The impact of arteriovenous fistulas on aortic stiffness in patients with chronic kidney disease

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Abstract
Background. The creation of arteriovenous fistulas (AVF) in patients with advanced chronic kidney disease (CKD) has been shown to have adverse effects on their central pulse wave profile suggesting a likely increase in arterial stiffness. The aim of the present study was to directly evaluate the effect of AVF on arterial stiffness.

Method. Thirty-one stage-5 CKD patients underwent haemodynamic assessment prior to and 3 months after creation of AVF. Haemodynamic assessment included measurement of blood pressure (BP), central and carotid pulse wave profile analysis, and carotid-femoral and carotid-radial pulse wave velocities (PWV). Pre-AVF and post-AVF haemodynamic parameters were compared using the Wilcoxon signed-rank test or the paired Student t-test as appropriate. Pearson correlations, single and multiple linear regressions, were used to determine the association between variables.

Results. After creation of AVF, peripheral and central BPs decreased without significant change in heart rate (HR) or pulse pressure. Carotid-femoral PWV (c-fPWV) fell from 13.2 ± 4.1 to 11.7 ± 3.1 m/s (P < 0.001). There was an increase in the central augmentation index (20.8% ± 11.5 versus 23.7% ± 11.6, P = 0.07) of borderline significance, and a significant reduction in the subendocardial viability ratio (153% ± 34 versus 143% ± 32, P < 0.05), which was mainly the result of a decrease in the diastolic pressure time index (DPTI) without any significant change in the diastolic duration. The reduction of c-fPWV was explained by changes in mean BP and HR (R² = 0.29). The reduction in DPTI was related to changes in central diastolic BP and changes in end-systolic BP (adjusted R² = 0.87). The significant improvement in aortic stiffness was mostly the result of the relative reduction of c-fPWV in the subgroup of patients with baseline c-fPWV above the median value of 13 m/s.

Conclusion. The creation of AVF is associated with a passive improvement of aortic stiffness especially in patients with stiffer arteries. This improvement in arterial stiffness could potentially be beneficial to the cardiovascular system despite an associated deterioration in the aortic pulse wave profile.

Keywords: arterial stiffness; arteriovenous fistula; augmentation index; chronic kidney disease; pulse wave velocity

Introduction
Cardiovascular complications are the main cause of morbidity and mortality in patients with advanced chronic kidney disease (CKD). The increased cardiovascular morbidity in this population cannot be fully explained by classical risk factors, suggesting that other factors may also play a role. Among these, increased aortic stiffness, as measured by carotid-femoral pulse wave velocity (c-fPWV), and enhanced and early central pulse wave reflection, as measured by the aortic augmentation index (AIx), have been shown to be predictors of cardiovascular mortality in chronic haemodialysis patients [1–6]. Despite the fact that an AVF is still considered to be the vascular access of choice, it does create a high flow and low resistance vascular system that increases cardiac output and may lead to left ventricular hypertrophy [7–10]. In addition, AVF can also alter the central pulse profile leading to decreased cardiac oxygen supply that could be deleterious to cardiovascular health in this population [11–14].

A longitudinal study by Savage et al. [13] showed a reduction in the diastolic pressure time index (DPTI) 3 months after the AVF was created without any significant change in the systolic pressure time index (SPTI). These changes resulted in a significant reduction in the subendocardial viability ratio (SEVR). However, while AIx increased after AVF creation, it failed to reach statistical significance in this study that included only nine patients [13]. In addition, Ferro et al. [12] described an association between the increased AIx and the presence of a functioning AVF in a cross-sectional study involving renal transplant recipients.
It is thought that increased central pulse pressure, early wave reflection, increased cardiac workload and reduced myocardial perfusion are some of the physiological consequences of aortic stiffness that may be clinically relevant to cardiovascular disease. Therefore, an increase in aortic stiffness is expected to reduce the travel time of the reflecting wave thereby increasing the AIx and decreasing the SEVR. Based on increased AIx and reductions in the SEVR, results from previous studies suggest that arterial stiffness may be either stable or increased in patients with AVF. Other factors apart from arterial stiffness, such as ventricular systolic duration and peripheral vascular tone, however, are important determinants of AIx [15–19].

In light of these observations, we hypothesized that a reduction in DPTI and a potential increase in AIx after AVF creation should be accompanied by an increase in aortic stiffness as measured by assessment of $c_{f}P_{\text{PWV}}$. To our knowledge, the effect of AVF on aortic stiffness has never been studied directly. The aim of the present study was to assess the impact of AVF on aortic stiffness and central pulse wave profile (PWP) prior to and 3 months after creation of AVF.

**Methods**

**Study design and patient population**

$c_{f}P_{\text{PWV}}$ and carotid-radial pulse wave velocity ($c_{f}P_{\text{PWV}}$) and PWP were performed within a month of AVF creation (pre-AVF) and 3 months after surgery (post-AVF), as described below. This longitudinal study was conducted at the Centre Hospitalier Universitaire de Québec, L’Hôtel-Dieu de Québec Hospital between October 2004 and 2007. All stage-5 CKD patients who were scheduled for their first AVF creation were invited to participate. Exclusion criteria were no functional AVF 3 months following the surgical intervention, extreme blood pressure (BP) values (systolic pressure $>\pm 190$ mmHg or $<80$ mmHg), severe congestive heart failure and patients having had a previous AVF. In addition, patients with acute heart failure, stroke or acute coronary syndrome in the preceding 3 months and during the study period were excluded. Demographics, medical history, medication and laboratory parameters were assessed from the patient’s chart. All patients gave informed consent to participate in this study, which was also approved by the ethic committee of the institution.

During the study period, 48 patients were enrolled. Seventeen patients were excluded for the following reasons: non-functional AVF ($n = 7$), transfer to another institution ($n = 7$), severe cardiac failure ($n = 1$), death ($n = 1$) and extremely low BP ($n = 1$). Among the 31 patients who completed the study, 16 were already on haemodialysis (median of 6 months) and 15 were being followed up in the predialysis clinic at the time of the follow-up visit. A total of 15 subjects had started on haemodialysis (median of 6 months) and 15 were being followed up in the predialysis clinic 6 months) or without AVF, we also used the non-processed arterial wave profile of the common carotid artery (caPWP) as a surrogate for cPWP ($n = 29$).

The pulse wave analysis was performed three times, and the average of the three measurements was used for analysis. Then, $c_{f}P_{\text{PWV}}$ and caPWP were assessed using the same system to determine the following parameters: central mean pressure of systole, central mean pressure of diastole, augmented pressure, heart rate adjusted AIx, ejection duration (ED) and diastolic duration (DD) as shown in Figures 1 and 2. In addition, the SERV was calculated by the dividing DPTI by SPTI (DPTI/SPTI) as shown in Figure 2. In our laboratory, the intrasession and intersession coefficients of variation were 2.9% and 8.9%, respectively.

PWP was assessed by arterial tonometry using the SphygmoCor® PXP Pulse Wave Analysis System (AtCor Medical Pty Ltd, West Ryde, Australia). Briefly, a Millar tonometer was placed over the radial artery to obtain a peripheral PWP (pPWP). The mean BP (MBP) was then derived using radial artery pulse wave analysis and brachial systolic and diastolic BPs. Thereafter, the central PWP (cPWP) was estimated by using the generalized transfer function [24]. However, in order to bypass the prerequisite validity of generalized transfer function in the advanced CKD patient, with or without AVF, we also used the non-processed arterial wave profile of the common carotid artery (caPWP) as a surrogate for cPWP ($n = 29$).

The pulse wave analysis was performed three times, and the average of the three measurements was used for analysis. Then, $c_{f}P_{\text{PWV}}$ and caPWP were analysed using the same system to determine the following parameters: central mean pressure of systole, central mean pressure of diastole, augmented pressure, heart rate adjusted AIx, ejection duration (ED) and diastolic duration (DD) as shown in Figures 1 and 2. In addition, the SERV was calculated by the dividing DPTI by SPTI (DPTI/SPTI) as shown in Figure 2. In our laboratory, the intrasession and intersession coefficients of variation for AIx were 2.6% and 6%, respectively.

**Haemodynamic measurements**

After 10 min of rest in the supine position, the brachial artery BP was recorded six times consecutively, with a 2-min interval between each measurement, using an automatic sphygmomanometer BPM-100 (BP-Tru, Coquitlam, Canada). The average of the last five measurements was used as brachial systolic and diastolic BPs [21,22]. All measurements (BP, PWP and PWV) were done on the opposite side of the expected or existing AVF. In haemodialysis patients, all measurements were done just prior to the second haemodialysis session of the week.

The $c_{f}P_{\text{PWV}}$ was determined according to the foot-to-foot method, using the Complior® device (Artech Medical, Pantin, France) as previously validated [23]. Briefly, two transducers were placed, one at the base of the neck over the common carotid artery and one over the femoral artery. The software automatically determines the transit time between the carotid and the femoral pulse waves by using the second derivative algorithm to identify the foot of the wave. The distance was assessed by direct measurement of the superficial distance between the two probes. Each measurement of PWV (m/s) was expressed as the mean of 8–10 consecutive cardiac cycles. The average of three separate measurements was used for analysis. The $c_{f}P_{\text{PWV}}$ was determined using the same technique by positioning the second sensor on the common carotid artery at the level of the wrist in our laboratory.

Data analysis was performed using the SPSS software (version 10.0 for Windows, SPSS Inc., Chicago, IL, USA). Data were expressed as means ± SD unless otherwise specified. Pre-AVF and post-AVF haemodynamic parameters were compared using the Wilcoxon signed-rank test or the paired student t-test as appropriate. The McNemar test was used to compare changes between groups. The McNemar test was used to assess any changes in the class of medication. Pearson correlations, single and multiple linear regressions, were used to determine the association between variables. A two-sided $P$-value of $<0.05$ was considered to be statistically significant. Using a two-sided one-sample $t$-test, a sample size...
AVF and aortic stiffness in CKD

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>20 (65%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 15</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 13.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.8 ± 5.6</td>
</tr>
<tr>
<td>Smoking (active or past history)</td>
<td>15 (48%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (84%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Haemodialysis at the beginning of the study</td>
<td>16 (52%)</td>
</tr>
<tr>
<td>Haemodialysis at the end of the study</td>
<td>22 (71%)</td>
</tr>
</tbody>
</table>

Values are expressed as number (percentage) or mean ± SD.

of 30 subjects would provide 91% power to detect a difference of 1.5 m/s in c-fPWV between the two periods, assuming a standard deviation of 2.5 with a significance level (alpha) of 0.05.

Results

Twenty men and 11 women, with a mean age of 58 ± 15 years, were studied. The baseline characteristics are listed in Table 1. The peripheral, central and carotid haemodynamic parameters and the PWV measurements prior to and 3 months following the AVF creation are summarized in Table 2.

There was a significant reduction in the peripheral systolic and diastolic CVPs by 7.3 ± 18.5 and 6.8 ± 10.8 mmHg, respectively (P < 0.05). The central systolic BP decreased from 119.8 ± 17.8 to 113.9 ± 22.9 mmHg (P = 0.07), and the central diastolic BP decreased from 78.6 ± 11.3 to 72.0 ± 12.3 mmHg (P < 0.005); however, there were no significant changes in heart rate (HR) in peripheral, central and carotid pulse pressures. The c-fPWV fell from 13.2 ± 4.1 to 11.7 ± 3.1 m/s (<0.001), but the c-rPWV showed only a slightly non-significant reduction (9.3 ± 2.2 versus 8.9 ± 1.6 m/s, P = 0.16). In contrast, despite the reduction in MBP and c-fPWV, there was a non-significant increase in the central AIx (20.8 ± 11.3 versus 23.7% ± 11.6, P = 0.08) and the carotid AIx (12.1% ± 11.8 versus 14.1% ± 15.8, P = 0.48). There was no significant change in the augmentation pressure and the timing of wave reflection. There was, however, a slight increase in the central systolic duration that failed to reach statistical significance (305 ± 42 versus 318 ± 30 ms, P = 0.08).

The DPTI decreased significantly and SPTI remained stable. As a result, there was a significant reduction in both central and carotid SEVRs (153% ± 34 versus 143% ± 32, P < 0.05 and 159% ± 33 versus 146% ± 26, P < 0.005, respectively). These results were consistent among the various groups of patients: younger or older than...
Table 3. Pre and post-AVF laboratory parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-AVF</th>
<th>Post-AVF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mmol/L)</td>
<td>22.5 ± 8.6</td>
<td>20.3 ± 6.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>590 ± 239</td>
<td>595 ± 235</td>
<td>0.84</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.20 ± 0.17</td>
<td>2.25 ± 0.16</td>
<td>0.19</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.78 ± 0.78</td>
<td>1.67 ± 0.33</td>
<td>0.47</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>38.3 ± 4.1</td>
<td>40.4 ± 5.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PTH (ng/L)</td>
<td>315 ± 272</td>
<td>324 ± 253</td>
<td>0.80</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>108 ± 15</td>
<td>118 ± 10</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

50 years of age and with or without previous cardiovascular disease, diabetes or haemodialysis.

Using linear regression, the reduction in end-systolic BP was the most important determinant of change in DPTI (adjusted $R^2 = 0.80$). In multivariate analysis, both end-systolic and diastolic BPs remained the most significant determinants of change in DPTI (adjusted $R^2 = 0.87$). The change in the central diastolic BP was the single most important determinant of the change in c-fPWV ($R^2 = 0.29$). However, physiologically it is more appropriate to adjust PWV for MBP and HR ($R^2 = 0.29$). After adjustment for changes in MBP and HR, there were no significant differences in either c-fPWV or c-ePWV.

Figure 3 shows the relative changes in c-fPWV, central diastolic and MBPs according to the baseline c-fPWV below or above the median value of 13 m/s. The figure clearly demonstrates that patients with higher initial c-fPWV were the most likely to experience a relative reduction of c-fPWV after creation of AVF.

After 3 months of follow-up, the mean access blood flow rate was 1050 ± 410 mL/min. There was no relationship, however, between the access blood flow rate and the change in BP, AIx, timing of wave reflection, DPTI or c-fPWV. The medication and laboratory parameters before and after AVF creation are listed in Tables 3 and 4. The number and class of antihypertensive drugs were similar throughout the study period. During the same period, there was no significant change in patient weight (78.2 ± 13.6 versus 78.0 ± 13.4 kg, $P = 0.73$); however, there was a slight but significant increase in the serum albumin level (38.3 ± 4.1 versus 40.4 ± 5.2 g/L, $P < 0.01$). No correlation was observed between the degree of change in the albumin level and the degree of change in systolic, diastolic or MBPs.

Discussion

The results of the present study show that the creation of an AVF in stage-5 CKD patients was associated with a reduction in both peripheral and central BPs and, for the first time, a reduction in aortic stiffness. The relative reduction in aortic stiffness was most significant in patients with stiffer arteries; however, this improvement in aortic stiffness was not associated with the expected improvement of arterial PWP. In fact, there was no change in the timing of wave reflection in addition to a non-significant increase in the central AIx and a significant reduction in the SEVR.

Aortic stiffness has been shown to have a negative impact on cardiovascular morbidity and mortality in patients with hypertension and in patients on haemodialysis [1,25]. As a structural change in arterial wall composition is highly unlikely during this short period of follow-up, it is believed that reduction of c-ePWV is due to BP-related change in arterial stiffness. This reduction in BP may relieve the tension from the collagen fibres and put the aorta in a more favourable pressure–diameter relationship, resulting in a passive improvement in aortic stiffness [16]. Indeed, the significant decrease in c-ePWV is best predicted by the reduction in central diastolic BP ($R^2 = 0.29$), or by changes in MBP and HR ($R^2 = 0.29$).

Normally, an improvement in aortic stiffness is expected to increase the travel time of the reflecting wave, reduce the AIx and increase the SEVR. However, this expected response is not supported by our findings. Our results show a statistically non-significant increase in the central AIx ($P = 0.08$) after AVF creation. This is in keeping with the
results published by Ferro et al. [12] in which they found a clear association between increased AIx and the presence of a functioning AVF in renal transplant recipients. A high AIx increases left ventricular after load and may potentially be a contributing factor in AVF-induced left ventricular hypertrophy [10,26,27]. However, in addition to PWV, other factors such as ventricular systolic duration and peripheral vascular tone are important determinants of AIx [15–19]. It is therefore hypothesized that other vascular compensatory mechanisms may play a role in outweighing the effects of the decrease in c-fPWV on central PWP. Indeed, previous studies have demonstrated that AIx can change independently of aortic PWV during administration of nitroglycerin or angiotensin II, which primarily has peripheral effects [28,29]. In this regard, AIx is no longer considered to be a reliable marker of arterial stiffness [29,30]. The absence of reduction in AIx after the creation of AVF in the present study could be accounted for by an increase in regional vascular tone, possibly splanchnic, that would proximalize the arterial reflection sites [19]. This contention is further supported by the association of AVF with reflex vasomotor change in blood vessels and increased sympathetic activity, which could lead to peripheral vasoconstriction and proximal displacement of the reflection sites in the aorta [31,32]. In addition, the constant timing of wave reflection despite a decrease in PWV is consistent with this hypothesis. In the study by Savage et al. [13], despite a rise in BP, there was a non-significant increase in AIx after creation of AVF in nine stage-5 CKD patients who were followed up prospectively for up to 6 months. Interestingly, the levels of baseline and follow-up AIx are similar in our present study as compared to the study by Savage et al. [13]. These findings suggest a potentially clinically relevant increase in AIx that does not reach statistical significance due to a small sample size.

In agreement with previous studies, our results also confirmed a reduction in the SEVR (DPTI/SPTI), which is a reflection of deteriorating endocardial/epicardial blood flow ratios [33]. Indeed, it was shown by Bos et al. [11] that acute compression of AVF is associated with an increase in the SEVR. In this study, since there was a reflex reduction in HR, it could be argued that the HR modification might interfere with the proper interpretation of the findings [11]. However, these results were also validated in the study by Savage et al. [13], who reported a reduction in the SEVR immediately after AVF creation that persisted throughout the 6 months of follow-up. As observed in previous studies, the reduction in the SEVR is mainly the result of a decrease in DPTI, as there was no significant change in the SPTI after 3 months. The change in DPTI is strongly related to changes in central or carotid end-systolic pressure (Figure 2), with a $R^2$ of 0.80. The addition of the diastolic BP value into the equation, although significant, increased the adjusted $R^2$ by only 0.07.

Taken together, there are presently no data supporting the impact of the reduced SEVR on mortality. In addition, contrary to the study by London et al. [4], the study by Covic et al. [34] failed to show a statistically significant impact of AIx on mortality in a group of middle-aged patients on haemodialysis. Therefore, negative clinical impact of AVF on central PWP should be interpreted with caution, especially in light of beneficial effect of AVF on aortic stiffness. Although there are no data to directly support that AVF-induced reduction in aortic stiffness is beneficial in terms of survival, data from Guérin et al. [35] suggest that a BP-dependent reduction in c-fPWV was associated with a better survival in a group of haemodialysis patients. It may therefore be argued that the cardiovascular survival benefit of AVF could be due, at least partly, to an improvement in aortic stiffness, especially in the group of patients at higher risk of mortality [36]. However, in the study by Guérin et al. [35], the reduction of c-fPWV was a result of pharmacological BP reduction, and therefore, the extension of these findings into BP reduction by any other means should be interpreted with caution.

There are also a number of other confounding factors in our study that need to be discussed. First, there was a lack of strict control on the anti-hypertensive drug therapies. However, BP medication did remain relatively constant and it is unlikely that they played a significant role in the main findings of the study. Second, although patient weight remained stable during the study period, there was an increase in serum albumin level that might indicate a better nutritional status or a better control of fluid overload. However, we found no association between the degree of decrease in the BP and the degree of increase in the albumin level that might suggest a significantly better control of fluid overload. Third, we acknowledge that six patients started HD and that HD might have had a significant influence on vascular function. In order to address this bias, we pooled data from patients who remained in the same treatment category and found similar findings. Fourth, although this is the largest longitudinal study, it was not designed to detect a small BP-independent (or structural) change in arterial stiffness because of the relatively short duration of the study that does not take into account the chronic adaptation of the cardiovascular system to an AVF. The strength of a longer duration of follow-up, however, might be hampered by the loss of AVF, loss of patients, change in medications and intercurrent illness. Finally, an evaluation of cardiac output and aortic diameter before and after creation of AVF could have shed more light on the comprehensive interpretation of these findings.

In summary, our findings show, for the first time, that AVF creation is associated with a BP-related reduction in aortic stiffness without the expected positive effect on central haemodynamic parameters. Future studies are required to re-evaluate cardiovascular risk assessment by aortic stiffness and central PWP analysis with regard to the type of vascular access.

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Conflict of interest statement. None declared.
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