V of the Korotkoff sounds were taken, respectively, as the systolic and diastolic BP, to suppress PP, which is the difference between systolic and diastolic BP. Five measurements determined at 2-minute intervals were averaged.

Common carotid artery pressure waveform was recorded noninvasively with a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments) on a Gould 8188 recorder (Gould Electronique) at 100 mm/s. A detailed description of this system has been published previously.[4,5] The tonometer is internally calibrated using a Millar preamplifier (TCB-500). For the determinations of carotid PP, brachial and radial artery systolic, diastolic, and mean BPs were considered equivalent, taking into account the small degree of pressure wave amplification between these 2 sites. The carotid and radial pressure waves were then recorded using for each site by use of local applanation tonometry. The carotid pressure wave was calibrated from the brachial pressure wave, assuming that the mean pressure (determined from mercury sphygmomanometer) and the diastolic BP were the same at both sites. For this purpose, the mean BP on the carotid and radial pressure waves was computed from the area of each wave in the corresponding heart period and set equal to brachial mean BP. Carotid pressure amplitude was then computed from the diastolic BP and the position of mean BP on the carotid pressure wave. Brachial PP and carotid PP were averaged for a series of waves over a 10-second period. Invasive validation[6] and reproducibility of measurements have been published in detail elsewhere.[5]

PWV was determined using transcutaneous Doppler flow recordings and the foot-to-foot method.[5,7] Two simultaneous Doppler flow tracings were taken at the aortic arch and the femoral artery in the groin by use of a nondirectional Doppler unit (SEGA M842, 10 MHz) with a handheld probe and were 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 (t) was measured between the feet 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 carotid artery, the distance from the suprasternal notch to the carotid was subtracted. PWV was calculated as PWV=D/t. All measurements were performed by the same observer (G.M.L.); the intraobserver repeatability of the aortic PWV measurement was 5.8±1%.[5] The heart period was determined from the 3-lead orthogonal ECG.

Baseline echocardiography was performed using a Hewlett-Packard Sonos 100 device, equipped with a 2.25-MHz probe, thus allowing M-mode, 2-dimensional, and pulsed Doppler measurements. Measurements were made according to the recommendations of the American Society of Echocardiography, and LV mass was calculated according to the Penn convention, as previously described.[4,5] Adequate echocardiographic tracings were obtained for 172 subjects. LV hypertrophy (LV mass index >132g/m² in men and >110g/m² in women) was present in 153 (89%) patients.

Analysis

Because CV and non-CV deaths are generally difficult to differentiate in the absence of autopsy—especially in ESRD subjects, in whom numerous CV and non-CV pathologies are often associated—and because CV cause is the leading cause of death in this population, only overall mortality was considered in this study.

Data are expressed as mean±SD. Student's *t* test was used for comparison of normally distributed continuous variables. Differences in frequency were tested by χ^2 analysis. Gender (male, 1; female, 2), previous history of CV disease (no, 1; yes, 2), and presence of LV hypertrophy (no, 1; yes, 2) were used as dummy variables. Prognostic factors of survival were identified using 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. Crude hazard ratios (HRs), estimated as the exponent raised to the power of the respective regression coefficient, were determined, along with 95% confidence limits, for 1-SD increments. Adjusted HRs were determined from models involving all prognosis-related nonhemodynamic parameters, namely age, time on dialysis before inclusion, and previous CV events. Survival curves were estimated using the Kaplan-Meier product-limit method and were compared by the Mantel (log-rank) test. To assess the performance of different hemodynamic factors considered as prognosis tests, area under receiver operating characteristic (ROC) curves were calculated.

Statistical analysis was performed using NCSS 6.0.21 software. Repeatability and reproducibility of the methods were defined previously.[2] A value of $P<0.05$ was considered significant. All tests were 2-sided.

Results

Table 1 compares the 2 groups of subjects, those still alive or those deceased at the end of the follow-up. In addition to the reduced body height ($P<0.01$), the latter group is characterized by higher values of age at inclusion ($P<0.001$), time on dialysis before inclusion ($P<0.001$), tobacco consumption

TABLE 1. Characteristic of the Patients at Inclusion According to Their Vital Status at the End of Follow-Up

Parameter	Patients Alive (n=110)	Deceased Patients (n=70)
Age at inclusion, y	47±16	65±10*
Gender, m/f ratio	1.4±0.5	1.5±0.5
Body height, cm	166±11	162±9†
Time on dialysis before inclusion, months	46±54	80±73*
Tobacco lifelong dose, pack/y	7±11	14±20*
Previous cardiovascular events, %	19	57*
Brachial systolic BP, mm Hg	151±26	165±28*
Brachial diastolic BP, mm Hg	86±15	79±14*
Brachial mean BP, mm Hg	108±17	108±17
Brachial PP, mm Hg	65±19	86±23*
Carotid systolic BP, mm Hg	143±26	165±29*
Carotid PP, mm Hg	57±18	86±24*
Brachial/carotid PP, %	116±17	100±7*
Aortic PWV, m/s	10.4±2.4	13.8±3.0*
R-R interval, ms	878±152	877±112
LV mass index, g/m²	161±43	188±46*
LV hypertrophy, %	86	92
Plasma total cholesterol, mmol/L	5.2±1.2	5.3±1.3
Plasma HDL cholesterol, mmol/L	1.1±0.5	1.2±0.7
Plasma triglycerides, mmol/L	1.8±1.0	1.9±1.0
Plasma parathormon, mmol/L	316±279	241±216
Hemoglobin, g/L	95±17	91±18

Values are mean±1 SD.
*$P<0.001$, †$P<0.01$.

($P<0.001$), brachial and carotid BP ($P<0.001$), and previous CV events ($P<0.001$). In deceased subjects versus survivors, brachial and carotid PP, aortic PWV, and cardiac mass are, respectively, as follows: 86±23 versus 65±19 mm Hg, 86±24 versus 57±18 mm Hg, 13.8±3.0 versus 10.4±2.0 m/s, and 188±46 versus 161±43 g/m² (all, $P<0.001$). The brachial/carotid PP ratio is 100±7% in deceased subjects

versus 116±17% in survivors ($P<0.001$), whereas R-R intervals are identical in the 2 groups.

Table 2 shows the HR for 1-SD increments of all mechanical factors, in crude and adjusted analysis. Although adjusted HR was not statistically significant for brachial PP, 3 mechanical factors emerged as significant: carotid PP, aortic PWV, and the brachial/carotid PP. For the latter, an HR of 0.5 (0.3 to 0.8) indicates that when the ratio tended toward 1, all-cause mortality increased significantly. Note that area under the ROC curve was the greatest (0.85±0.11) for this parameter. For multivariate analysis, adjustments were made on age at inclusion, time on dialysis before inclusion, and previous CV events. The other parameters—such as anemia, presence of erythropoietin, or use of antihypertensive drugs—did not enter the multivariate prediction model.

Figure 1 shows the probabilities of survival as a function of carotid PP and PP amplification divided into tertiles. Comparisons between survival curves were highly significant (respectively, $\chi^2=39.85$, $P<0.001$, and $\chi^2=33.52$, $P<0.001$).

Discussion

The salient findings of this study were that in ESRD patients undergoing hemodialysis, the disappearance of aortic-brachial PP amplification was a significant predictor of all-cause mortality, independent of age and other standard confounding factors, and carotid PP was more powerful than brachial PP in the prediction of overall mortality.

Epidemiological studies and therapeutic trials in hypertensive subjects generally assume that the brachial BP level is proportional to CV risk and that the reduction of brachial BP using appropriate antihypertensive drug treatment significantly reduces this risk. Accordingly, it is commonly believed that the mechanical factor represented by brachial BP is directly responsible for the CV hypertensive complications. In fact, this latter assumption may be questioned on the basis of numerous investigations that indicate that aortic BP and brachial BP differ significantly. This finding is important to consider because the heart "sees" the aortic BP and not the brachial BP. Using invasive techniques, Pauca et al[6] have shown that in terms of

TABLE 2. Area Under the ROC Curve, Crude, and Adjusted HRs of All-Cause Mortality per 1-SD Increment of Mechanical Variables

Prognostic Variable	Mean±SD	Area Under ROC Curve	Crude HR per 1SD Increment (95% CI)	Adjusted HR per 1SD Increment (95% CI)
Brachial systolic BP, mm Hg	156±28	0.64±0.10	**1.3 (1.0–1.7)**	1.1 (0.8–1.3)
Carotid systolic BP, mm Hg	152±29	0.71±0.11	**1.6 (1.2–2.1)**	1.2 (0.8–1.4)
Diastolic BP, mm Hg	83±15	0.65±0.10	**0.5 (0.4–0.7)**	0.8 (0.6–1.0)
Mean BP, mm Hg	108±17	0.50±0.09	0.8 (0.7–1.1)	0.7 (0.9–1.2)
Brachial PP, mm Hg	73±23	0.78±0.11	**1.8 (1.5–2.3)**	1.2 (0.9–1.5)
Carotid PP, mm Hg	68±25	0.84±0.11	**2.2 (1.7–2.7)**	**1.4 (1.1–1.8)**
Brachial/carotid PP, %	110±16	0.85±0.11	**0.2 (0.1–0.4)**	**0.5 (0.3–0.8)**
PWV, m/s	11.7±3.1	0.83±0.11	**2.1 (1.7–2.6)**	**1.3 (1.0–1.7)**
LV mass index, g/m²	172±46	0.68±0.11	**1.5 (1.2–1.8)**	1.2 (0.9–1.6)

Adjustments were made on age at inclusion, time on dialysis before inclusion and, previous CV events. HRs in bold are significantly different from 1.
95% CI indicates 95% confidence interval.
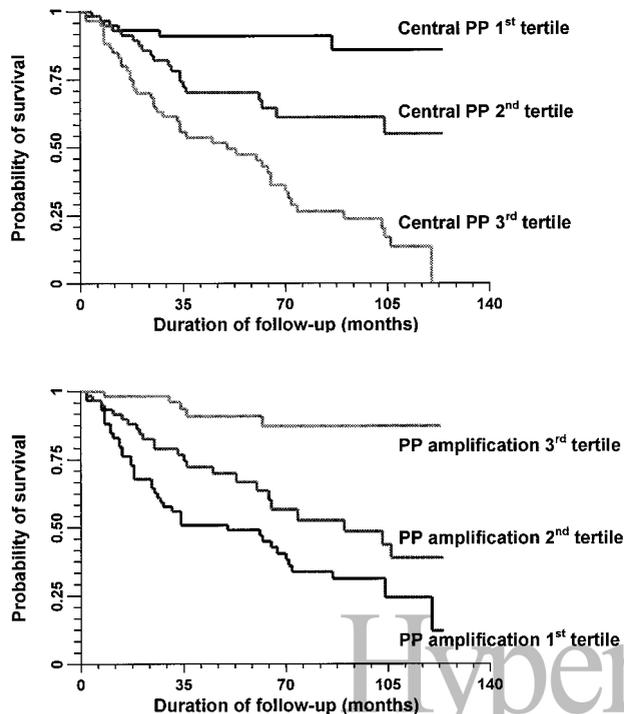
Probabilities of survival in the study population according to the level of central PP and PP amplification divided into tertiles. Comparisons between survival curves were highly significant (*P*<0.001 for both).

mean values, brachial systolic BP is 12 mm Hg higher than aortic systolic BP, whereas aortic diastolic BP is only 1 to 2 mm Hg lower than brachial diastolic BP. This hemodynamic pattern, which is the direct consequence of the physiological PP amplification observed within the arterial tree, is accentuated in the presence of increased heart rate and significantly attenuated by aging.[3] In the present population, heart rate was similar in the 2 studied groups, and only age interfered substantially (but independently of PP amplification) in the Cox model involving all-cause mortality.

Regarding PP determinations, the present noninvasive measurements have been previously validated using intraarterial methods. This validation has shown that carotid PP, a close surrogate of aortic PP, may be determined adequately by use of applanation tonometry.[3,8–13] Repeatability studies, checks made with Bland and Altman diagrams, and modern computer technology clearly show that it is possible to directly record the carotid BP curve and to calibrate the corresponding local PP, even without any help of a mathematical transfer function derived from the radial artery pressure wave. Using this procedure, the major finding of this study was that in subjects with ESRD who were undergoing hemodialysis, a lack of PP amplification was a significant independent predictor of all-cause mortality. Nevertheless, because PP amplification implies by definition the measurements of carotid and brachial systolic and diastolic BPs all taken together, the interpretation of the results should be made very cautiously. It was important to show that PP amplification was a stronger predictor than each of its 4 different components. In the present study, it was shown that

brachial BP measurements had no predictive value after adjustment to confounding variables and that the predictive value of PP amplification was equal or even superior to that of carotid PP, as calculated by the area under ROC curves.

For the interpretation of the results, it is noteworthy that the disappearance of PP amplification is principally caused by an increase in central systolic BP in relation with an age-related increase of both arterial stiffness and wave reflections, with a resulting increase in end-systolic stress and development of cardiac hypertrophy. Interestingly, in this report, in multivariate analysis, we found that the reduction of PP amplification, a parameter significantly associated with the degree of cardiac hypertrophy, was predictive of prognosis, whereas LV mass was not.

In conclusion, this report has shown for the first time that in ESRD patients who were undergoing hemodialysis, the disappearance of PP amplification, a classical consequence of the age-induced increase of arterial stiffness and alteration of wave reflections, is a significant predictor of all-cause mortality. Measurement of central BP gives additional value in terms of overall mortality.

Acknowledgments

References

1. Safar ME. Pulse pressure, arterial stiffness, and cardiovascular risk. *Curr Opin Cardiol*. 2000;15:258–263.
2. Blacher J, Guerin A, Pannier B, Marchais S, Safar M, London G. Impact of aortic stiffness on survival in end-stage renal failure. *Circulation*. 1999;99:2434–2439.
3. Nichols WW, O'Rourke M. *McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles*, 4th ed. London: Arnold E; 1998:54–113, 201–222, 284–292, 347–401.
4. Topouchian J, Asmar R, Sayegh F, Rudnicki A, Benetos A, Bacri AM, Safar ME. Changes in arterial structure and function under trandolapril-verapamil combination in hypertension. *Stroke*. 1999;30:1056–1064.
5. London GM, Guerin AP, Marchais SJ, Pannier B, Safar ME, Day M, Metivier F. Cardiac and arterial interactions in end-stage renal disease. *Kidney Int*. 1996;50:600–608.
6. Pauca AL, Wallenhaupt SL, Kon ND, Tucker WY. Does radial artery pressure accurately reflect aortic pressure? *Chest*. 1992;102:1193–1198.
7. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac A-M, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. *Hypertension*. 1995;26:485–490.
8. Chen CH, Nevo E, Fetics B, Pak PH, Yin FCP, Maughan L, Kass DE. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure: validation of generalized transfer function. *Circulation*. 1997;95:1827–1836.
9. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J*. 1993;14:160–167.
10. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension*. 2001;38:932–937.
11. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, and Webb DJ. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens*. 1998;16:2079–2084.
12. Filipovsky J, Svobodova V, Pecen L. Reproducibility of radial pulse wave analysis in healthy subjects. *J Hypertens*. 2000;18:1033–1040.
13. Cockcroft JR, Wilkinson IB. Large arterial stiffness: an important therapeutic target. *J Hum Hypertens*. 2000;14:533–535.