ORIGINAL RESEARCH

Prognostic Value of Carotid and Radial Artery Reservoir-Wave Parameters in End-Stage Renal Disease

Catherine Fortier, PhD; Gabrielle Côté, MD; Fabrice Mac-Way, MD; Rémi Goupil, MD; Louis-Charles Desbiens; Marie-Pier Desjardins, MD, MSc; Karine Marquis, PhD; Bernhard Hametner, PhD; Siegfried Wassertheurer, PhD; Martin G. Schultz, PhD; James E. Sharman, PhD; Mohsen Agharazii, MD

***Background*—**Reservoir-wave approach is an alternative model of arterial hemodynamics based on the assumption that measured arterial pressure is composed of volume-related (reservoir pressure) and wave-related components (excess pressure). However, the clinical utility of reservoir-wave approach remains debatable.

***Methods and Results*—**In a single-center cohort of 260 dialysis patients, we examined whether carotid and radial reservoir-wave parameters were associated with all-cause and cardiovascular mortality. Central pulse pressure and augmentation index at 75 beats per minute were determined by radial arterial tonometry through generalized transfer function. Carotid and radial reservoir-wave analysis were performed to determine reservoir pressure and excess pressure integral. After a median follow-up of 32 months, 171 (66%) deaths and 88 (34%) cardiovascular deaths occurred. In Cox regression analysis, carotid excess pressure integral was associated with a hazard ratio of 1.33 (95% CI, 1.14–1.54; $P<0.001$ per 1 SD) for all-cause and 1.45 (95% CI: 1.18–1.75; $P<0.001$ per 1 SD) for cardiovascular mortality. After adjustments for age, heart rate, sex, clinical characteristics and carotid-femoral pulse wave velocity, carotid excess pressure integral was consistently associated with increased risk of all-cause (hazard ratio per 1 SD, 1.30; 95% CI: 1.08–1.54; $P=0.004$) and cardiovascular mortality (hazard ratio per 1 SD, 1.31; 95% CI: 1.04–1.63; $P=0.019$). Conversely, there were no significant associations between radial reservoir-wave parameters, central pulse pressure, augmentation index at 75 beats per minute, pressure forward, pressure backward and reflection magnitude, and all-cause or cardiovascular mortality after adjustment for comorbidities.

***Conclusions*—**These observations support the clinical value of reservoir-wave approach parameters of large central elastic vessels in end-stage renal disease. **(*J Am Heart Assoc*. 2019;8:e012314. DOI: 10.1161/JAHA.119.012314.)**

Key Words: aortic stiffness • end-stage renal disease • excess pressure • pulse wave analysis • pulse wave velocity • wave separation analysis

Subjects with chronic kidney disease are at high risk of cardiovascular disease. Aortic stiffness and increased wave reflection—parameters based on the wave propagation model—have been proposed to contribute to the excess cardiovascular risk in this population.[1,2] However, in an elderly dialysis cohort, aortic stiffness and augmentation index (AIx) were not significantly associated with increased risk of death upon adjustment for age and comorbidities.[3,4] Given that the wave propagation model does not consider the reservoir function of the arterial tree, a reservoir-wave approach has been proposed to circumvent this limitation.[5–9] This approach hypothesizes that the measured arterial pressure is the sum of a reservoir pressure wave (RP), which accounts for the dynamic storage and release of blood by the compliant arteries (the Windkessel effect), and an excess pressure wave (XSP), which is responsible for local changes in the pulse waveform.

It is proposed that aortic reservoir pressure is the minimum left ventricular work required to generate blood flow into the aorta, whereas the excess pressure provides information about the surplus of work performed by left ventricle.[8–10] The added value of reservoir-wave approach has been demonstrated in patients with hypertension, in high risk patients, in patients with heart failure and in a hemodialysis

From the CHU de Québec Research Center, L'Hôtel-Dieu de Québec Hospital, Québec City, Québec, Canada (C.F., F.M.-W., L.-C.D., M.-P.D., K.M., M.A.); Division of Nephrology, Faculty of Medicine, Université Laval, Québec City, Québec, Canada (C.F., G.C., F.M.-W., L.-C.D., M.-P.D., M.A.); Hôpital du Sacré-Cœur de Montréal, Montréal, Québec, Canada (R.G.); Center for Health & Bioresources, AIT Austrian Institute of Technology, Vienna, Austria (B.H., S.W.); Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia (M.G.S., J.E.S.).

Accompanying Tables S1 through S6 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012314

Correspondence to: Mohsen Agharazii, MD, Service de Néphrologie, CHU de Québec – L'Hôtel-Dieu de Québec, 11, Côte du Palais, Québec, Quebec, Canada G1R 2J6. E-mail: mohsen.agharazii@crchudequebec.ulaval.ca

Received February 14, 2019; accepted May 17, 2019.

Clinical Perspective

What Is New?

- This study shows that central excess pressure integral is of prognostic value in patients with end-stage kidney disease, but this was not the case for radial excess pressure integral.
- Among traditional mechanical biomarkers, central excess pressure integral of carotid was the only biomarker that was independently and consistently associated with increased risk of both all-cause and cardiovascular mortality.

What Are the Clinical Implications?

- The reservoir-wave approach applied to large central vessels has a clinical relevance in terms of risk assessment and its clinical utility needs to be further assessed.

population without established cardiovascular disease.[11–16] Recently, Peng and colleagues,[17] through invasive determination of pressure waves, have shown that whereas reservoir pressure remains relatively similar along the aortic-radial axis, the excess pressure tends (on average) to be amplified from the aorta to the radial artery, and that XSP amplification is associated with systolic blood pressure (SBP) amplification. Given the substantial individual variation in aortic-to-radial SBP amplification, there may be significant differences in the excess pressure at central compared with peripheral arterial sites, thus potential differences in the prognostic utility of central compared with peripheral XSP.[18]

Accordingly, we hypothesized that centrally derived reservoir-wave parameters would be more strongly associated with clinical outcomes. Therefore, our aims were to examine whether carotid derived reservoir-wave parameters (surrogate for central artery) and radial artery reservoir-wave parameters were independently associated with all-cause and cardiovascular mortality in a cohort of unselected dialysis patients.

Methods

Study Design and Patient Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. This was a single center observational longitudinal study conducted in adult patients with end stage renal disease treated by dialysis (hemodialysis and peritoneal dialysis) at L'Hôtel-Dieu de Québec Hospital, CHU de Québec Research Center. From August 2006 to June 2014, 328 patients underwent at least one extensive evaluation for medical history, laboratory data, pharmacological treatment and hemodynamic parameters of arterial stiffness. This cohort of patients was composed of adult patients on chronic dialysis (>3 months), with single-pool KT/V >1.4 in hemodialysis patients and a weekly KT/V of >1.7 in patients on peritoneal dialysis, stable dry weight and blood pressure medication. Patients were excluded if they had an acute episode of illness (infection, recent cardiovascular events) or any clinical conditions that would hamper hemodynamic measurements (absence of femoral pulse, systolic blood pressure of <90 mm Hg). For the analysis, we further excluded patients with unavailable or unreliable measurements of either radial or carotid pulse waveforms or aortic stiffness (n=68), leaving 260 subjects in the study (Figure 1). Patients were censored at the time of renal transplantation, renal recovery, or at the last follow-up (October 2016). Coronary artery disease was defined as myocardial infarction, coronary artery revascularization or ischemic heart disease as shown by either a treadmill, echocardiography, or thallium stress tests. History of atherosclerotic cardiovascular disease was defined by a history of non-hemorrhagic stroke, coronary artery disease, lower extremity amputation or revascularization. Hypertension was defined as brachial blood pressure ≥140/90 mm Hg or antihypertensive drug usage. Patients were considered to have cardiovascular mortality when a cardiovascular event such as myocardial infarction, ischemic heart disease, heart failure, sudden death, arrhythmia, peripheral vascular disease, ischemic bowel disease, or stroke led to death as described previously.[19] Date of death was ascertained by consultation of the Attestation of Death certificate which was available for all deceased patients. All hospital files were reviewed by 2 reviewers (M.A. and K.M.) to determine whether cardiovascular disease was the cause of death. No patient was lost to follow-up. This protocol had been approved by the *Comité d'éthique de la recherche du CHU de Québec* and was conducted in accordance with the Declaration of Helsinki. All procedures followed were in accordance with institutional guidelines and each patient provided informed written consent.

Objectives

The primary objective of the study was to examine the impact of central excess pressure on all-cause mortality. The secondary outcome was to examine the impact of central excess pressure on cardiovascular death. The exploratory aims included the impact of other parameters derived from reservoir-wave analysis both at carotid and radial sites. We also explored the impact of traditional brachial and central blood pressure parameters, and the parameters related to wave separation analysis and their association with all-cause and cardiovascular mortality.

Hemodynamic Assessments

All measurements were performed in the same visit after 15 minutes of rest in a supine position. In hemodialysis patients, all assessments were performed before their mid-

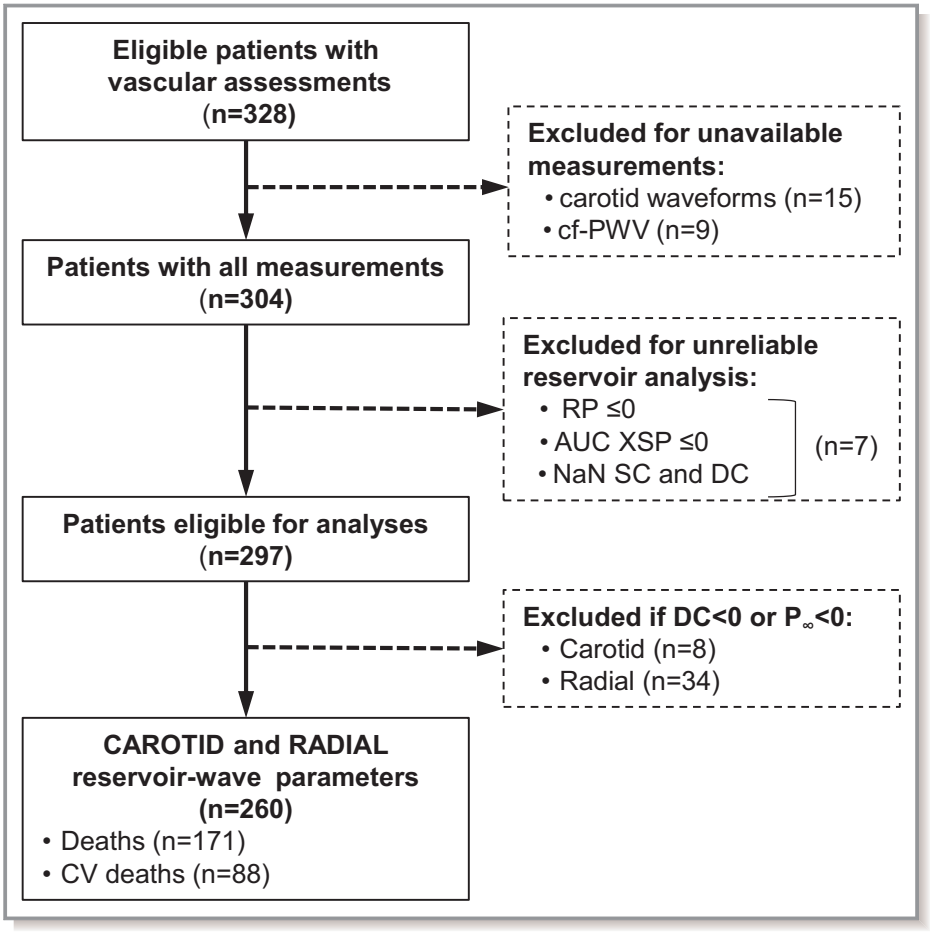

Figure 1. Study flowchart. AUC, are under curve; cf-PWV, carotid-femoral pulse wave velocity; CV, cardiovascular; DC, diastolic constant rate; NaN, not a number; P_{∞}, asymptote of the exponential decay of the pressure during diastole; RP, peak reservoir pressure; SC, systolic rate constant; XSPI, area under curve of excess pressure.

week dialysis session. Brachial artery blood pressure (BP) was recorded 6 times, with a 2-minute interval using an automatic oscillometric sphygmomanometer BPM-100 (BP-Tru, Coquitlam, Canada) by an experienced operator who was present in the room. In case of an arteriovenous fistula, measurements were performed on the contralateral arm. Immediately after BP measurements, radial and carotid pulse wave profiles were sequentially recorded in the same order by aplanation tonometry (SphygmoCor system, AtCor Medical Pty. Ltd., Sydney, Australia). Three consecutive recordings were performed for each site. Central pressure parameters were obtained by radial artery tonometry through generalized transfer function from which central systolic pressure (SP), diastolic pressure (DP), pulse pressure (PP), and augmentation index adjusted for heart rate of 75 bpm (AIx@75) were derived after calibration for brachial systolic and diastolic BPs. Carotid pressure wave form was obtained by tonometry after calibration for brachial diastolic and mean arterial pressure, which was obtained by integration of the arterial pressure waveform.[20] Immediately after pulse wave recordings, we determined carotid-femoral pulse wave velocity (cf-PWV) in triplicate by Complior SP (Artech Medical, Pantin, France), using the maximal upstroke algorithm and direct measurements as previously described.[19,21]

Reservoir-wave parameters were obtained using the pressure wave approach as previously described.[12,22] Reservoir pressure (RP), its integral (RPI), excess pressure (XSP) and its integral (XSPI), diastolic rate constant (DC) and systolic rate constant (SC) were acquired from radial and carotid pressure waveforms obtained without application of a generalized transfer function. Accordingly, SC is the rate of system filling which is inversely proportional to the product of characteristic impedance (Z_0) and compliance (C), whereas DC is the rate of system emptying, which is inversely proportional to the product of peripheral vascular resistance (R) and compliance (C). RP was derived based on pressure alone approach and XSP was defined as the difference between total measured pressure and RP. A reservoir pressure analysis was

considered valid with RP>0, XSPI>0, a numerical SC and DC, DC>0 and P_{∞}>0. RP proportion and XSP proportion were, respectively, the ratio of RP integrals or XSPI to total pressure integral×100. The XSP:RP is the ratio of XSP proportion to RP proportion. Figure 2 summarizes the key parameters of reservoir-wave approach of the carotid and radial artery.

Wave separation analysis was conducted to derive central pressure forward (Pf), pressure backward (Pb) and reflection magnitude (RM). This was performed on the central pressure waveform after application of a generalized transfer function on the radial artery pressure waveform and on untransformed carotid pressure waveforms as previously described.[23,24]

Statistical Analysis

Data are expressed as mean±SD, n (%) or median [25th–75th percentiles]. Cox proportional hazard regression was used to assess the association of parameters derived from the carotid and radial sites with all-cause and cardiovascular mortality. We determined the hazard ratio associated with a change of 1 standardized deviation for each hemodynamic parameter. The proportionality assumption was assessed by fitting an interaction term between each hemodynamic parameter and follow-up time. Transformations were used in cases where the proportionality assumption was not met. We subsequently adjusted these models for potential confounding factors which included age, sex, atherosclerotic cardiovascular disease, diabetes mellitus, smoking, history of hypertension, dialysis type, heart rate, and cf-PWV. A 2-tailed P<0.05 was considered statistically significant. As part of sensitivity analysis, we further assessed a possible non-linear relationship between each hemodynamic parameter and clinical outcome. As such each parameter was modeled using restricted cubic splines with 3 knots (10th, 50th, and 90th percentiles). The non-linear term of each restricted cubic spline was then tested against the null hypothesis using a Chi-Squared test to assess whether the parameter was non-linearly associated with mortality. A conservative P-value cut point of 0.2 was used for linearity testing, in which case tertiles of the parameters were examined; none showed a clear U- or J-shaped relationship with clinical outcomes.[25] We also tested whether potential non-linearities in the associations between confounders and mortality could influence the obtained results. Furthermore, we tested the appropriateness of the large sample approximation by comparing principal results to the one obtained using Firth penalization.[26] Finally, we compared the P-values obtained in the main analysis to the ones corrected for multiple comparisons using the Benjamini–Hochberg procedure. A 2-tailed P<0.05 was considered statistically significant. Statistical analyses were performed in SAS version 9 and R Software 3.5.1 (The R Project for Statistical Computing) with the *rms* package was used for linearity testing.

Results

Figure 1 shows the study flowchart. To directly compare the association of carotid reservoir-wave parameters versus radial and central pressure parameters, we restricted the analysis to

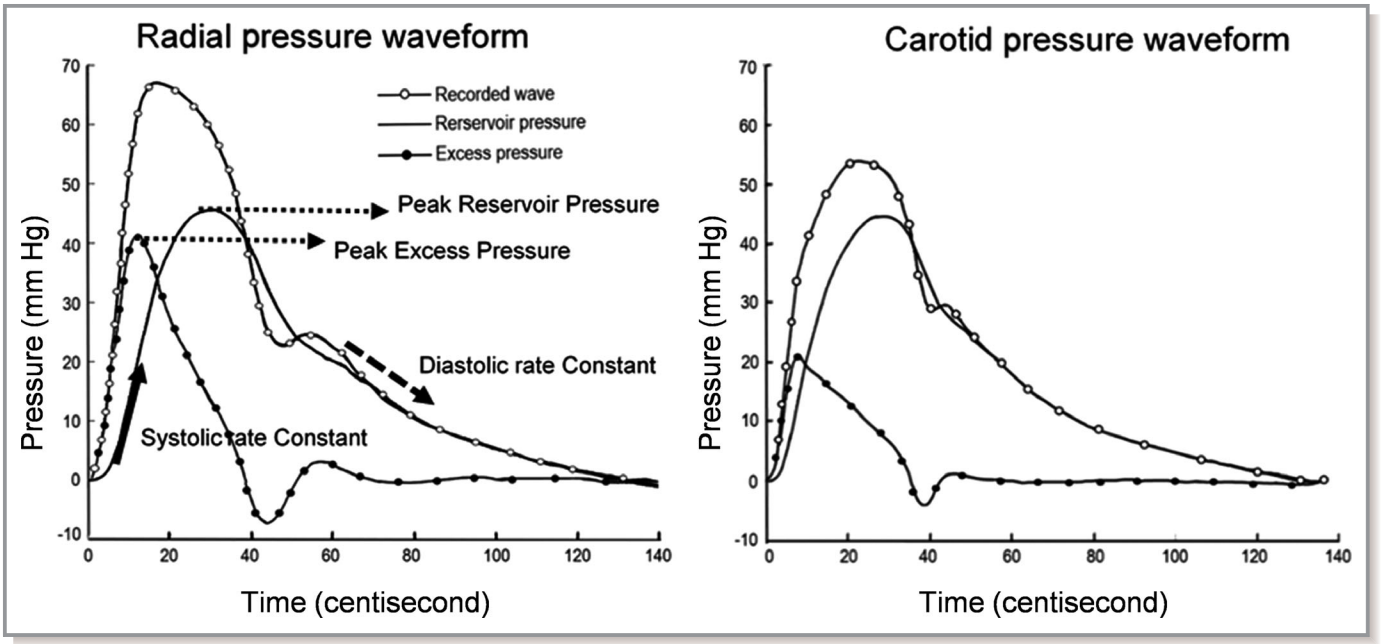

Figure 2. Reservoir-wave parameters. The left panel shows radial artery pressure waveform decomposed into reservoir pressure and excess pressure waveforms, systolic and diastolic rate constants. The right panel shows the corresponding carotid pressure waveforms from the same subject.

Table 1. Characteristics of Patients

	n=260
Male	155 (60)
Age, y	70 (57–77)
Weight, kg	72.9±15.6
Body mass index, kg/m^2	27.0±5.3
Smoking (active or past)	102 (39)
Hypertension	242 (93)
Diabetes mellitus	114 (44)
CVD	142 (55)
Coronary artery disease	127 (49)
Peripheral artery disease	66 (25)
Stroke	30 (12)
Heart failure (ejection fraction <50%)	44 (17)
Dialysis vintage, y	1.5 (0.4–3.3)
Dialysis modality	
Peritoneal	53 (20)
Hemodialysis	207 (80)
Hemodialysis access*	
Arteriovenous fistula/graft	115 (56)
Catheter	92 (44)
Medication	
β-blockers	154 (59)
ACEi/ARB	123 (47)
CCB	95 (37)
Nitrate	46 (18)
Warfarin	49 (19)
CRP, mg/L	6.6 (2.5–15.0)
Lipid profile	
Total cholesterol, mmol/L	3.84±0.99
HDL, mmol/L	1.08±0.38
LDL, mmol/L	1.93±0.77
TG, mmol/L	1.90±1.06
Central pressure	
SP, mm Hg	123.6±25.3
DP, mm Hg	72.0±13.3
MAP, mm Hg	92.6±16.7
PP, mm Hg	51.6±20.7
AIx@75, %	27.0±10.4
Heart rate, bpm	66.9±9.8
Pulse wave velocity	
cf-PWV, m/s	13.97±4.07

Results are mean±SD, n (%) or median [25th–75th percentiles]. Central pressure parameters were obtained with generalized transfer function applied on radial waveforms. ACEi indicates angiotensin-converting-enzyme inhibitor; AIx@75, heart rate adjusted central augmentation index; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; cf-PWV, carotid-femoral pulse wave velocity; CRP, C-reactive protein; CVD, cardiovascular disease; DP, central diastolic pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure derived from integration of radial artery pressure waveform; PP, central pulse pressure; SP, central systolic pressure; TG, triglyceride.
*Percentage based on hemodialysis patients only.

the 260 patients for whom the reservoir-wave parameters were available for both vascular sites. Table 1 shows baseline characteristics, central pressure parameters obtained with generalized transfer function applied to radial waveforms and aortic stiffness.

Reservoir-wave approach derived parameters for both carotid and radial waveforms are presented in Table 2. Despite similar RP parameters between carotid and radial waveforms, carotid XSP parameters were lower and the carotid SC was 2-fold higher compared with respective parameters obtained from the radial artery.

Table 2. Reservoir Wave Parameters From Carotid and Radial Waveforms

Parameters	Carotid (n=260)	Radial (n=260)	*P* Value
RP, mm Hg	39.1 (29.6–52.6)	36.5 (25.6–52.4)	<0.001
RPI, kPa.s	1.89 (1.37–2.56)	1.58 (1.15–2.45)	<0.001
Time to peak RP, cs	31.7 (29.3–34.0)	29.7 (26.0–33.3)	<0.001
SC, $\times10^{-2}$	18.7 (14.0–24.2)	9.24 (6.51–16.57)	<0.001
DC, $\times10^{-2}$	3.35 (2.46–4.41)	2.50 (1.67–3.54)	<0.001
XSP, mm Hg	18.1 (13.4–24.6)	33.2 (25.0–46.0)	<0.001
XSPI, kPa.s	0.383 (0.260–0.560)	0.605 (0.436–0.910)	<0.001
Time to peak XSP, cs	9.7 (8.7–12.0)	12.0 (11.0–13.1)	<0.001
RP proportion, %	83.7 (78.4–87.3)	72.1 (64.6–78.8)	<0.001
XSP proportion, %	16.3 (12.7–21.6)	27.9 (21.2–35.4)	<0.001
XSP:RP	0.19 (0.15–0.28)	0.39 (0.27–0.55)	<0.001

Results are expressed as median (25–75 percentiles). *P* values were obtained with Wilcoxon signed-rank test. RP, reservoir pressure; RPI, reservoir pressure integral; SC, systolic rate constant; DC, diastolic rate constant; XSP, excess pressure; XSPI, excess pressure integral; cs, centisecond.

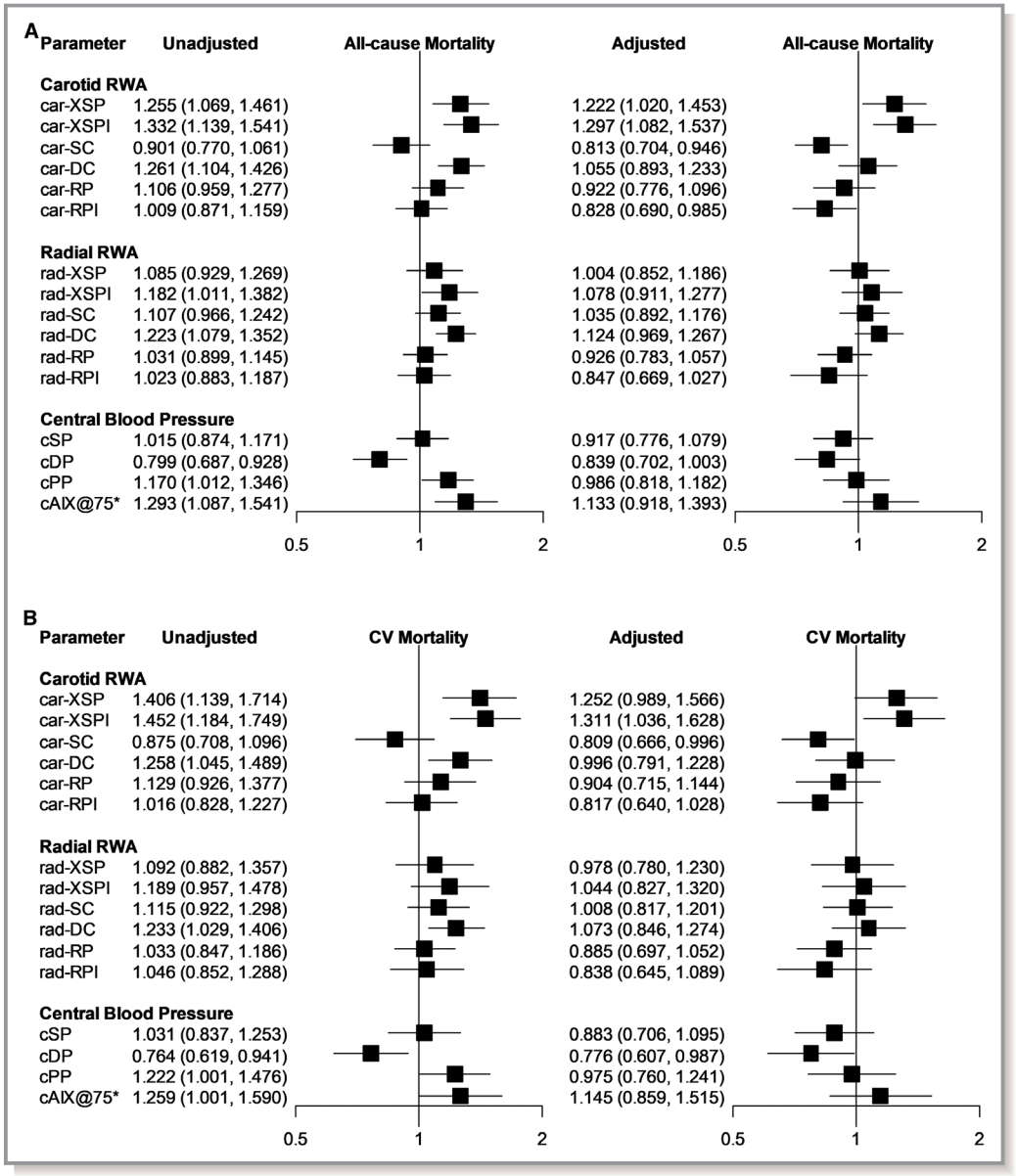

Figure 3. Univariate and multivariable adjusted hazard ratio of carotid and radial reservoir-wave approach (RWA) parameters, and central pressure (generalized transfer function) for all-cause and cardiovascular mortality. The unadjusted and adjusted Hazard ratios for changes in 1 standard deviation with 95% CI (error bars) for all-cause (**A**) and cardiovascular mortality (**B**) are reported. The adjusted models include age, sex, diabetes mellitus, cardiovascular disease, history of hypertension, smoking status, type of dialysis, dialysis vintage, heart rate, and cf-PWV. Variables of interest include excess pressure (XSP), excess pressure integral (XSPI), systolic rate constant (SC), diastolic rate constant (DC) reservoir pressure (RP), reservoir pressure integral of carotid (car-) and radial arteries (rad-), central systolic pressure (cSP), diastolic pressure (cDP), pulse pressure (cPP) and augmentation index for a heart rate of 75 beats per minute (AIx@75). Since augmentation index is already reported for a heart rate of 75 beats per minute, AIx@75* designates that the adjusted model for this parameter does not include heart rate. car-SC, car-RP, rad-XSP, rad-XSPI, rad-RPI were log-transformed before inclusion into the model. rad-SC and rad-RP were elevated to the third power before inclusion into the model.

Carotid Reservoir-Wave Approach Parameters, All-Cause and Cardiovascular Mortality

Among these 260 patients, 171 deaths occurred during a median follow-up of 32 months (16–63), of which 88 (34%) were cardiovascular deaths. Figure 3 summarizes the association of main hemodynamic and reservoir-wave parameters for univariate and adjusted all-cause (Figure 3A) and cardiovascular mortality (Figure 3B).

In univariate analysis, carotid XSP and XSPI were significantly associated with both all-cause and cardiovascular mortality. However, after adjustments for heart rate, age, sex, comorbidities, type of dialysis, dialysis vintage,

and cf-PWV, only carotid XSPI was consistently predictive of all-cause and cardiovascular mortality. Kaplan–Meier survival curves (Figure 4) show higher all-cause mortality (Figure 4A) and cardiovascular mortality (Figure 4B) with higher values of XSPI ($P<0.01$ for both). As part of sensitivity analysis, we tested the robustness of our findings by including brachial systolic pressure into the multivariable adjusted model, which did not alter the associations of carotid XSPI with all-cause and cardiovascular mortality (Table S1). Replacing systolic pressure by either diastolic pressure or mean arterial pressure in these multivariable models did not alter the results (Table S1). Further sensitivity analysis was performed by excluding cf-PWV from the adjusted model (Table S2) or by including all patients with valid carotid reservoir wave analysis (Table S3), and neither approach altered the interpretation of the findings. We also conducted additional sensitivity analysis by applying the Firth correction (Table S4) or adding non-linear terms and interactions for confounders in the fully adjusted model (Table S5) which showed similar results. Finally, as a precautionary measure, we adjusted the P values for multiple comparisons given the 6 parameters derived from the carotid reservoir wave approach (Table S6), which showed similar association between XSPI and all-cause mortality, but the association between XSPI and cardiovascular mortality was no longer statistically significant ($P=0.11$).

Among other parameters of reservoir-wave, the carotid SC, which was not associated with clinical outcomes in the univariate analysis, was statistically significant in the adjusted model showing that higher SC was associated with lower all-cause and cardiovascular mortality. To understand why carotid SC becomes significant in the adjusted model, we used Spearman rank correlation to further explore the relationship between carotid SC and each parameter that was used in the adjusted model. Among these parameters, carotid SC was associated with heart rate ($r=0.226$, $P<0.001$), cf-PWV ($r=0.198$, $P=0.001$), age ($r=0.179$, $P=0.004$) and female sex ($r=0.167$, $P=0.007$), but not with other parameters. The higher carotid DC was significantly associated with both all-cause and cardiovascular mortality in univariate analysis, but this association was no longer statistically significant after adjustments for heart rate, age, sex, comorbidities, type of dialysis, dialysis vintage, and cf-PWV.

Radial Reservoir-Wave Approach Parameters, All-Cause and Cardiovascular Mortality

The association of radial artery derived parameters with all-cause and cardiovascular mortality is reported in Figure 3. Contrary to carotid XSPI, the radial XSPI was only associated with higher all-cause mortality in univariate analysis and was not associated with all-cause or cardiovascular mortality in adjusted models.

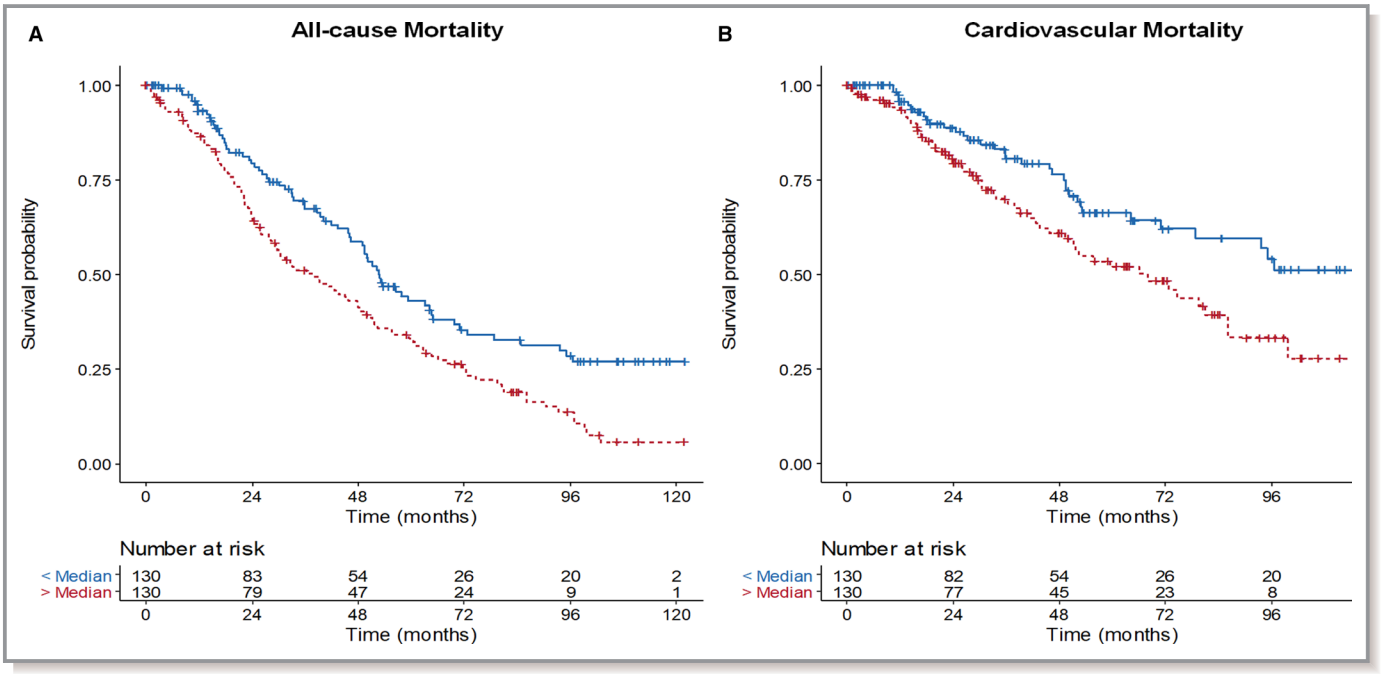

Figure 4. Survival curves according to the median of carotid XSPI for all-cause and cardiovascular mortality. The Kaplan–Meier analysis show that higher values of carotid XSPI are associated with higher (**A**) all-cause mortality ($P=0.001$) and (**B**) cardiovascular mortality ($P=0.009$). XSPI median value was 0.383 kPa.s. XSPI indicates excess pressure integrals.

Central, Carotid, and Brachial Pressures, All-Cause and Cardiovascular Mortality

The impact of central BP (derived from generalized transfer function applied to radial artery) and carotid BP parameters on all-cause and cardiovascular mortality are shown in Figure 3 and Table 3, respectively. Among central parameters of interest, AIx@75 was associated with increased all-cause mortality (P=0.004) and cardiovascular mortality (P=0.024) in univariate analysis. In the adjusted model, AIx@75 was not associated with either all-cause or cardiovascular mortality. Carotid AIx@75 was not associated with clinical outcomes in unadjusted and adjusted models. Overall, lower diastolic BP and higher PP were associated with clinical outcomes, but not the systolic BP. Similar results were obtained for brachial BP.

Wave Separation, All-Cause and Cardiovascular Mortality

The Pf, Pb, and RM derived from the carotid artery were not associated with increased risk of all-cause and cardiovascular mortality. Radial artery derived central wave separation shows that higher Pb and RM are both associated with increased risk of all-cause and cardiovascular mortality in univariate analysis. However, after adjustment, these associations were no longer statistically significant (Table 4).

Aortic Stiffness

In this cohort, the unadjusted hazard ratio per 1SD of cf-PWV was 1.031 (95% CI: 1.002–1.060, P=0.031) and 1.040 (95% CI: 1.000–1.080, P=0.043) for all-cause and cardiovascular mortality, respectively. However, after adjusting for comorbidities (heart rate, age, sex, cardiovascular disease, diabetes mellitus, smoking status, hypertension, type of dialysis, log of dialysis vintage), cf-PWV was not associated with increased risk for all-cause and cardiovascular mortality (hazard ratio: 1.003 (95% CI: 0.969–1.037, P=0.868) and hazard ratio: 1.002 (95% CI: 0.957–1.048, P=0.924) per 1 SD, respectively).

Discussion

In patients with end-stage kidney disease, this study shows that central excess pressure, as derived from the reservoir wave approach at the carotid artery (large central elastic

Table 3. Hazard Ratios for Parameters of Carotid, Brachial Blood Pressures and Outcomes

Parameters	Model	All-Cause Mortality		Cardiovascular Mortality	
		1-SD HR (95% CI)	*P* Value	1-SD HR (95% CI)	*P* Value
Carotid pressure					
SBP	Unadjusted	1.019 (0.880, 1.173)	0.794	1.031 (0.840, 1.249)	0.765
	Adjusted	0.921 (0.782, 1.082)	0.323	0.878 (0.703, 1.086)	0.239
DBP	Unadjusted	0.798 (0.687, 0.927)	0.003*	0.759 (0.616, 0.934)	0.009*
	Adjusted	0.841 (0.705, 1.003)	0.054	0.775 (0.610, 0.983)	0.037*
PP	Unadjusted	1.155 (1.002, 1.324)	0.042*	1.200 (0.987, 1.445)	0.061
	Adjusted	0.986 (0.824, 1.173)	0.872	0.961 (0.755, 1.213)	0.740
AIx@75	Unadjusted	1.169 (0.981, 1.401)	0.085	1.178 (0.925, 1.515)	0.195
	Adjusted†	1.063 (0.859, 1.317)	0.573	1.101 (0.815, 1.487)	0.531
Brachial					
SBP	Unadjusted	1.023 (0.882, 1.179)	0.763	1.036 (0.843, 1.258)	0.727
	Adjusted	0.932 (0.790, 1.095)	0.400	0.891 (0.713, 1.103)	0.298
DBP	Unadjusted	0.800 (0.689, 0.929)	0.004*	0.767 (0.622, 0.944)	0.013*
	Adjusted	0.848 (0.709, 1.013)	0.070	0.786 (0.615, 1.000)	0.052
PP	Unadjusted	1.167 (1.010, 1.342)	0.033*	1.212 (0.993, 1.464)	0.053
	Adjusted	0.999 (0.836, 1.188)	0.987	0.974 (0.766, 1.229)	0.825
MAP	Unadjusted	0.882 (0.759, 1.023)	0.102	0.869 (0.704, 1.067)	0.189
	Adjusted	0.861 (0.731, 1.010)	0.068	0.815 (0.654, 1.007)	0.063

Adjusted models included: heart rate, age, sex, cardiovascular disease, diabetes mellitus, smoking status, hypertension, type of dialysis, log of dialysis vintage, and carotid-femoral pulse wave velocity. AIx@75 indicates augmentation index at 75 beats per minute; DBP, diastolic blood pressure; HR, hazard ratio; MAP, mean arterial pressure derived from integration of radial artery pressure waveform; PP, pulse pressure; SBP, systolic blood pressure.

*P<0.05.

†Since AIx@75 is already adjusted for a heart rate of 75 beats per minute, the adjusted model does not include heart rate.

Table 4. Hazard Ratio for Central and Carotid Wave Separation Parameters and Outcomes

Parameters	Model	All-Cause Mortality		Cardiovascular Mortality	
		1-SD HR (95% CI)	*P* Value	1-SD HR (95% CI)	*P* Value
Central (GTF)					
Pf	Unadjusted	1.148 (0.992, 1.320)	0.059	1.200 (0.982, 1.450)	0.066
	Adjusted	0.990 (0.827, 1.178)	0.908	0.978 (0.770, 1.232)	0.855
Pb	Unadjusted	1.169 (1.014, 1.340)	0.028*	1.211 (0.996, 1.457)*	0.048*
	Adjusted	0.972 (0.808, 1.164)	0.761	0.955 (0.746, 1.215)	0.713
RM	Unadjusted	1.252 (1.054, 1.494)	0.011*	1.230 (0.973, 1.569)	0.089
	Adjusted	1.054 (0.858, 1.299)	0.619	1.000 (0.758, 1.326)	0.999
Carotid pressures					
Pf	Unadjusted	1.134 (0.983, 1.303)	0.079	1.201 (0.987, 1.450)	0.061
	Adjusted	0.996 (0.835, 1.182)	0.966	0.987 (0.772, 1.228)	0.850
Pb	Unadjusted	1.135 (0.987, 1.296)	0.067	1.169 (0.964, 1.398)	0.100
	Adjusted	0.944 (0.790, 1.122)	0.522	0.926 (0.728, 1.166)	0.522
RM†	Unadjusted	1.163 (0.968, 1.416)	0.120	1.156 (0.902, 1.522)	0.278
	Adjusted	0.943 (0.770, 1.171)	0.585	0.947 (0.703, 1.304)	0.730

Adjusted models included: heart rate, age, sex, cardiovascular disease, diabetes mellitus, smoking status, hypertension, type of dialysis, log of dialysis vintage, and carotid-femoral pulse wave velocity. GTF indicates generalized transfer function; HR, hazard ratio; Pb, pressure backward; Pf, pressure forward; RM, reflection magnitude.

*$P<0.05$.

†car-RM was inversed transformed before inclusion into the model. Results are thus presented for 1 SD decrease in 1/(car-RM).

vessel), is associated with increased risk of all-cause and cardiovascular mortality, even after adjustment for comorbidities, aortic stiffness and brachial systolic blood pressure. However, the excess pressure parameters of the radial artery (peripheral muscular artery) were not of prognostic value. Furthermore, parameters obtained through conventional wave separation did not provide additional prognostic information after adjustment for comorbidities and aortic stiffness.

Other investigators have also examined the impact of reservoir-wave approach on clinical outcomes. First, Davies et al[12] using data from the Conduit Artery Functional Evaluation study (a sub-study of the Anglo-Scandinavian Cardiac Outcomes Trial) showed that excess pressure integral of the radial artery, without the application of a generalized transfer function, predicted cardiovascular events independently of other risk factors. However, in our study, the radial XSPI was not associated with clinical outcomes. Hametner et al[14] showed that only the amplitude of reservoir pressure remained a significant predictor of cardiovascular events in high-risk patients after adjustment for conventional risk factors, including brachial systolic pressure. However, they did not show that the reservoir-wave approach provided additional prognostic value compared with traditional wave separation analysis. In contrast, using a cohort of heart failure patients, Wang et al[15] showed that carotid XSPI was an independent predictor of all-cause mortality.

In the context of kidney disease, Huang and colleagues,[16] recently showed carotid XSPI was associated with increased risk of all-cause and cardiovascular mortality in hemodialysis patients without cardiovascular disease at baseline. Compared with their study population, our North American population is older by 16 years (aged 54 versus 70 years), had established cardiovascular disease (55%), had a higher prevalence of diabetes mellitus (16% versus 44%) and included patients on peritoneal dialysis (20%). These differences in comorbidities likely explain the differences in the duration of follow-up (15.3 years versus 2.7 years) for a similar rate of all-cause (46% versus 66%) and cardiovascular mortality (35% versus 34%). Nevertheless, carotid XSPI remained statistically significant, despite incorporation of these comorbidities into the adjusted model, and remained statistically significant using various sensitivity analyses. This observation strengthens the prognostic value of XSPI in end-stage kidney disease even in the presence of these comorbidities and presence of established cardiovascular disease.

In our study, SC, which is inversely proportional to the product of characteristic impedance and compliance ($1/(Z_0 \cdot C)$), was not associated with clinical outcomes in univariate analysis. However, in the adjusted model, a higher SC was associated with better clinical outcomes. This is in agreement with a study by Narayan and colleagues,[11] who proposed that this is likely the consequence of a higher aortic stiffness as they lacked the measurement of aortic stiffness in their

non-kidney population. In contrast, Cheng et al[13] reported that higher central SC was associated with increased risk of clinical events in multivariable adjusted model. They underlined this disagreement with the previous study and proposed that the worsening of reservoir function could result in faster filling of the arterial reservoir (ie, poorer accommodation ability of the vascular system to physiological stress). In our study, SC was protective in the multivariable-adjusted model, even when considering aortic stiffness as measured by cf-PWV. Nevertheless, cf-PWV may not entirely capture the mechanical property of the proximal aorta and may underestimate its stiffness. Moreover, the rate of vascular filling (SC) may also depend on myocardial contractility and ejection volume, which were not simultaneously assessed in our population. These apparent contradictions underline the complexity of interpreting SC in the reservoir-wave model.

There is good physiological reason to expect different magnitudes of association between central and peripheral reservoir-wave approach parameters and clinical outcomes. Indeed, excess pressure is on average amplified along the aortic-radial axis, and this amplification is proportional to the SBP amplification that varies greatly in individual patients.[17,18] Given that aortic excess pressure provides information about the surplus of work performed by left ventricle, it is reasonable to expect that central excess pressure could be of better prognostic value.

This study has several strengths as it provides a direct comparison of carotid and radial reservoir-wave parameters with robust findings supported by various sensitivity analyses. In addition, all cardiovascular deaths were confirmed by 2 reviewers using each patient's hospital records. There are also limitations that need to be mentioned. First, the radial pressure wave was calibrated to the brachial systolic and diastolic blood pressures. Second, 13% of the radial pressure waves were not amenable to reservoir-wave analysis in this population. In contrast, reservoir-wave analysis of carotid pressure waves was successful in >95% of the cohort. Third, despite a recent validation study in humans,[27] the reservoir parameters were derived using pressure-only approach by assuming that the excess pressure has the same shape as the flow wave. Fourth, since several parameters were tested simultaneously, it increases the risk of type I error, but care was taken to adjust for multiple comparisons. Finally, a small number of patients might have had significant carotid stenosis above the measurement site with potential alterations of blood pressure and flow, however, it is unlikely to affect the findings of the study as the prevalence is expected to be low.

Acknowledgments

We are thankful to the dialysis personnel and the study subjects for their kind contribution and precious collaboration.

Sources of Funding

Dr. Fortier holds a scholarship from the Kidney Foundation of Canada (KFOC). Dr. Desjardins holds a scholarship from the Société québécoise d'hypertension artérielle – through contribution from Servier. Desbiens holds a scholarship from the Canadian Institutes of Health Research (CIHR) and the Fonds de Recherche du Québec - Santé (FRQ-S). Dr Agharazii holds the Nephrology-Amgen research Chair at Université Laval. Drs Mac-Way and Goupil hold scholarships from the Fonds de Recherche Québec-Santé.

Disclosures

None.

References

1. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation*. 1999;99:2434–2439.
2. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. *Hypertension*. 2001;38:434–438.
3. Yu WC, Lin YP, Chuang SY, Lin IF, Chenb CH. Cardiovascular determinants of prognosis in normotensive hemodialysis patients. *BMC Nephrol*. 2012;13:115.
4. Fortier C, Mac-Way F, Desmeules S, Marquis K, De Serres SA, Lebel M, Boutouyrie P, Agharazii M. Aortic-brachial stiffness mismatch and mortality in dialysis population. *Hypertension*. 2015;65:378–384.
5. Wang JJ, O'Brien AB, Shrive NG, Parker KH, Tyberg JV. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. *Am J Physiol Heart Circ Physiol*. 2003;284:H1358–H1368.
6. Tyberg JV, Davies JE, Wang Z, Whitelaw WA, Flewitt JA, Shrive NG, Francis DP, Hughes AD, Parker KH, Wang JJ. Wave intensity analysis and the development of the reservoir-wave approach. *Med Biol Eng Comput*. 2009;47:221–232.
7. Davies JE, Baksi J, Francis DP, Hadjiloizou N, Whinnett ZI, Manisty CH, Aguado-Sierra J, Foale RA, Malik IS, Tyberg JV, Parker KH, Mayet J, Hughes AD. The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. *Am J Physiol Heart Circ Physiol*. 2010;298:H580–H586.
8. Parker KH, Alastruey J, Stan GB. Arterial reservoir-excess pressure and ventricular work. *Med Biol Eng Comput*. 2012;50:419–424.
9. Tyberg JV, Bouwmeester JC, Parker KH, Shrive NG, Wang JJ. The case for the reservoir-wave approach. *Int J Cardiol*. 2014;172:299–306.
10. Schultz MG, Davies JE, Hardikar A, Pitt S, Moraldo M, Dhutia N, Hughes AD, Sharman JE. Aortic reservoir pressure corresponds to cyclic changes in aortic volume: physiological validation in humans. *Arterioscler Thromb Vasc Biol*. 2014;34:1597–1603.
11. Narayan O, Davies JE, Hughes AD, Dart AM, Parker KH, Reid C, Cameron JD. Central aortic reservoir-wave analysis improves prediction of cardiovascular events in elderly hypertensives. *Hypertension*. 2015;65:629–635.
12. Davies JE, Lacy P, Tillin T, Collier D, Cruickshank JK, Francis DP, Malaweera A, Mayet J, Stanton A, Williams B, Parker KH, McG Thom SA, Hughes AD. Excess pressure integral predicts cardiovascular events independent of other risk factors in the conduit artery functional evaluation substudy of Anglo-Scandinavian Cardiac Outcomes Trial. *Hypertension*. 2014;64:60–68.
13. Cheng HM, Chuang SY, Wang JJ, Shih YT, Wang HN, Huang CJ, Huang JT, Sung SH, Lakatta EG, Yin FC, Chou P, Yeh CJ, Bai CH, Pan WH, Chen CH. Prognostic significance of mechanical biomarkers derived from pulse wave analysis for predicting long-term cardiovascular mortality in two population-based cohorts. *Int J Cardiol*. 2016;215:388–395.
14. Hametner B, Wassertheurer S, Hughes AD, Parker KH, Weber T, Eber B. Reservoir and excess pressures predict cardiovascular events in high-risk patients. *Int J Cardiol*. 2014;171:31–36.
15. Wang WT, Sung SH, Wang JJ, Wu CK, Lin LY, Lee JC, Cheng HM, Chen CH. Excess pressure integral predicts long-term all-cause mortality in stable heart failure patients. *Am J Hypertens*. 2017;30:271–278.

16. Huang JT, Cheng HM, Yu WC, Lin YP, Sung SH, Wang JJ, Wu CL, Chen CH. Value of excess pressure integral for predicting 15-year all-cause and cardiovascular mortalities in end-stage renal disease patients. *J Am Heart Assoc*. 2017;6: e006701. DOI: 10.1161/JAHA.117.006701.
17. Peng X, Schultz MG, Picone DS, Black JA, Dwyer N, Roberts-Thomson P, Davies JE, Sharman JE. Arterial reservoir characteristics and central-to-peripheral blood pressure amplification in the human upper limb. *J Hypertens*. 2017;35:1825–1831.
18. Picone DS, Schultz MG, Peng X, Black JA, Dwyer N, Roberts-Thomson P, Chen CH, Cheng HM, Pucci G, Wang JG, Sharman JE. Discovery of new blood pressure phenotypes and relation to accuracy of cuff devices used in daily clinical practice. *Hypertension*. 2018;71:1239–1247.
19. Utescu MS, Couture V, Mac-Way F, De Serres SA, Marquis K, Lariviere R, Desmeules S, Lebel M, Boutouyrie P, Agharazii M. Determinants of progression of aortic stiffness in hemodialysis patients: a prospective longitudinal study. *Hypertension*. 2013;62:154–160.
20. Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, Kass DA. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation*. 1997;95:1827–1836.
21. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension*. 1995;26:485–490.
22. Schultz MG, Hughes AD, Davies JE, Sharman JE. Associations and clinical relevance of aortic-brachial artery stiffness mismatch, aortic reservoir function, and central pressure augmentation. *Am J Physiol Heart Circ Physiol*. 2015;309:H1225–H1233.
23. Hametner B, Wassertheurer S, Kropf J, Mayer C, Holzinger A, Eber B, Weber T. Wave reflection quantification based on pressure waveforms alone—methods, comparison, and clinical covariates. *Comput Methods Programs Biomed*. 2013;109:250–259.
24. Weber T, Wassertheurer S, Rammer M, Haiden A, Hametner B, Eber B. Wave reflections, assessed with a novel method for pulse wave separation, are associated with end-organ damage and clinical outcomes. *Hypertension*. 2012;60:534–541.
25. Harrell FE. General aspects of fitting regression models. *Regression modeling strategies*. Cham: Springer International Publishing; 2015:13–44.
26. Heinze G, Schemper M. A solution to the problem of monotone likelihood in Cox regression. *Biometrics*. 2001;57:114–119.
27. Michail M, Narayan O, Parker KH, Cameron JD. Relationship of aortic excess pressure obtained using pressure-only reservoir pressure analysis to directly measured aortic flow in humans. *Physiol Meas*. 2018;39:064006.

SUPPLEMENTAL MATERIAL

Table S1. Hazard ratios for reservoir parameters of interest and outcomes after further adjustment for brachial blood pressures.

Parameters	Pressure adjustment	All-cause mortality		CV mortality	
		1-SD HR (95% CI)	*P*	1-SD HR (95% CI)	*P*
car-XSP	SBP	1.269 (1.055, 1.513)	0.0095	1.317 (1.037, 1.650)	0.0197
	DBP	1.201 (1.003, 1.429)	0.0419	1.229 (0.973, 1.535)	0.0765
	MAP	1.247 (1.043, 1.480)	0.0135	1.291 (1.023, 1.611)	0.0271
car-XSPI	SBP	1.330 (1.110, 1.576)	0.0014	1.351 (1.070, 1.674)	0.0082
	DBP	1.271 (1.059, 1.509)	0.0079	1.275 (1.008, 1.587)	0.0348
	MAP	1.311 (1.096, 1.551)	0.0022	1.322 (1.057, 1.649)	0.0113
car-SC*	SBP	0.812 (0.697, 0.954)	0.0094	0.821 (0.668, 1.026)	0.0712
	DBP	0.835 (0.718, 0.978)	0.0225	0.848 (0.692, 1.052)	0.1207
	MAP	0.836 (0.717, 0.983)	0.0261	0.848 (0.690, 1.057)	0.1284

CV, Cardiovascular; SD, Standard deviation; HR, Hazard ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Adjusted models included: heart rate, age, sex, cardiovascular disease, diabetes mellitus, smoking status, hypertension, type of dialysis, log of dialysis vintage, and carotid-femoral pulse wave velocity.

*car-SC was log-transformed before inclusion into the model.

Table S2. Hazard ratios for reservoir parameters of interest and outcomes without adjustment for cf-PWV.

Parameters	All-cause mortality		CV mortality	
	1-SD HR (95% CI)	*P*	1-SD HR (95% CI)	*P*
car-XSP	1.230 (1.031, 1.457)	0.0190	1.261 (0.999, 1.572)	0.0446
car-XSPI	1.303 (1.092, 1.538)	0.0024	1.318 (1.046, 1.631)	0.0144
car-SC*	0.813 (0.702, 0.948)	0.0066	0.811 (0.662, 0.994)	0.0434

CV, Cardiovascular; SD, Standard deviation; HR, Hazard ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. Adjusted models included: heart rate, age, sex, cardiovascular disease, diabetes mellitus, smoking status, hypertension, type of dialysis, log of dialysis vintage, and carotid-femoral pulse wave velocity.

*car-SC was log-transformed before inclusion into the model.

Table S3. Hazard ratios for reservoir parameters of interest and outcomes using all patients with valid Carotid reservoir wave analysis.

Parameters	N	All-cause mortality		CV mortality	
		1-SD HR (95% CI)	*P*	1-SD HR (95% CI)	*P*
car-XSP	288	1.199 (1.05, 1.407)	0.0294	1.242 (1.000, 1.525)	0.0441
car-XSPI	288	1.275 (1.076, 1.497)	0.0039	1.301 (1.045, 1.595)	0.0142
car-SC*	288	0.810 (0.705, 0.937)	0.0038	0.806 (0.669, 0.983)	0.0278

CV, Cardiovascular; SD, Standard deviation; HR, Hazard ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.
Hazard ratios are adjusted for: heart rate, age, sex, cardiovascular disease, diabetes mellitus, smoking status, hypertension, type of dialysis, log of dialysis vintage, and carotid-femoral pulse wave velocity.
*car-SC was log-transformed before inclusion into the model.

Table S4. Hazard ratios for reservoir parameters of interest and outcomes after Firth's correction.

Parameters	Model	All-cause mortality		CV mortality	
		1-SD HR (95% CI)	*P*	1-SD HR (95% CI)	*P*
car-XSP	Unadjusted	1.258 (1.072, 1.465)	0.0039	1.413 (1.146, 1.721)	0.0008
	Adjusted	1.224 (1.022, 1.454)	0.0252	1.255 (0.992, 1.568)	0.0529
car-XSPI	Unadjusted	1.338 (1.145, 1.547)	0.0001	1.462 (1.194, 1.759)	0.0001
	Adjusted	1.300 (1.086, 1.540)	0.0033	1.316 (1.043, 1.632)	0.0167
car-SC*	Unadjusted	0.899 (0.769, 1.058)	0.1919	0.871 (0.705, 1.090)	0.2148
	Adjusted	0.811 (0.702, 0.943)	0.0058	0.804 (0.664, 0.989)	0.0325

CV, Cardiovascular; SD, Standard deviation; HR, Hazard ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.
Adjusted models included: heart rate, age, sex, cardiovascular disease, diabetes mellitus, smoking status, hypertension, type of dialysis, log of dialysis vintage, and carotid-femoral pulse wave velocity.
*car-SC was log-transformed before inclusion into the model.

Table S5. Hazard ratios for reservoir parameters of interest and outcomes after non-linear treatment of confounders and adjustment for interactions between confounders.

Parameters	All-cause mortality		CV mortality	
	1-SD HR (95% CI)	*P*	1-SD HR (95% CI)	*P*
car-XSP	1.240 (1.028, 1.497)	0.0247	1.260 (0.984, 1.615)	0.0670
car-XSPI	1.317 (1.096, 1.582)	0.0033	1.382 (1.090, 1.751)	0.0075
car-SC*	0.791 (0.674, 0.928)	0.0040	0.763 (0.604, 0.963)	0.0230

CV, Cardiovascular; SD, Standard deviation; HR, Hazard ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. Adjusted models included: heart rate, age, sex, cardiovascular disease, diabetes mellitus, smoking status, hypertension, type of dialysis, log of dialysis vintage, and carotid-femoral pulse wave velocity. Continuous confounders were treated with restricted cubic splines with 3 knots. Age-sex interaction and interactions of age and sex with cardiovascular disease, diabetes, smoking and hypertension were also added.

*car-SC was log-transformed before inclusion into the model.

Table S6. Hazard ratios, crude p-values and corrected p-values for reservoir parameters of interest and outcomes.

Parameters	Model	All-cause mortality			CV mortality		
		1-SD HR (95% CI)	Crude P	Corrected P (6 comparisons)	1-SD HR (95% CI)	Crude P	Corrected P (6 comparisons)
car-XSP	Unadjusted	1.255 (1.069, 1.461)	0.0044	0.009	1.406 (1.139, 1.714)	0.0010	0.003
	Adjusted	1.222 (1.020, 1.453)	0.0262	0.052	1.252 (0.989, 1.566)	0.0548	0.110
car-XSPI	Unadjusted	1.332 (1.139, 1.541)	0.0002	0.001	1.452 (1.184, 1.749)	0.0002	0.001
	Adjusted	1.297 (1.082, 1.537)	0.0036	0.018	1.311 (1.036, 1.628)	0.0186	0.110
car-SC*	Unadjusted	0.901 (0.770, 1.061)	0.2021	0.242	0.875 (0.708, 1.096)	0.2321	0.278
	Adjusted	0.813 (0.704, 0.946)	0.0060	0.018	0.809 (0.666, 0.996)	0.0379	0.110

CV, Cardiovascular; SD, Standard deviation; HR, Hazard ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.
Adjusted models included: heart rate, age, sex, cardiovascular disease, diabetes mellitus, smoking status, hypertension, type of dialysis, log of dialysis vintage, and carotid-femoral pulse wave velocity.
Corrected p-values are displayed after a Benjamini–Hochberg procedure with correction for 6 comparisons of carotid reservoir-wave parameters

*car-SC was log-transformed before inclusion into the model.