Nephrol Dial Transplant (2011) 26: 3296–3302
doi: 10.1093/ndt/gfq851
Advance Access publication 11 February 2011

Original Articles

NDT
Nephrology Dialysis Transplantation

Effects of arteriovenous fistula formation on arterial stiffness and cardiovascular performance and function

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Abstract

Background. Native arteriovenous fistula (AVF) is the vascular access of choice and its use cf. catheters is associated with sustained reduction in mortality. This may be due to factors beyond dialysis catheter-associated sepsis. This study aimed to investigate the impact of AVF formation on the spectrum of cardiovascular factors that might be important in the pathophysiology of cardiovascular diseases in chronic kidney disease (CKD) patients.

Methods. We recruited 43 pre-dialysis patients who underwent AVF formation. Patients were studied 2 weeks prior to AVF operation and 2 weeks and 3 months post-operatively. Haemodynamic variables were measured using pulse wave analysis, carotid femoral pulse wave velocity (CF-PWV) by applanation tonometry and AVF blood flow by Doppler ultrasound. Bioimpedence analysis was performed and patients underwent serial transthoracic echocardiography.

Results. AVF formation was successful in 30/43 patients. Two weeks post-operatively, total peripheral resistance decreased ($-17 \pm 18\%$, $P = 0.001$), stroke volume tended to rise (12 ± 30 mL, $P = 0.053$) and both heart rate (4 ± 8 bpm, $P = 0.01$) and cardiac output (1.1 ± 1.5 L/min, $P = 0.001$) increased. Systolic and diastolic blood pressures (BPs) reduced (-9 ± 18 mmHg; -9 ± 10 mmHg; $\leq P = 0.006$) and CF-PWV reduced (-1.1 ± 1.5 m/s, $P = 0.004$). Left ventricular ejection fraction (LVEF) increased ($6 \pm 8\%$, $P < 0.001$). All the observed changes were largely maintained after 3 months. No change in hydration status/body composition was observed.

Conclusions. AVF formation resulted in a sustained reduction in arterial stiffness and BP as well as an increase in LVEF. Overall, post-AVF adaptations might be characterized as potentially beneficial in these patients and supports the widespread use of native vascular access, including older or cardiovascular compromised individuals.

Keywords: arterial stiffness; arteriovenous fistula; cardiac output; pulse wave velocity; vascular access

Introduction

Upper extremity native arteriovenous fistula (AVF) is the vascular access of choice, supported by the Kidney Dialysis Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation [1]. The use of definitive vascular access in haemodialysis (HD) patients, rather than tunnelled central venous catheters, is associated with sustained reduction in mortality [2]. This difference in survival has previously been entirely attributed to differences in access-related sepsis. Little is currently known concerning the systemic structural and functional cardiovascular changes that occur as a consequence of AVF formation. Several case reports indicate that high fistula flows can be associated with inducing a high cardiac output (CO) status and subsequent cardiac failure [3–5], and the presence of an AVF may modulate sympathetic outflow [4] and markers of volume status such as B-type natriuretic peptide [6].

Cardiac failure develops in as many as 25–50% of HD patients and confers a dramatic reduction of survival [7]. HD patients are particularly susceptible to demand myocardial ischaemia. In addition to the high prevalence of coronary atheroma [8], diabetic dialysis patients have been shown to have a reduced coronary flow reserve, even in the absence of coronary vessel stenoses [9]. Increased arterial stiffness leads to alteration of central blood pressures (BPs), increasing myocardial oxygen demand while reducing supply due to the reduction in diastolic BP reinforcement from the returning pressure wave. These factors increase the risk of myocardial hypoperfusion [10]. Studies of myocardial blood flow during HD in adult patients with normal coronary angiograms [11] and dialysis-induced cardiac segmental ischaemia in children on HD [12] have highlighted the existence of demand myocardial ischaemia during HD in the absence of atheromatous large vessel coronary artery disease. Such repeated injury results in systolic dysfunction, increased cardiac arrhythmias and markedly reduced survival [13, 14].

The impact of AVF creation on arterial stiffness (as a critical determinant of demand ischaemia and increased mortality) in chronic kidney disease (CKD) patients with no previous dialysis experience has not been extensively studied. The few studies that have been performed have tended to be small, focus on only limited elements of the cardiovascular system and/or rely on extrapolation of data derived from closure of troublesome AVFs in established HD patients.

The aim of this study was to prospectively investigate the impact of AVF formation on arterial stiffness, other key haemodynamic variables and echocardiographic indices in predialysis patients, acutely and after AVF maturation (3 months).

Materials and methods

Subjects

Patients who were referred for AVF formation were approached from a single low clearance clinic over a recruitment period of 18 months. The study cohort consisted of 43 pre-dialysis patients with CKD Stages 4 and 5. Main inclusion criteria were >18 years, clinically stable, did not receive any dialysis modality before this study and provided written informed consent. There were no significant exclusion criteria (except previous cardiac transplantation). Successful AVF formation was defined as an arteriovenous anastomosis with clinical (palpation and auscultation) and Doppler ultrasound confirmed blood flow 2 weeks post-operatively. The project was approved by the Local Regional Ethics Committee.

All the subjects were studied 2 weeks prior to their planned operation date and then 2 weeks and 3 months post-operatively. No acute illness or major post-operative complication was recorded during the follow-up period. In addition, all medications remained unchanged during the study period.

Haemodynamic and arterial stiffness studies

On the study days, patients were allowed to rest in bed in a dedicated clinical research facility for 15 min before data collection. Three BP recordings were taken using an automated AND® UA-767 oscillometric device on the non-fistula arm. Haemodynamic measurements were taken non-invasively using Finometer® (Finapres Medical Systems, Amsterdam, The Netherlands). This technology uses pulse wave analysis obtained at the digital artery to measure beat-to-beat BP and heart rate (HR). Modelflow™-derived changes in CO, stroke volume (SV) and total peripheral resistance (TPR) were calculated using a reconstructed aortic pulse wave. Measurement of CO has been demonstrated to compare well with echocardiogram-based measures in end-stage renal disease patients [15].

Carotid femoral pulse wave velocity (CF-PWV), aortic augmentation index (AIx) and central BPs were measured using Sphygmacor® (AtCorTM; PWV Inc., West Ryde, Australia). The software has a validated integral transfer function that can be applied to derive a central aortic waveform. This can be utilized to calculate central BPs and AIx [16]. All CF-PWV and AIx measurements were repeated three times and the average was calculated.

Echocardiographic and Doppler ultrasound studies

All echographic studies were conducted using Vivid 3® ultrasound machine with a dedicated cardiac probe (1.5–3.6 MHz 3S probe; GE Medical Systems, Munich, Germany). M-mode ventricular parameters were measured according to the recommendations of the American Society of Echocardiography [17]. A single experienced operator carried out all measurements with the patients in the left lateral position. Echocardiographic evaluations were performed by another experienced observer, who was completely blinded to operation outcome. Left ventricular ejection fraction (LVEF) was calculated using left ventricular diameters at end systole and end diastole obtained from M-Mode images.

All vascular flow measurements were done by a single experienced user using a dedicated vascular probe (4–10 MHz 10L-Linear Probe; GE Medical Systems). All patients were studied in sitting position. Examination followed the blood flow from the afferent artery into the anastomosis, the access and draining veins. All the flow rate measurements were done in a straight access segment free of turbulent flow. The transverse diameter of the vessel was multiplied by the average flow velocity to obtain the volume flow rate in millilitre per minute.

Body composition and blood tests

Bioelectrical impedance was measured using InBody S20® body composition analyser (Biospace, Seoul, Korea) to detect changes in total body water and soft tissue composition. Blood samples collected during each session included full blood count, electrolytes, urea, creatinine, bone profile, albumin, C-reactive protein and troponin T.

Sample size estimation. Sample size was calculated with reference to the primary outcome of change in PWV with formation of an AVF. A change of 1 m/s was identified as being potentially clinically significant. Power calculation was performed using data generated in HD patients within this centre utilizing identical investigation methods [18]. Mean CF-PWV of patients with predialysis CKD was 9 m/s with a SD of 1.6 m/s. A sample size of 29 was required to detect a difference in PWV of 1 m/s with a significance level of 5% at 90% power. Planned study number was 45 patients, to allow for primary failure of access and eventualities, such as patient death or withdrawal.

Statistical methods. Results are expressed as mean ± SD. For comparing data, paired *t*-test was used to compare the preoperative and post-operative data within individuals in both successful and unsuccessful groups. An alpha error at $P < 0.05$ was judged to be significant. Simple linear relationship between different variables was measured using Pearson's or Spearman's correlation. Stepwise multivariate regression analysis was performed to determine independent predictors of Qa and change in CF-PWV (ΔPWV). Factors for the models were considered because either they were established determinants of the dependant variables (ΔPWV, Qa) or they achieved significant value in the initial univariate linear regression analysis. Based on these earlier initial regression analysis, factors were only included if they achieved a significance value of <0.05.

One-way repeated measures analysis of variance (ANOVA) was used to investigate the effect of AVF creation where the element of time was given as discrete time points on different haemodynamic variables.

The value of CF-PWV was adjusted to HR and mean arterial pressure (MAP) using linear regression analysis. All statistical analyses were was performed using the SPSS software package, version 12 (SPSS Inc.).

Results

Baseline characteristics

All patients had an end-to-side anastomosis. Operations were done as a day-case procedure under local anaesthetic. One patient died before attending the second study session from unrelated causes. Two patients who had an unsuccessful AVF operation initially were re-recruited and consequently had a successful AVF formed.

Thirty of forty-three patients had a successful AVF operation performed (22/29 brachiocephalic, 3/3 brachiobasilic and 5/11 radiocephalic). Patients with failed AVF (13/43) procedures were utilized as sham-operated controls. Demographics, biochemical, haemodynamic and preoperative blood vessels measurements from which the AVF was constructed in both the successful and unsuccessful groups are listed in Table 1.

Mean age was 68 ± 13 years. Forty per cent were female and 60% male. The causes for CKD among the cohort were diabetic nephropathy 37%, primary glomerulonephritis 14%, unknown 21% and other causes (polycystic disease, vasculitis, renovascular diseases and obstructive uropathy) 28%. None of the patients in the cohort had a documented clinical diagnosis of cardiac failure. However, baseline echocardiography revealed that ejection fraction (EF) was <50% in 15/30 patients with successful AVF formation.

Haemodynamic indices and arterial stiffness (2 weeks post-AVF formation)

The baseline and post-operative haemodynamic data in both groups are summarized in Table 2. All the significant

haemodynamic changes occurred only in patients who had a successful AVF formation with no detectable alteration in any of the variables in the group who had undergone an unsuccessful procedure.

Both peripheral systolic and diastolic BPs were significantly decreased (−9.7 ± 18 and −9.5 ± 10.3 mmHg, respectively). There was a similar significant reduction in central systolic (−12.4 ± 16.2 mmHg) and central diastolic BPs (−7.8 ± 7.9 mmHg).

Arterial stiffness markedly decreased with both CF-PWV (−1.1 ± 1.5 m/s, P = 0.004) and AIx (−3.7 ± 5.4%, P = 0.002) significantly reduced.

TPR decreased (−0.2 ± 0.021 mmHg·s/mL, P = 0.001), SV tended to increase (12 ± 30 mL, P = 0.053) and HR increased (4 ± 8.0 b.p.m., P = 0.01). These changes resulted in an increase in CO (1.1 ± 1.5 L/min, P = 0.001).

In a stepwise multivariate analysis in patients with successful AVF, change in peripheral diastolic BP (ΔD-BP) and the presence of diabetes mellitus were independently associated with observed change in CF-PWV (ΔPWV, $R^2 = 0.393$, P = 0.001), with ΔD-BP independently contributing by 25% to the model ($R^2 = 0.25$, P = 0.004). Neither age nor sex entered the final model. Factors that entered the initial regression models were age, sex, body mass index, co morbidities including presence of diabetes, hypertension and hyperlipidaemia and haemodynamic variables (systolic and diastolic BPs, SV, TPR and HR). Based on these earlier initial regression analysis, factors were only included if they achieved a significance value of <0.05.

Physiologically, since PWV is dependent on HR and MAP, the values for pre- and 2 weeks post-CF-PWV were adjusted to the changes in HR and MAP. After this adjustment, patients who had a successful AVF formed showed a significant reduction in their CF-PWV 2 weeks post-operatively. However, in patients with unsuccessful AVF formation, 2 weeks post-operative CF-PWV did not change significantly (see Table 2).

Table 1. Demographics, biochemical, cardiovascular risk factors and pre-operative blood vessels measurements in both groups[a]

	Unsuccessful AVF ($n = 13$)	Successful AVF ($n = 30$)	P
Age	66.7 ± 15	68.7 ± 12	0.7
Gender (male:female)	6:7	20:10	0.2
BMI	30.5 ± 5.2	28.6 ± 6.3	0.3
Ischaemic heart disease	39%	37%	0.9
Diabetes	46%	37%	0.5
Hypertension	92%	77%	0.1
Dyslipidaemia	69%	70%	0.9
Smoking	69%	60%	0.6
ACE inhibitors/ARB	62%	73%	0.4
Pre eGFR (mL/min)	17 ± 4	17 ± 4	0.2
Albumin (g/L)	37 ± 3	36 ± 4	0.7
Hb (g/dL)	11.8 ± 1.3	11.4 ± 1.4	0.3
Artery diameter (mm)	33 ± 10	45 ± 12	0.007
Artery blood flow (mL/min)	43 ± 22	77 ± 44	0.01
Vein diameter (mm)	32 ± 10	40 ± 11	0.07

[a]BMI, body mass index; ACE inhibitors, angiotesin-converting enzyme inhibitors; ARB, angiotensin receptor blockers, eGFR, estimated glomerular filtration rate.

Body composition and laboratory data (2 weeks post-AVF formation)

There were no significant changes in total body water (intra- and extracellular water) and soft tissue composition in either group post-operatively. Furthermore, no significant differences in any of the biochemical and haematological parameters were observed. There was no change in renal function.

Echocardiographic and Doppler ultrasound assessment (2 weeks post-AVF formation)

Two weeks post-operatively, patients who had a successful AVF formation demonstrated an increase in their EF (6.5 ± 8.5%, P = 0.001). This was in contrast to patients with unsuccessful AVF, who showed no change. Not all patients exhibited an increase in EF, 5/30 had a small mean reduction (−2.6 ± 1.1%). These patients were older (75 ± 9) with higher baseline systolic BP and had stiffer arteries (see Table 5). However, their arterial stiffness indices, BPs and TPR were reduced after AVF formation in a manner similar to the others.

Table 2. Baseline and 2 weeks post-operative haemodynamic data in both groups[a]

	Successful AVF				Unsuccessful AVF			
Parameter	Pre	Post	%	P	Pre	Post	%	P
Peripheral SBP	144 ± 28	134 ± 21	−5 ± 13	0.006	137 ± 19	138 ± 20	1	0.6
Peripheral DBP	75 ± 12	66 ± 11	−12 ± 13	0.001	74 ± 12	75 ± 13	−1	0.7
Central SBP	133 ± 26	121 ± 19	−8 ± 12	0.001	127 ± 17	129 ± 19	1	0.6
Central DBP	73 ± 13	67 ± 11	−9 ± 11	0.001	76 ± 12	75 ± 13	−2	0.8
CF-PWV (m/s)	12.6 ± 3.5	11 ± 3	−8 ± 13	0.004	10.8 ± 2	10.9 ± 2.4	1	0.7
Adjusted CF-PWV	12.3 ± 1.8	11 ± 1.4	−10 ± 9	0.001	10.6 ± 1.2	10.8 ± 1.7	1	0.7
AIx%	22 ± 9	19 ± 9	−3 ± 2	0.002	25 ± 9	23 ± 9	−2	0.4
SV (mL)	113 ± 33	124 ± 41	11 ± 22	0.053	116 ± 41	116 ± 41	1	0.9
HR (b.p.m.)	60 ± 11	64 ± 10	8 ± 14	0.01	61 ± 11	59 ± 7	−3	0.3
CO (L/min)	6.5 ± 1.5	7.6 ± 2	19 ± 25	0.001	7 ± 3	6.8 ± 2.5	−3	0.7
CI (L/min/m^2)	3.45 ± 0.7	4.1 ± 1.0	19 ± 25	0.001	3.7 ± 1.6	3.5 ± 1.2	−3	0.7
TPR (mmHg·s/mL)	1.0 ± 0.2	0.8 ± 0.2	−17 ± 18	0.001	1.0 ± 0.4	1.1 ± 0.7	15	0.4
EF (%)	45 ± 13	52 ± 12	6 ± 8	0.001	45 ± 13	45 ± 14	−1	0.8

[a]SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, cardiac index.

In patients with successful AVF formation, the diameter of the supplying artery increased to 53 ± 15 mm and the flow increased to 735 ± 600 mL/min. The diameter of the access vein increased to 67 ± 17 mm. Mean AVF flow (Qa) varied according to the type of the fistula constructed, with brachiobasilic fistulas exhibiting a mean Qa of 1500 ± 1100 mL/min, brachiocephalic fistulas 1300 ± 600 mL/min and radiocephalic fistulas 600 ± 170 mL/min.

On multivariate regression analysis, the major determinants of the Qa flow were diameter of the AVF itself and post-operative blood flow in the supplying artery ($R^2 = 0.63$, P = 0.001 and 0.02, respectively, summarized in Table 3). There was no effect of cardiac performance on AVF blood flow.

Haemodynamic indices and arterial stiffness after AVF maturation

The following results belong to the total of 21 patients, who had successful AVFs created and continued to participate in the 3-month follow-up session. Patients who were censored were those who died ($n = 2$), started HD ($n = 3$) and patients who withdrew consent ($n = 4$). Patients who did not have successful AVFs were not entered into the second follow-up session. Although the number was less than our initial calculation, the results were statistically and clinically significant.

Three months post-operatively, all the previously observed changes were largely maintained. Mean CF-PWV remained reduced (11 ± 2.8 m/s, see Figure 1) as did AIx (20 ± 10%). Mean peripheral systolic (132 ± 20 mmHg) and diastolic (63 ± 10 mmHg) BP remained low compared to their preoperative readings. This was also true for central systolic (120 ± 21 mmHg) and central diastolic BP (64 ± 11 mmHg), CO (7.3 ± 1.3 L/min), TPR (0.8 ± 0.15 mmHg·s/mL), SV (126 ± 37 mL/min) and HR (62 ± 10 b.p.m.).

Table 3. Multivariate analysis of factors affecting Qa

Variables	Unstandardized coefficients		Standardized coefficients	P
	B	Standard error	*β*	
AVF diameter	212.8	55.526	0.548	0.001
Post-operative arterial flow	0.351	0.145	0.347	0.022

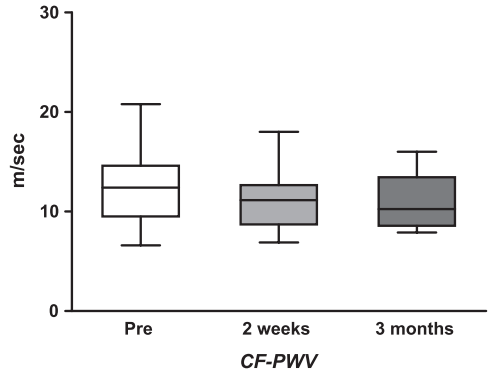

Fig. 1. CF-PWV pre-operative, 2 weeks and 3 months post-operatively.

Table 4 shows the effect of successful AVF creation on markers of arterial stiffness, haemodynamic variables, EF and central BPs in the 21 patients who completed all three study sessions comparing individual time points using one-way ANOVA repeated measurements. It can be appreciated that AVF creation resulted in significant reduction in arterial stiffness, BPs and TPR. CO was significantly increased post-AVF creation. SV changes did not reach statistical significance (P = 0.18).

Body composition and laboratory data after AVF maturation

There were no significant changes in body water and soft tissue composition after 3 months. Renal function as measured by estimated glomerular filtration rate was stable (17 ± 5 mL/min).

Echocardiographic and Doppler ultrasound after AVF maturation

Three months post-operatively, LVEF remained high (53 ± 11%, see Figure 2). Mean Qa increased in both radiocephalic AVF (643 ± 190 mL/min) and brachiocephalic AVF (1390 ± 550 mL/min). The diameter of the artery supplying the AVF increased to 61 ± 14 mm and the flow increased to 1170 ± 600 mL/min. The mean diameter of the access part of the AVF increased to 83 ± 21 mm from the 2-week post-operative value of 67 ± 17 mm.

Discussion

Although there has been some limited study of the effect of AVF formation on isolated aspects of the cardiovascular system, this study prospectively investigates the observed effects in detail on arterial stiffness in concert with other measures of cardiovascular structure and function. Furthermore, it is the first study to exclusively investigate the effects in patients without previous vascular access or exposure to dialysis. The inclusion of patients with primary technical failure provides the opportunity to study those effects controlled against a group of patients undergoing the same progression of uraemic factors, but without a formed shunt.

The results demonstrate that formation of an AVF in predialysis CKD 4–5 patients was associated with significant, and persistent reduction in BP and arterial stiffness, increase in HR and SV and reduction in TPR. Echocardiographically, LVEF increased and this increase persisted up to 3 months post-operatively after AVF creation.

From the previous physiological studies looking into compensation of CO and other haemodynamic variables in animals post-AVF formation, it is believed that increase in CO is mediated by two mechanisms [4]. The acute response that happens within seconds of AVF formation is caused by increases in venous return and secondary to reduction in TPR and cardiac adaptation (in accordance with Starling's principle). Subsequent responses appear to

Table 4. Effect of AVF creation on arterial stiffness, systemic haemodynamics, BPs and EF in 21 patients with successful AVF formation who completed all three study sessions using repeated measures one-way ANOVA design[a]

	Baseline	2 Weeks	3 Months	Overall significance
CF-PWV (m/s)	12.6 ± 3.5	11 ± 3	11 ± 2.8	0.02
AIx%	22 ± 9	19 ± 9	20 ± 10	0.04
CO (L/min)	6.5 ± 1.5	7.6 ± 2	7.3 ± 1.3	0.01
TPR (mmHg·s/mL)	1.0 ± 0.2	0.8 ± 0.2	0.8 ± 0.15	0.01
SV (mL)	113 ± 33	124 ± 41	126 ± 37	0.18
HR (b.p.m.)	60 ± 11	64 ± 10	62 ± 10	0.05
Central SBP (mmHg)	133 ± 26	121 ± 19	120 ± 21	0.01
Central DBP (mmHg)	73 ± 13	67 ± 11	64 ± 11	0.001
EF%	45 ± 13	52 ± 12	53 ± 11	0.001

[a]SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 5. Haemodynamic and arterial stiffness parameters pre- and 2 weeks post-operatively in patients with increased EF compared to patients with reduced EF ($n = 5$) in the successful group[a]

	Increased EF		Reduced EF	
Parameter	Pre	Post	Pre	Post
Peripheral SBP	142 ± 28	132 ± 20	155 ± 25	138 ± 20
Peripheral DBP	76 ± 13	64 ± 12	74 ± 3	69 ± 6
Central SBP	132 ± 27	118 ± 19	143 ± 23	134 ± 19
Central DBP	73 ± 14	65 ± 12	75 ± 3	70 ± 6
CF-PWV (m/s)	12.2 ± 3	10.9 ± 3	13.4 ± 2	12.1 ± 2.4
AIx%	22 ± 10	18 ± 10	25 ± 8	22 ± 8
SV (mL)	117 ± 27	127 ± 23	84 ± 27	86 ± 12
HR (b.p.m.)	60 ± 13	64 ± 10	60 ± 10	62 ± 10
CO (L/min)	6.6 ± 1.5	7.2 ± 1.4	5.2 ± 1	6.2 ± 0.5
CI (L/min/m^2)	3.5 ± 0.7	3.8 ±0.66	3.25 ± 0.83	4.2 ± 1.58
TPR (mmHg·s/mL)	0.97 ± 0.17	0.83 ± 0.17	1.18 ± 0.4	0.93 ± 0.3

[a]SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, cardiac index.

occur secondary to neurohormonal and autonomic nervous system modifications [4].

The significant increase in CO within individuals demonstrated in our study is similar to the observation made within the limited number of clinical studies (utilizing a range of different techniques to measure central haemodynamics) that have looked at the effect of AVF formation on CO [5, 6, 19].

This study has demonstrated that both central and peripheral BPs fall significantly after AVF formation. This is probably largely attributable to the observed matched reduction in TPR. Interestingly, even this fairly simple consequence of AVF formation has been subjected to very little formal study. Ori *et al*. also showed reduction in systolic and diastolic BPs, but to a lesser extent, possibly due to the smaller sample size ($n = 10$).

We also looked into the association between AVF formation and CF-PWV allowing correlation with changes in other haemodynamic variables. Savage *et al*. [20] measured AIx in nine patients, reporting that this composite marker of arterial compliance and cardiac performance did not change significantly after AVF formation. More recently, Utescu *et al*. [21] demonstrated that successful AVF formation was associated with reduction in CF-PWV and mean BP and a non-significant increase in AIx. Interestingly, although baseline CF-PWV and the decrease in CF-PWV over 3 months are similar in our study to the study by Utescu *et al*., our present study showed that as markers of arterial stiffness, both CF-PWV and AIx were significantly reduced 2 weeks post-operatively and it persisted for 3 months afterwards. One of the crucial differences between the two studies is that none of our patients were commenced on HD treatment before the last study session. In contrast, Utescu *et al*. reported that 52% of their

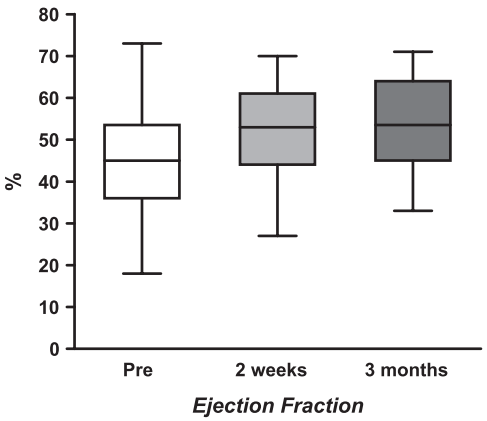

Fig. 2. LVEF pre-operative, 2 weeks and 3 months post-operatively.

participants were already receiving HD at the beginning of the study and this increased to 71% at the end of the study. HD *per se* has been reported to affect both AIx and PWV measurements significantly [22–24]. Recognizing this fact, we deliberately designed our study to avoid potential effects of HD on arterial stiffness, haemodynamics and body composition parameters. It is also widely recognized that although PWV and AIx are two different measurements of arterial stiffness, they are not interchangeable or superimposable [22]. These important factors could well explain the difference in AIx trend between the two studies.

It can be assumed that AVF creation affecting the structure of the arterial wall in such a short period is unlikely. Physiologically, stiffness is defined as the change in pressure due to a change in volume (stiffness = Δpressure/Δvolume). This is translated into the ability of the arteries to accommodate the volume ejected by the left ventricle. It is well known that arterial stiffness depends on the structure of the arterial wall and it is largely affected by changes in the BP. A higher BP can result in a functional increase in arterial stiffness and this can be reversed pharmacologically by reducing the BP [25]. On the basis of this principle, a more accurate explanation of the acute reduction of CF-PWV in our study is that it is largely driven by the reduction in the BPs. Indeed, when we closely examined the relationship between the change in CF-PWV and other haemodynamic variables, to determine if reduction in CF-PWV can be partially explained by the changes in the other haemodynamic variables, it was determined that changes in peripheral diastolic BP remained the most significant determinant of change in CF-PWV contributing ~25% to the model. None of the other haemodynamic variables including changes in SV, TPR and HR contributed significantly. This finding was also very similar to findings by Utescu *et al*.

Furthermore, after adjusting the pre- and post-operative CF-PWV for HR and MAP changes, the results showed that there still was a significant difference in the pre- and 2 weeks post-CF-PWV in patients who had a successful AVF formed. In Utescu *et al*. study, only the post-operative CF-PWV values were adjusted.

On analysing the 3-month data from our cohort, it was evident that the initial reduction in PWV persisted (as indeed did the other cardiovascular changes).

Arterial stiffness has been previously demonstrated to be associated with cardiovascular risk factors and cardiovascular diseases in pre-dialysis population [26]. It has also been demonstrated that in end stage renal failure (ESRF) patients, increased arterial stiffness is an independent predictor of all-cause and cardiovascular mortality [27]. Furthermore, previous studies have showed in the presence of ESRF that arterial stiffness is less dependent on the BP and it is mainly affected by the structural changes affecting the arterial wall [28] and that survival of ESRF patients was significantly better for patients whose aortic PWV declined in response to BP lowering compared to those whose PWV was not reduced in response to the BP changes [29]. It can be hypothesized that this persistent reduction in CF-PWV may contribute to the improved outcome in patients who have native AVF compared to other types of dialysis access. A longer term survivability study is required to prove this in a more formal way.

Uniquely, we have investigated the changes in systemic haemodynamics including CO in the pre-dialysis population, without the confounders that would be involved in using a dialysis-based population (changing volume status, resolution of uraemia, medication changes etc.). The view that higher flow within the AVF is associated with high-output cardiac failure is widely held. However, this assertion has not been previously tested in a prospective rigorous study. Patients who had a successful AVF formed showed an increase in their mean CO; however, there did not appear to be any relationship between higher Qa values and CO. There was no clinical evidence of cardiac decompensation, with no change in body water. Echocardiography data demonstrated that even 2 weeks post-operatively, there was a significant increase in the mean EF in patients who had a successful AVF formed. This is similar to changes noted in previous studies [6, 19]. The observed change in EF continued to be persistent up to 3 months post-operatively when the vascular access had matured.

This study has a number of limitations. We have not studied the longer term adaptive changes that might be associated with the AVF in use. Furthermore, the study did not include any patient with arteriovenous graft or those patients who were expected to dialyse via tunnelled venous catheters. Moreover, the study sample was typical for CKD 4/5 in a hospital-based low clearance setting and clearly a degree of selection for patients potentially suitable for HD would occur.

Another potential limitation of the studies looking into the haemodynamic effects of AVFs lies in the interpretation of the results. To our knowledge, no simulation experiment that resembles AVF creation studying the relationships among haemodynamic variables in great vessels and the basic properties of the vascular bed has been published. Thus, using Windkessel models to interpret the baseline measurements in these situations has not been independently validated. This is also true when looking into measuring the changes between any two time points if any of the viscoelastic properties of the assumptions change.

Conflict of interest statement. None declared.

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Received for publication: 28.5.09; Accepted in revised form: 27.12.10