

Increased Excess Pressure After Creation of an Arteriovenous Fistula in End-Stage Renal Disease

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BACKGROUND

Reservoir-wave analysis (RWA) separates the arterial waveform into reservoir and excess pressure (XSP) components, where XSP is analogous to flow and related to left ventricular workload. RWA provides more detailed information about the arterial tree than traditional blood pressure (BP) parameters. In end-stage renal disease (ESRD), we have previously shown that XSP is associated with increased mortality and is higher in patients with arteriovenous fistula (AVF). In this study, we examined whether XSP increases after creation of an AVF in ESRD.

METHODS

Before and after a mean of 3.9 ± 1.2 months following creation of AVF, carotid pressure waves were recorded using arterial tonometry. XSP and its integral (XSPI) were derived using RWA through pressure wave analysis alone. Aortic stiffness was assessed by carotid–femoral pulse wave velocity (CF-PWV).

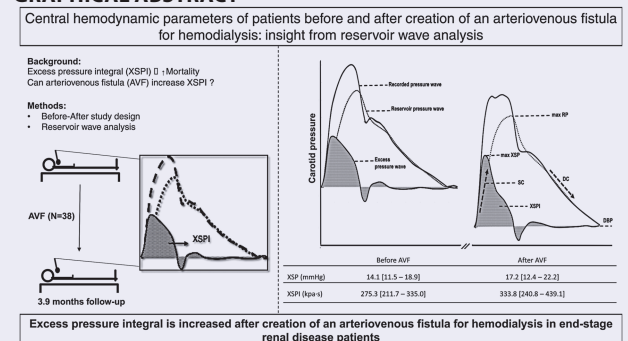
RESULTS

In 38 patients (63% male, age 59 ± 15 years), after AVF creation, brachial diastolic BP decreased (79 ± 10 vs. 72 ± 12 mm Hg, $P = 0.002$), but the reduction in systolic BP, was not statistically significant (133 ± 20 vs. 127 ± 26 mm Hg, $P = 0.137$). However, carotid XSP (14 [12–19] to 17 [12–22] mm Hg, $P = 0.031$) and XSPI increased significantly (275 [212–335] to 334 [241–439] kPa·s, $P = 0.015$), despite a reduction in CF-PWV (13 ± 3.6 vs. 12 ± 3.5 m/s, $P = 0.025$).

CONCLUSIONS

Creation of an AVF resulted in increased XSP in this population, despite improvement in diastolic BP and aortic stiffness. These findings underline the complex hemodynamic impact of AVF on the cardiovascular system.

GRAPHICAL ABSTRACT



Keywords: blood pressure; cardiovascular disease; hemodynamics; hypertension; nephrology and kidney.

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Patients with end-stage renal disease (ESRD) require renal replacement therapy through either hemodialysis or peritoneal dialysis. To perform hemodialysis, large quantities of blood are required to achieve sufficient clearance of uremic toxins. Access to this amount of blood is achieved through a central venous catheter or a surgically created arteriovenous fistula (AVF). Creation of an AVF involves connecting an artery to a nearby vein. On average, a mature AVF achieves

a blood flow of 500–1,000 ml/min.¹ Creation of an AVF is known to have important hemodynamic consequences, as the creation of a high flow and low resistance environment increases venous return, stroke volume, and myocardial contractility.^{2,3} Furthermore, the increase in cardiac output causes increased myocardial oxygen demand, and can result, over time, in left ventricular hypertrophy.^{4–7} On the other hand, a recent meta-analysis by Scholz *et al.* provided

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estimates of AVF-induced changes in systolic, diastolic, and mean blood pressures (BPs), which were reduced by an average of 8.7, 5.9, and 6.6 mm Hg, respectively.⁸ These observations are in line with reductions of BP achieved by nonpharmacological treatment of resistant hypertension through creation of AVF between the iliac artery and vein.⁹

While brachial systolic and diastolic BPs are convenient, they are relatively simplistic compared with the information that is provided through the analysis of the arterial pressure waveforms. The reservoir-wave analysis (RWA) is an alternative approach to pulse wave analysis, which aims to incorporate arterial reservoir function with wave propagation. The RWA hypothesizes that the measured arterial pressure is the sum of a reservoir pressure (RP) wave and an excess pressure (XSP) wave.¹⁰ The RP accounts for the dynamic storage and release of blood by the compliant arteries (the Windkessel effect) and is related to minimal left ventricular work required to generate blood flow into the aorta. The XSP, which is obtained by subtracting RP from the acquired pressure waveform, is responsible for local changes in the pulse waveform, is analogous to flow, and can provide information about surplus work performed by the left ventricle.^{11,12}

Using RWA, we and others have shown that higher excess pressure integral (XSPI) is associated with increased cardiovascular and all-cause mortality in ESRD, above and beyond all other available hemodynamic parameters, including aortic stiffness as assessed by carotid–femoral pulse wave velocity (CF-PWV).^{13,14} In addition, our previous findings show that XSPI was statistically higher in ESRD patients with an AVF.¹⁵ Indeed, if XSP is analogous to flow, it is conceivable the creation of AVF could increase XSP. In the present study, our aim was to assess the impact of creation of an AVF on reservoir-wave parameters in ESRD patients, in a before and after study design.

METHODS

Patient population and study design

This longitudinal study looks at the central hemodynamic parameters of patients before and after creation of an AVF for hemodialysis. All adult patients with ESRD who were scheduled for an AVF within the following month were invited to participate. Exclusion criteria included a nonfunctional AVF at follow-up time, extreme BP values (systolic BP >190 or <80 mm Hg), severe congestive heart failure, patients having had a previous AVF, those for whom follow-up evaluation was conducted more than 6 months after surgery and those who were transferred to satellite units. The study was conducted at CHU de Québec-Université Laval, L'Hôtel-Dieu de Québec Hospital between November 2004 and December 2007. The study was approved by the institutional ethics committee and all participants gave written informed consent.

All hemodynamic assessments were performed within 1 month prior to AVF creation and within a mean follow-up of 3.9 ± 1.2 months following the surgery. Figure 1 shows the study flowchart. Overall, 57 participants were initially recruited, however, 19 patients were subsequently excluded for the following reasons: severe cardiac failure ($N = 1$), extremely low BP ($N = 1$), transfer to another facility ($N = 7$),

death ($N = 1$), nonfunctional AVF ($n = 7$), and a follow-up >6 months ($N = 2$). Twenty-nine of these subjects have been described previously with regard to central BPs and pulse wave velocity.¹⁶ All routine laboratory tests were performed on the mid-week hemodialysis session for patients on hemodialysis and in morning in patients on peritoneal dialysis. Ejection fractions reported in this study were taken from available echocardiographic assessments made prior to creation of AVF for a variety of clinical reasons.

Hemodynamic parameters

All hemodynamic measurements were done on the opposite side of the AVF (expected or present). If patients were already on dialysis at baseline ($N = 19$), all measurements were performed just prior to the mid-week dialysis session. Briefly, after 15 minutes of rest in a supine position, brachial artery BP was recorded 6 times, with a 2-minute interval between each recording using an automatic oscillometric sphygmomanometer BPM-100 (BP-Tru, Coquitlam, Canada). 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, Sydney, Australia). Three consecutive recordings were performed for each site. Central pressure waveform was obtained from radial artery tonometry through application of a generalized transfer function. Central systolic BP, diastolic BP, pulse pressure, and heart rate adjusted augmentation index (AIx@75) were derived after calibration of central waveform for brachial systolic and diastolic BPs.¹⁷ Carotid pressure waveform was obtained by carotid artery tonometry after calibration for diastolic and mean arterial pressure, or mean BP, which was obtained by integration of the radial artery pressure waveform. Immediately after pulse wave recordings, we determined CF-PWV in triplicate by Complior SP (Artech Medical, Pantin, France), using

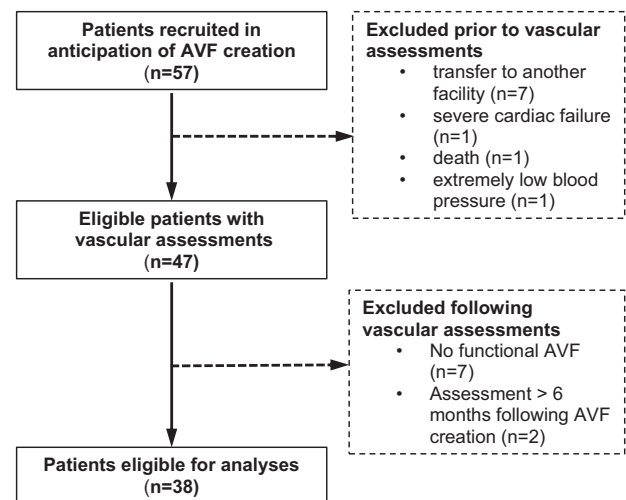


Figure 1. Study flowchart. The figure shows the number of patients excluded before vascular hemodynamic assessment due to severe illness or death, as well as clinical and methodological reasons. Also shown on the chart are exclusions which occurred following vascular hemodynamic assessment due to no functional AVF or assessment past the predetermined 6 months delay. Abbreviation: AVF, arteriovenous fistula.

the maximal upstroke algorithm and direct measurements as previously described.¹⁸

Wave separation analysis was conducted to derive central pressure forward (Pf), pressure backward (Pb), and reflection magnitude (RM = $(100 \times Pb)/Pf$) and reflection index (RI = $(Pb \times 100)/(Pb + Pf)$) were calculated. This was performed on the central pressure waveform after application of a generalized transfer function on the radial artery pressure waveform.^{19,20}

Reservoir-wave parameters were obtained from carotid pressure waveforms using the pressure wave approach as previously described.^{21,22} RP, its integral (RPI), XSPI, diastolic rate constant (DC), and systolic rate constant (SC) were acquired from carotid pressure waveforms. 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 and XSP was defined as the difference between total measured pressure and RP. A RP analysis was considered valid with $RP > 0$, $XSPI > 0$, a numerical SC and DC, $DC > 0$ and $P_\infty > 0$, where P_∞ is the minimal pressure of the system, as modeled by asymptotic decay. Figure 2 summarizes the key parameters of RWA of the carotid artery.

Statistical analysis

All analyses were done with SPSS, version 25.0 (SPSS, Chicago, IL). Results are reported as the mean \pm standard

deviation or median [25th–75th percentiles] as appropriate. The variations between pre-AVF and post-AVF creation were evaluated through a paired sample *t*-test or Wilcoxon tests as appropriate. As part of sensitivity analyses, generalized estimating equation models were used to verify whether the impact of AVF on reservoir-wave parameters was modified by changes in the number of antihypertensive medications. Models considered timing of measurement (pre-AVF vs. post-AVF) as within-subject effect and included number of antihypertensive medication, before and after AVF as covariate. As part of the sensitivity analyses, we examined if the hemodynamic response to AVF was different in subjects according to the dialysis or predialysis status, and baseline clinical and biochemical parameters. For all analyses, a 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Baseline demographic and clinical characteristics are presented in Table 1. Among the 38 subjects, 19 were already treated by hemodialysis, 1 by peritoneal dialysis and 18 were in predialysis care without renal replacement therapy. Of those 18 participants, 9 were still on predialysis care at follow-up, whereas others had begun hemodialysis treatment. The number of subjects with aspirin ($N = 17$) and statins ($N = 25$) did not change significantly over the observation period. Overall, the participants can be considered

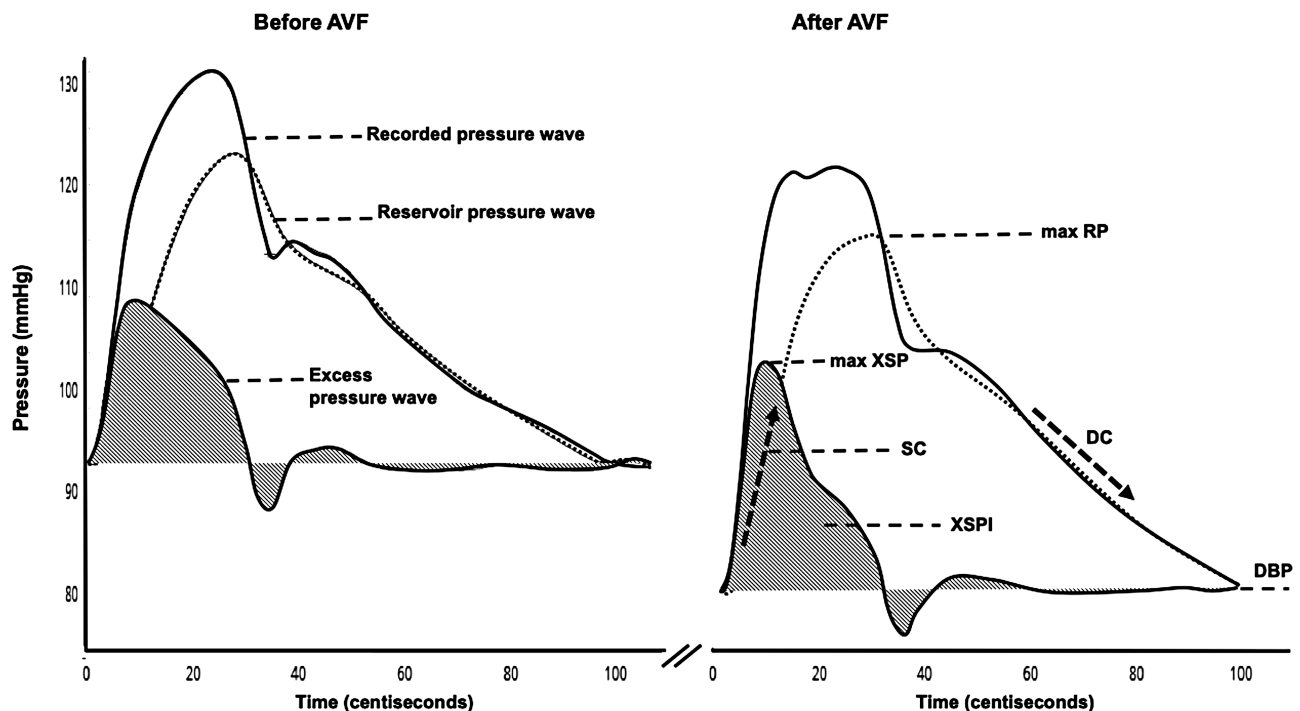


Figure 2. Relevant parameters and outcomes of reservoir-wave analysis (RWA). The figure shows 2 carotid pressure waveforms sampled from a single subject, the left one obtained before arteriovenous fistula (AVF) creation, the right one after AVF creation. Each waveform has been decomposed into reservoir and excess pressure waves, designated as such on the left waveform. Relevant parameters of RWA are indicated with broken lines on the right waveform. After AVF creation, DBP, diastolic blood pressure decreases; DC, diastolic rate constant decreases; max RP, peak reservoir pressure does not change; max XSP, peak excess pressure increases; RPI, reservoir pressure integral/area under the curve does not change; SC, systolic rate constant decreases; XSPI, excess pressure integral/area under the curve increases.

a representative sample of the ESRD population, with high prevalence of hypertension, diabetes, and cardiovascular disease. Accordingly, the participants were taking various medications including antihypertensive medication. Before AVF creation, on average participants were taking 2 [1–3] different antihypertensive drugs and 1.5 [1–3] after creation of AVF ($P = 0.267$). Given potential differences and confounding factors, we examined baseline characteristics of participants on predialysis care at baseline and compared them to those already on dialysis. Patients on hemodialysis were in general younger (54 ± 17 vs. 65 ± 10 , $P = 0.014$), had a lower serum albumin level (36.1 ± 3.33 vs. 40.1 ± 4.43 g/l, $P = 0.008$), plasma urea concentration (19.9 [15.3–22.9] vs. 26.1 [22.0–33.0] mmol/l, $P < 0.001$), but higher creatinine levels (690 [435–869] vs. 425 [346–539] $\mu\text{mol/l}$, $P = 0.026$). However, they were similar in terms of cardiovascular disease, diabetes, hypertension, left ventricular mass, and hemoglobin levels.

Brachial and central pressure changes after AVF creation

Table 2 summarizes hemodynamic parameters, namely brachial and central BP obtained through generalized transfer function and CF-PWV. After AVF creation, diastolic BP and mean BP decreased significantly at the brachial level but pulse pressure did not change significantly because of a small but nonsignificant reduction in brachial systolic BP. A similar response was observed for central and carotid diastolic BPs, systolic BPs, and pulse pressures (Table 3). After creation of an AVF, the average heart rate did not change, the ejection duration increased slightly without reaching statistical significance ($P = 0.084$), but the subendocardial viability ratio decreased significantly. Subendocardial viability ratio is a marker of subendocardial perfusion expressed as the ratio of the diastolic pressure time index and systolic pressure time index.¹⁶ Despite a reduction in CF-PWV there

was a statistically nonsignificant increase in AIx@75 and a significant increase in RM.

Carotid reservoir-wave analysis

Table 3 summarizes the carotid BP and parameters of reservoir-wave analysis obtained before and after AVF creation. Figure 2 shows a representative carotid reservoir-wave analysis in a subject before and after creation of AVF. We observed a significant increase in XSP, XSPI, and time to maximum XSP. However, there were no changes in RP, RP integral or time to maximum RP. There were also significant reductions in SC and DC. These observed changes in XSP, XSPI, SC, and DC remained statistically significant even after adjustment for the number of antihypertensive medications. Also, despite differences in baseline characteristics of patients already on dialysis and those on predialysis care, there were no statistically significant differences in hemodynamic response to AVF creation between subgroups.

DISCUSSION

In ESRD patients, this study shows an increase in XSP following AVF creation, despite a reduction in diastolic BP and aortic stiffness. Given that increased XSP has a prognostic value above and beyond aortic stiffness and other potential confounders in this population,¹³ our observations provide important information on the complex hemodynamic effects of AVF that cannot be captured through traditional systolic and diastolic BPs alone.

The RWA, an alternative approach to pulse wave analysis, aims to integrate arterial reservoir function with wave propagation. In the RWA model, it is proposed that the measured arterial pressure is the sum of a RP and XSP waves¹⁰ where the RP wave accounts for the dynamic storage and release of blood by the compliant arteries (the Windkessel effect) and is related to minimal left ventricular work required to generate blood flow into the aorta. In this model, the XSP wave is responsible for local changes in the pulse waveform, is related to flow, and can provide information about the work performed by left ventricle. As such, the increased XSP after creation of an AVF that we observed in this study is in keeping with increased flow and increased cardiac workload. Indeed, all parameters related to XSP, such as peak XSP, timing of the peak XSP and XSPI increased significantly after creation of AVF.

There were also changes in other parameters of RWA such as the SC and the DC. However, the interpretation of these parameters is more complex, and their clinical relevance are less well established. In fact, SC represents the rate of system filling and it is inversely proportional to the product of characteristic impedance (Z_0) and compliance (C). Our findings show a decrease in SC after AVF (i.e., lower rate of system filling), which could be explained by an increase in C and possibly through increased Z_0 . According to water hammer equation, Z_0 is proportional to the aortic PWV divided by aortic cross-sectional area in diastole. In our study, CF-PWV decreased, but since there was a reduction in the diastolic BP, aortic diameter in diastole may also have decreased after AVF creation. Therefore, the amplitude

Table 1. Baseline demographic

	Pre-AVF (N = 38)
Age (years)	59 \pm 15
Men	24 (63)
BMI (kg/m ²)	28 \pm 6
Hypertension	34 (90)
Diabetes	16 (42)
Dialysis	19 (50)
Dialysis vintage (N = 19, months)	57 [19–338]
History of smoking	21 (55)
History of cardiovascular disease	23 (61)
Hemoglobin (g/l)	110 \pm 14
Albumin (g/l)	40 \pm 4
Left ventricular mass (g/m ²)	118 \pm 40
Ejection fraction (%)	63 \pm 10

Values are mean \pm SD, median (25th–75th percentiles or N (%)). Abbreviations: AVF, arteriovenous fistula; BMI, body mass index.

Table 2. Hemodynamic parameters and wave separation analysis before–after AVF

	Before AVF (N = 38)	After AVF (N = 38)	P
HR (bpm)	71.6 ± 13.7	71.0 ± 13.4	0.766
Brachial BP			
SBP (mm Hg)	132.7 ± 19.6	127.3 ± 25.7	0.137
DBP (mm Hg)	78.5 ± 10.3	71.7 ± 12.2	0.002
PP (mm Hg)	54.1 ± 17.2	55.6 ± 19.7	0.572
MBP (mm Hg)	96.7 ± 12.5	91.3 ± 16.9	0.040
Central BP (GTF)			
SBP (mm Hg)	120.9 ± 19.1	116.8 ± 25.2	0.251
DBP (mm Hg)	79.5 ± 10.5	73.0 ± 12.6	0.004
PP (mm Hg)	41.3 ± 17.1	43.7 ± 19.3	0.350
AP (mm Hg)	11.5 ± 9.5	13.5 ± 11.0	0.171
Alx (%)	24.9 ± 13.3	27.6 ± 13.3	0.169
Alx@75 (%)	23.2 ± 12.0	25.6 ± 12.5	0.131
SEVR	149.0 ± 33.8	139.2 ± 32.3	0.030
Tr (ms)	135.1 ± 10.1	136.9 ± 11.1	0.217
ED (ms)	309.2 ± 37.6	320.3 ± 28.0	0.084
Pf (mm Hg)	27.5 ± 9.6	28.4 ± 11.2	0.568
Pb (mm Hg)	16.4 ± 7.5	18.2 ± 9.3	0.135
RM	0.59 ± 0.12	0.63 ± 0.12	0.044
PWV			
CF-PWV (m/s)	13.2 ± 3.6	12.0 ± 3.5	0.025

Values are mean ± SD with a corresponding *P* values obtained by paired *t*-test, or median [25th–75th percentiles] with corresponding *P* values obtained by Wilcoxon Signed Rank Test. Abbreviations: Alx@75, heart rate adjusted augmentation index; AP, augmentation pressure; AVF, arteriovenous fistula; BP, blood pressure; CF-PWV, carotid–femoral pulse wave velocity; DBP, diastolic blood pressure; ED, ejection duration; GTF, generalized transfer function; HR, heart rate; MBP, mean blood pressure; Pb, pressure backward; Pf, pressure forward; PP, pulse pressure; RM, reflection magnitude; SBP, systolic blood pressure; SEVR, subendocardial viability ratio; Tr, time of return of reflected wave.

and directionality of change in Z_0 , as well as its contribution to SC cannot be quantified. While, the ability of SC to predict clinical outcomes has yielded conflicting results across various populations,^{23,24} a lower SC has been associated with increased cardiovascular and overall mortality after adjustment for confounding factors (including aortic stiffness) in ESRD patients.¹³ On the other hand, DC represents the rate of system emptying and is inversely proportional to the product of peripheral resistance (*R*) and compliance (*C*). While an increase in compliance may contribute to the decrease in DC, as with SC, the contribution of *R* to the decline in DC remains unclear, due to the interplay with P_∞ .

Using classical wave separation analysis, we observed a nearly significant increase in ejection duration as well as an increase in augmentation index and increased RM. Given the concurrent decrease in carotid–femoral PWV, these changes most likely indicate an increase in ventricular filling and/or contractility, rather than increased wave reflection.^{25,26}

While our findings suggest that AVF could have a negative impact on the RWA parameters that are associated with increased cardiovascular and overall mortality in ESRD, AVF may also some beneficial hemodynamic effects. The aforementioned meta-analysis by Scholz *et al.* provided estimates of AVF-induced changes in systolic, diastolic, and mean BPs,

which were reduced by an average of 8.7, 5.9, and 6.6 mm Hg, respectively.⁸ This reduction in traditional BP measurement has been proposed to explain a slightly slower loss of renal function, following AVF creation, in predialysis ESRD patient.²⁷ Also, epidemiological observational studies using administrative databases show that hemodialysis with an AVF gives a better survival advantage over the use of central venous catheters and remains the vascular access of choice for hemodialysis.^{28,29} However, this view has recently been challenged, as newer approaches associate these findings rather to a better general health of patients referred for AVF creation and who develop a functioning AVF.^{30,31} Taken together, these findings suggest that although AVF creation might be beneficial in preserving residual renal function, it may also increase the risk of cardiovascular and all-cause mortality in ESRD patients. Further studies are needed to determine whether certain subgroups of ESRD patients are more likely to benefit from the creation of an AVF and whether other groups are at higher risk of its consequences.

The study has several strengths that need to be mentioned. In a previous cross-sectional study, we showed an association between the presence of an AVF and higher XSP in dialysis patients. With the current study, we have provided a direct comparison of each individual before and after creation of

Table 3. Carotid reservoir-wave analysis before and after arteriovenous fistulae creation

	Before AVF (N = 38)	After AVF (N = 38)	P
Carotid BP			
SBP (mm Hg)	122.8 ± 20.0	119.4 ± 27.0	0.380
DBP (mm Hg)	79.4 ± 10.4	72.6 ± 12.4	0.003
PP (mm Hg)	43.4 ± 17.6	46.9 ± 21.5	0.212
Carotid artery RWA			
RP carotid (mm Hg)	34.9 [24.5–42.4]	35.8 [23.7–44.8]	0.455
RPI carotid (kPa s)	1,515 [1,088–1,952]	1,672 [1,096–2,179]	0.482
Time to max RP (cs)	30.4 ± 4.4	31.8 ± 3.7	0.083
XSP carotid (mm Hg)	14.1 [11.5–18.9]	17.2 [12.4–22.2]	0.031
XSPI (kPa s ^a)	275.3 [211.7–335.0]	333.75 [240.8–439.1]	0.015
Time to max XSP (cs)	9.0 [8.6–10.7]	10.3 [9.0–11.5]	0.034
SC × 10 ⁻²	20.2 ± 7.1	17.3 ± 7.7	0.025
DC × 10 ⁻²	3.4 ± 1.4	2.9 ± 1.3	0.019
P _∞	75.1 ± 11.0	68.7 ± 17.9	0.009

Values are mean ± SD with a corresponding *P* values obtained by paired *t*-test, or median [25th–75th percentiles] with corresponding *P* values obtained by Wilcoxon Signed Rank Test. Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; DC, diastolic rate constant; P_∞, pressure infinity; PP, pulse pressure; RP, reservoir pressure; RPI, reservoir pressure integral; RWA, reservoir-wave analysis; SBP, systolic blood pressure; SC, systolic rate constant; XSP, excess pressure; XSPI, excess pressure integral.

^aTo convert from kPa s to mm Hg s, multiply by 7.5.

a functioning AVF, supporting a causal link between AVF and increased XSP. The relative short-term follow-up of a maximum of 6 months after AVF was specifically chosen to ensure that AVFs had undergone maturation, providing the desired blood flow, which usually occurs from 2 to 6 months after the procedure. We limited follow-up to no later than 6 months to avoid confounding effect due to significant changes in BP medication and potential chronic adaptation of cardiovascular system to the creation of a high flow AVF. There are also some limitations that need to be underlined. First, the AVF blood flow was not measured at the time of hemodynamic assessment during follow-up. Second, aortic flow and cardiac output were not assessed during the study, thus RP was calculated using a pressure-only approach. Third, there was some heterogeneity regarding changes in medication and dialysis treatment from baseline. However, using a generalized estimating equation model adjusting for the number of antihypertensive medication and dialysis status at baseline, there was no statistically significant difference in hemodynamic response to AVF creation between subgroups. Forth, the pressure-only approach for calculation of RP waves builds on the assumption that resultant XSP is proportional to volume flow rate out of the left ventricle, but this assumption has been recently validated in humans.³² Finally, as for all models, there are conceptual limitations to the RWA that have been reviewed previously,^{33–35} but still many experts agree on the utility of XSPI as a prognostic marker.^{13,14,36–38}

In conclusion, the creation of an AVF has a complex impact on the cardiovascular system, that cannot solely be assessed through traditional brachial systolic and diastolic BPs. Indeed, our study shows that despite a reduction in diastolic BP and aortic stiffness, the creation

of an AVF resulted in increased XSP, a parameter that has been shown to be independently associated with increased adverse clinical outcomes in this population. Besides patients with ESRD, our findings may have clinical implications in treatment of resistant hypertension by AVF, an experimental nonpharmacological approach, for which long-term effectiveness on clinical outcomes remain unknown.^{9,39}

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

- He Y, Shiu YT, Pike DB, Roy-Chaudhury P, Cheung AK, Berceci SA. Comparison of hemodialysis arteriovenous fistula blood flow rates measured by Doppler ultrasound and phase-contrast magnetic resonance imaging. *J Vasc Surg* 2018; 68:1848–1857.e2.
- Casagrande G, Lanzarone E, Miglietta F, Remuzzi A, Fumero R, Costantino ML. Determination of cardiovascular mechanics evolution in the presence of the arteriovenous fistula. *ASAIO J* 2009; 55:484–493.
- Wégria R, Nakano J, McGiff JC, Rochester DF, Blumenthal MR, Muraviev T. Effect of arteriovenous fistula on mean arterial blood pressure, coronary blood flow, cardiac output, oxygen consumption, work and efficiency. *Am J Physiol* 1958; 193:147–150.
- Bos WJ, Zietse R, Wesseling KH, Westerhof N. Effects of arteriovenous fistulas on cardiac oxygen supply and demand. *Kidney Int* 1999; 55:2049–2053.
- Unger P, Velez-Roa S, Wissing KM, Hoang AD, van de Borne P. Regression of left ventricular hypertrophy after arteriovenous fistula closure in renal transplant recipients: a long-term follow-up. *Am J Transplant* 2004; 4:2038–2044.
- Rao NN, Stokes MB, Rajwani A, Ullah S, Williams K, King D, Macaulay E, Russell CH, Olakkengil S, Carroll RP, Faull RJ, Teo KSL, McDonald SP, Worthley MI, Coates PT. Effects of arteriovenous fistula ligation on cardiac structure and function in kidney transplant recipients. *Circulation* 2019; 139:2809–2818.
- Harada T, Obokata M, Kurosawa K, Sorimachi H, Masuda K, Ishida I, Ito K, Ogawa TM, Negishi K. Relationships of high cardiac output with ventricular morphology myocardial energetics, and energy costs in patients on hemodialysis. *Int J Cardiovasc Imaging* 2019; 35:469–479.
- Scholz SS, Vukadinović D, Lauder L, Ewen S, Ukena C, Townsend RR, Wagenpfeil S, Böhm M, Mahfoud F. Effects of arteriovenous fistula on blood pressure in patients with end-stage renal disease: a systematic meta-analysis. *J Am Heart Assoc* 2019; 8:e011183.
- Lobo MD, Sobotka PA, Stanton A, Cockcroft JR, Sulke N, Dolan E, van der Giet M, Hoyer J, Furniss SS, Foran JP, Witkowski A, Januszewicz A, Schoors D, Tsioufis K, Rensing BJ, Scott B, Ng GA, Ott C, Schmieder RE; ROX CONTROL HTN Investigators. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. *Lancet* 2015; 385:1634–1641.
- Tyberg JV, Bouwmeester JC, Parker KH, Shrive NG, Wang JJ. The case for the reservoir-wave approach. *Int J Cardiol* 2014; 172:299–306.
- Parker KH, Alastruey J, Stan GB. Arterial reservoir-excess pressure and ventricular work. *Med Biol Eng Comput* 2012; 50:419–424.
- 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.
- Fortier C, Côté G, Mac-Way F, Goupil R, Desbiens LC, Desjardins MP, Marquis K, Hametner B, Wassertheurer S, Schultz MG, Sharman JE, Agharazii M. Prognostic value of carotid and radial artery reservoir-wave parameters in end-stage renal disease. *J Am Heart Assoc* 2019; 8:e012314.
- 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.
- Paré M, Goupil R, Fortier C, Mac-Way F, Madore F, Marquis K, Hametner B, Wassertheurer S, Schultz MG, Sharman JE, Agharazii M. Determinants of increased central excess pressure in dialysis: role of dialysis modality and arteriovenous fistula. *Am J Hypertens* 2020; 33:137–145.
- Utescu MS, LeBoeuf A, Chbinou N, Desmeules S, Lebel M, Agharazii M. The impact of arteriovenous fistulas on aortic stiffness in patients with chronic kidney disease. *Nephrol Dial Transplant* 2009; 24:3441–3446.
- Chen CH, Nevo E, Fetis 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.
- Utescu MS, Couture V, Mac-Way F, De Serres SA, Marquis K, Larivière 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.
- 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.
- Hametner B, Parragh S, Weber T, Wassertheurer S. Wave intensity of aortic root pressure as diagnostic marker of left ventricular systolic dysfunction. *PLoS One* 2017; 12:e0179938.
- 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.
- 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.
- 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.
- 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.
- Sharman JE, Davies JE, Jenkins C, Marwick TH. Augmentation index, left ventricular contractility, and wave reflection. *Hypertension* 2009; 54:1099–1105.
- Fok H, Guilcher A, Li Y, Brett S, Shah A, Clapp B, Chowienczyk P. Augmentation pressure is influenced by ventricular contractility/relaxation dynamics: novel mechanism of reduction of pulse pressure by nitrates. *Hypertension* 2014; 63:1050–1055.
- Dupuis M-È, Laurin L-P, Goupil R, Bénard V, Pichette M, Lafrance J-P, Elftouh N, Pichette V, Nadeau-Fredette A-C. Arteriovenous fistula creation and glomerular filtration rate in advanced kidney disease: a matched cohort study. *Kidney360* 2020; 2:42–49.
- Polkinghorne KR, McDonald SP, Atkins RC, Kerr PG. Vascular access and all-cause mortality: a propensity score analysis. *J Am Soc Nephrol* 2004; 15:477–486.
- Ozeki T, Shimizu H, Fujita Y, Inaguma D, Maruyama S, Ohyama Y, Minatoguchi S, Murai Y, Terashita M, Tagaya T. The type of vascular access and the incidence of mortality in Japanese dialysis patients. *Intern Med* 2017; 56:481–485.
- Grubbs V, Wasse H, Vittinghoff E, Grimes BA, Johansen KL. Health status as a potential mediator of the association between hemodialysis vascular access and mortality. *Nephrol Dial Transplant* 2014; 29:892–898.
- Ravani P, Palmer SC, Oliver MJ, Quinn RR, MacRae JM, Tai DJ, Pannu NI, Thomas C, Hemmelgarn BR, Craig JC, Manns B, Tonelli M, Strippoli GF, James MT. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol* 2013; 24:465–473.
- 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.
- Westerhof N, Segers P, Westerhof BE. Wave separation, wave intensity, the reservoir-wave concept, and the instantaneous wave-free ratio: presumptions and principles. *Hypertension* 2015; 66:93–98.
- Mynard JP, Smolich JJ. The case against the reservoir-wave approach. *Int J Cardiol* 2014; 176:1009–1012.
- Westerhof BE, Westerhof N. Waves and Windkessels reviewed. *Artery Res* 2017; 18:102–111.
- Segers P, O'Rourke MF, Parker K, Westerhof N, Hughes A. Towards a consensus on the understanding and analysis of the pulse waveform: results from the 2016 Workshop on Arterial Hemodynamics: past, present and future. *Artery Res* 2017; 18:75–80.
- Hughes A, Parker K. The modified arterial reservoir: an update with consideration of asymptotic pressure (P_{∞}) and zero-flow pressure (P_{zf}). *Proc Inst Mech Eng H* 2020; 234:1288–1299.
- 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; 6:1–11.
- MacRae JM, Pandeya S, Humen DP, Krivitski N, Lindsay RM. Arteriovenous fistula-associated high-output cardiac failure: a review of mechanisms. *Am J Kidney Dis* 2004; 43:e17–e22.