Heart, Lung and Circulation (2019) **28,** 884–892
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.04.282

ORIGINAL ARTICLE

Right Ventricular Function After Creation of an Atriovenous Fistula in Patients With End Stage Renal Disease

Karim Said, MD [a*], Mohamed Hassan, MD [a], Mahmoud Farouk, MD [a], Essam Baligh, MD [a], Bahaa Zayed, MD [b]

[a]Cardiovascular Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[b]Nephrology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

Received 25 July 2017; received in revised form 13 February 2018; accepted 4 April 2018; online published-ahead-of-print 18 April 2018

Background Right ventricular (RV) dysfunction is associated with increased risk of heart failure and mortality in end stage renal disease (ESRD) patients. Accumulating evidence suggests an association between atriovenous fistula (AVF) and RV dysfunction; however, there is no adequate data on the relation between AVF characteristics and risk of RV dysfunction after AVF creation.

Methods The study included 30 ESRD patients (median age: 44 years, 17 male) who had their first autogenous mature AVF. Before and 6 months after AVF creation the following were measured: myocardial performance index of RV (MPI-RV) using tissue Doppler imaging echocardiography and flow rate (Qa), feeding artery and receiving vein diameters using colour-flow Doppler ultrasound. Change (Δ) in MPI-RV was calculated by subtracting follow-up value from baseline value. Worsening RV function was defined as Δ MPI-RV > 0.015 and high AVF flow as Qa $\geq$ 950 ml/min.

Results Compared to patients with lower AVF flow, patients with higher flow showed increased Δ in MPI-RV (0.12 vs. −0.03, p = 0.04), basal RV diameter (0.3 vs. −0.02 cm, p = 0.014), left ventricular end diastolic volume index (9.9 vs. 0 ml/m^2, p = 0.004) and left atrial volume index (3 vs. 1 ml/m^2, p = 0.016). Among all clinical, echocardiographic and AVF-related parameters, univariate predictors of worsening of RV function were: high Qa, upper arm AVF, and large feeding artery diameter at baseline. Δ MPI-RV showed significant correlations with feeding artery diameter at baseline (r = 0.46, p = 0.01), and Qa (0.37, p = 0.04) and no significant correlation with pulmonary artery pressures. Qa $\geq$ 950 ml/min, feeding artery diameter at baseline $\geq$ 4 mm and upper arm AVF can predict worsening of RV function with 73%, 73%, 75% sensitivity and 67%, 67%, 70% specificity, respectively.

Conclusions In patients with ESRD, higher AVF flow adversely affects RV remodelling, manifested as increased size and worsening function. Predictors of worsening of RV function are: higher AVF flow rate, AVF in the upper arm, and large feeding artery diameter.

Keywords Atrioventricular fistula • Haemodialysis • Right ventricular dysfunction

Introduction

Heart failure is a leading cause of death in end stage renal disease (ESRD) patients on dialysis [1]. One of the major predictors of mortality and heart failure among these patients is the development of right ventricular (RV) dysfunction [2]. Several pathophysiologic mechanisms may adversely affect RV function in patients on haemodialysis

*Corresponding author at: Cardiovascular Department, Kasr El-Aini Hospital, Faculty of Medicine, Cairo University. Cairo, Egypt. Tel.: +201001221256., Email: karimsaid@kasralainy.edu.eg

including the volume load posed by the creation of atriovenous fistula (AVF) [3–5]. Accumulating evidence suggests that AVF is associated with haemodynamic changes that may induce or exacerbate structural and functional cardiac changes. These changes are well characterised on the left side of the heart and currently there is growing interest to study the impact of AVF on the RV [6,7]. In a recent study, worsening of RV function was detected in 34% of patients after AVF creation [8]. The adverse impact of AVF on RV dysfunction is supported by evidence showing higher prevalence of RV dysfunction among patients on haemodialysis compared to patients on peritoneal dialysis and in patients with higher flow brachial AVF compared to patients with lower flow radial AVF [7]. Nevertheless, it is difficult to determine the exact contribution of AVF to worsening of RV function since RV dysfunction can be attributed to several other pathogenic mechanisms and risk factors that are highly prevalent in ESRD patients. In addition, there is no study to address the relation between AVF haemodynamics and RV remodelling after AVF creation. Identification of AVF-related variables that increase risk of RV dysfunction is important since recent data suggest that, once RV remodelling has occurred, AVF ligation may not be completely effective at reducing the mortality risk [8]. Accordingly, this study was conducted primarily to study the potential relation between AVF flow rate (Qa) and subsequent changes in RV function in ESRD patients and also to characterise clinical or AVF-related variables that can predict worsening of RV function.

Materials and Methods

This was a prospective study conducted in Kasr El-Aini Hospital, Cairo University. The study recruited patients with ESRD scheduled for surgical creation of autogenous AVF for the first time. All patients underwent an echocardiographic examination and colour-flow Doppler ultrasound (CDU) study of upper limb vessels before and 6 months following AVF surgery. The follow-up study was performed while patients were at dry weight within 1 hour of a complete non-complicated dialysis session. A written informed consent was obtained from all eligible patients. The research protocol was approved by the institute's ethics committee.

Exclusion criteria for this study were: age less than 18 or older than 65 years; failure of AVF maturation before the follow-up study; or presence of any of the following: coronary artery disease, valvular lesions beyond mild severity, atrial fibrillation or paced rhythm, pericardial effusion with evident cardiac compression by echocardiography, constrictive pericarditis, haemoglobin less than 8 g/dl, or patients with advanced chronic obstructive pulmonary disease, interstitial pneumopathy, or chronic thromboembolic disease.

Echocardiographic Examination

Images were obtained via Philips iE33 with 2 and 2.5 MHz sector transducer equipped with tissue Doppler imaging (TDI) mode while the patient in the left lateral decubitus position. All measurements were taken on three consecutive beats and the mean values were used. Left atrial (LA) and left ventricular (LV) volumes indexed to body surface area were measured according to criteria provided by the American Society of Echocardiography [9]. Left ventricular ejection fraction (LVEF) was calculated using Simpson's rule. Left ventricular hypertrophy was defined as LV mass index $>110\ g/m^2$ for women and $>130\ g/m^2$ for men [9]. Three RV dimensions were taken in the apical four-chamber view at end diastole: basal RV measurement (RVD1) at the level of tricuspid annulus; mid RV measurement (RVD2) at the level of LV papillary muscles; and base-to-apex measurement (RVD3) [9]. Pulmonary artery systolic pressure (PASP) was calculated as: $4 \times (\text{peak tricuspid regurge velocity})^2 +$ - right atrial pressure [10,11]. Right atrial pressure was estimated from the diameter and respiratory motion of inferior vena cava in the subcostal view [10]. Pulmonary hypertension was defined as a value of PASP > 35 mmHg. Mean pulmonary artery pressure (PAP) in mmHg was calculated according to the equation: mean PAP = 80 – (RV outflow acceleration time/2) [12,13].

TDI

In the apical four-chamber view, the sample volume was placed at the lateral margin of the tricuspid annulus and the cursor was oriented so that it was parallel to the direction of the annulus motion. Peak systolic (s′), early diastolic (e′), and late diastolic (a′) annular velocities were measured (Figure 1). Myocardial performance index of RV (MPI-RV) was calculated by measuring two time intervals in the same cardiac cycle: A interval which represents the time interval between the end of a′ wave and onset of the next e′ wave, and B

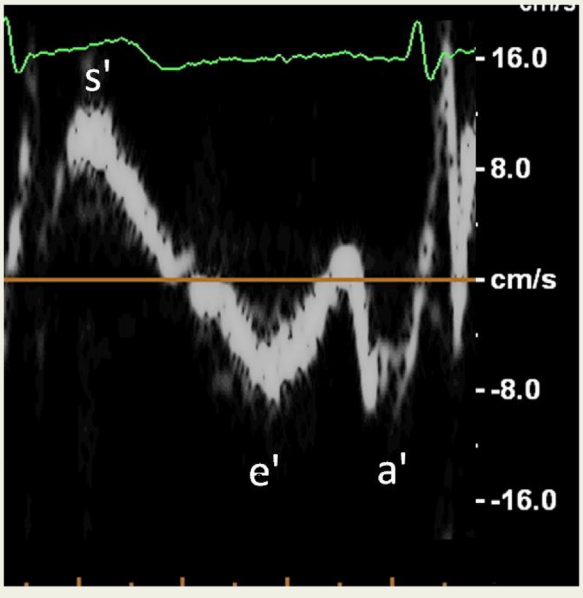

Figure 1 Tissue Doppler image of lateral tricuspid annulus demonstrating early (e′) and late (a′) diastolic waves and peak systolic (s′) wave.

interval which is the duration of s′ wave. Myocardial performance index was calculated as (A-B)/B [14]. Similarly, MPI-LV was calculated by pulsed TDI analysis of lateral margin of the mitral annulus. MPI-RV > 0.55 or s′-wave velocity of tricuspid annulus < 10 cm/s were considered to indicate RV dysfunction [10].

CDU

For all eligible patients, upper extremity arteries and veins used in AVF creation were mapped by CDU. Images were obtained by Philips iE33 and Philips Envisor CHD C1.3 (Philips Medical Systems, Andover, MA, USA) with 7 MHz linear transducer. Patients were studied in the supine position without angling of the elbow or wrist joints. All measurements were taken on three consecutive beats and the mean values were used. Examinations were performed by one skilled operator. Before AVF creation, diameters of feeding artery (radial or brachial artery) and receiving vein (cephalic or basilic vein) were measured.

At follow-up study, the following parameters were measured: (1) diameters of the feeding artery and receiving vein (measured 2 cm proximal and distal to the site of fistula respectively); (2) resistivity index of the fistula calculated as (peak systolic velocity − end diastolic velocity)/peak systolic velocity and (3) AVF flow rate (Qa) calculated as: CSA (cm^2) × TVI (cm) × HR (bpm). In this equation, CSA is the systolic cross sectional area of the feeding artery 5 cm proximal to the site of fistula; TVI is time velocity integral of the spectrum obtained in a longitudinal plane at the site where the CSA was measured; and HR is the heart rate. CSA was calculated by two methods using B-mode ultrasonography then readings of both methods were averaged; in the first method CSA was determined by tracing and plannimetry of the artery lumen in the transverse plane while, in the second method, CSA was determined by measuring the artery diameter in the longitudinal plane and then CSA was calculated as: $(\text{diameter}/2)^2 \times \pi$.

Statistical Analysis

Using Kolmogorov-Smirnov test, all continuous variables showed abnormal distribution with the exception of body mass index (BMI), estimated glomerular filtration rate (eGFR), and fistula resistivity index. Qualitative data were presented as number (percentage) while quantitative data were presented as median (range) or mean ± standard deviation, as appropriate. Comparisons between continuous variables were performed using Mann Whitney test or Wilcoxon signed-rank test, as appropriate. For categorical variables comparisons were performed using Chi-square analysis. Bivariate correlation was performed using Spearman correlation coefficient. Probability value of <0.05 was considered statistically significant. Change (Δ) at follow-up for a specific parameter was calculated by subtracting the value of this parameter at follow-up from its corresponding value at baseline study. Taking median value as a cut-off, worsening of RV function was defined as Δ MPI-RV > 0.015 and high AVF flow as Qa index ≥ 950 ml/min/m^2. To determine factors associated with RV dysfunction, patients with and without worsening of RV function were compared regarding all baseline clinical (including age, diabetes status, and BMI), echocardiographic (including MPI-RV, MPI-RV > 0.55, and LV mass index); and AVF variables. Intraobserver variability was judged by calculation of the mean of differences between repeated measurements in 10 randomly selected patients performed by the same investigator then intraclass correlation coefficient was obtained. Values of intraclass correlation coefficient were 0.79 for MPI-RV, 0.90 for feeding artery diameter at baseline, 0.82 for Qa, and 0.92 for RV1.

Results

Forty-three (43) consecutive ESRD patients were eligible for this study; however 13 patients were excluded due to: failed AVF maturation (four patients); missed follow-up visit (four patients); development of severe anaemia (two patients); atrial fibrillation (two patients); or death (one patient). Accordingly, 30 patients completed the study protocol. Eighteen patients (60%) underwent forearm ''radio-cephalic'' AVF and the remaining patients underwent upper arm ''brachio-cephalic or brachio-basilic'' AVF. Median time from AVF creation to follow-up study was 90 days (range: 80–105).

Clinical and Echocariographic Characteristics

Clinical and echocardiographic data at baseline and follow-up are shown in Tables 1 and 2 No significant changes were noticed between both studies in terms of heart rate, blood pressure, haemoglobin and haematocrit levels, or renin-angiotensin blockers treatment. All patients were ambulant and no patient had heart failure during the course of the study. Underlying aetiologies of ESRD were: chronic glomerulonephritis and interstitial nephritis (67%), diabetic nephropathy (13%), hypertensive nephropathy (10%), obstructive uropathy (7%), and autosomal dominant polycystic kidney disease (3%).

At baseline, LV hypertrophy was detected in 19 patients (63%) and five patients (17%) had LVEF < 55%; of whom one patient had moderate (EF 43%) and another patient had severe (EF 28%) dysfunction. Calculation of PASP was feasible in 26 patients at baseline and in 24 patients at follow-up with corresponding prevalence of pulmonary hypertension of 38.5% (10 patients) and 37.5% (nine patients). Compared to baseline study, there was significant increase in basal RV diameter (RV1) after AVF creation; all other echocardiographic measurements showed no significant change including indicators of RV function (MPI-RV and s′- wave velocity of tricuspid annulus).

High Flow Versus Low Flow AVF

Colour-flow Doppler ultrasound study was feasible in all patients. Haemodynamics and characteristics of AVF are summarised in Table 2. When changes (Δ) in echocardiographic variables between baseline and follow-up studies were measured, patients with high AVF flow compared to

Table 1 Baseline Clinical Characteristics.

Variables	All patients (n = 30)	Qa > 950 ml/min (n = 15)	Qa ≤ 950 ml/min (n = 15)
Age, year	44 (21–65)	47 (27–65)	42 (21–65)
Male gender	17 (57)	10 (67)	7 (47)
Hypertension	25 (83)	14 (93)	11 (73)
Diabetes mellitus	5 (17)	2(13)	3 (20)
BMI, Kg/m^2	24.3 ± 4.8	24.6 ± 4.2	23.8 ± 4.0
eGFR, ml/min	11.3 ± 2.9	11 ± 2.4	10.8 ± 2.1
Haemoglobin, gm/dl	9.2 (8.1–13.1)	9.0 (8.2–13.1)	9.2 (8.1–9.6)
Current medications			
ACE-I/ARBs	8 (27)	4 (27)	4 (27)
Beta blockers	8 (27)	5 (33)	3 (20)
Calcium channel blockers	9 (30)	3 (20)	6 (40)
Statins	5 (17)	2 (13)	3 (20)

Data are presented as median (range); mean ± SD; no (%)

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; Qa, atriovenous fistula flow rate

For all variables, there was no significant difference ($p > 0.05$) between low versus high Qa groups.

Table 2 Echocardiographic and CDU measurements.

Variable	Baseline	FU
LV end diastole volume index, ml/m^2	65.8 (54.1–129.5)	72.4 (36–125.7)
LV end systole volume index, ml/m^2	22.6 (11.6–79.5)	23.7 (11–67)
LVEF, %	64.5 (28–78)	66 (33–73)
MPI-LV	0.73 (0.44–1.4)	0.7 (0.4–1.1)
LV mass index, g/m^2	133.7 (95–186.5)	131.3 (94–188.5)
LA volume index, ml/m^2	26.9 (16.6–52.8)	28.4 (18.4–55.4)
RVD_1, cm	2.79 (2.0–4.7)	2.95 (2.0–5.1)*
RVD_2, cm	2.2 (1.5–4.2)	2.4 (1.4–4.0)
RVD_3, cm	6.9 (5.6–9.5)	6.85 (5.6–8.9)
Mean PAP, mmHg	23.5 (12–41)	21.5 (14–43)
TDI of lateral tricuspid annulus		
s′ wave, cm/sec	11.8 (5.5–23.6)	11.7 (5.7–16.8)
e′ wave, cm/sec	10.3 (6.0–19.5)	10.5 (4.6–16.4)
a′ wave, cm/se	18.2 (8.6–28)	15.8 (8.4–24.5)
MPI-RV	0.65(0.33–1.2)	0.66 (0.3–1.0)
MPI-RV > 0.55	12 (40)	13 (43)
s′ wave < 10 cm/s	10 (33)	9(30)
AVF measurements		
Qa, ml/min	–	951 (228–3208)
Feeding artery diameter, mm	3.1 (2.2–5.6)	5 (2.9–8.5)†
Receiving vein diameter, mm	3.4(2.0–5.0)	6.4 (3.2–11.2)†
Fistula resistivity index	–	0.41 ± 0.1

Data are presented as median (range) or number (%) or mean ± (standard deviation).

Abbreviations: AVF, arteriovenous fistula; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; MPI-LV, myocardial performance index of the left ventricle; MPI-RV, myocardial performance index of the right ventricle; PAP, pulmonary artery pressure; Qa, flow rate of the arteriovenous fistula; RVD1, right ventricular diameter at basal level; RVD2, right ventricular diameter at the level of left ventricular papillary muscles; RVD3, base-to-apex measurement of the right ventricle; TDI, tissue Doppler imaging ; CDU, colour-flow Doppler ultrasound.

*$p = 0.002$.

†$p = < 0.00001$.

patients with lower flow showed significant increase in MPI-RV, basal RV diameter, LV end diastolic volume index, and LA volume index and a trend toward increased base-to-apex length of RV (Table 3).

Predictors of Worsening of RV

Among all predefined clinical, echocardiographic, and AVF-related variables, univariate predictors of worsening of RV function (defined as Δ MPI-RV > 0.015) were: higher Qa, AVF in the upper arm versus forearm, and large feeding artery at baseline (Table 4). Table 5 shows sensitivity and specificity of each of these predictors for the prediction of worsening RV function.

Δ RVMPI showed significant positive linear correlations with feeding artery diameter at baseline (r = 0.46, p = 0.01), and Qa (0.37, p = 0.04) (Figures 2 and 3). Alternatively, Δ MPI-RV showed no significant correlation with mean or systolic pulmonary artery pressures both at baseline or follow-up. The group of patients with pulmonary hypertension at follow-up showed similar MPI-RV (0.61 vs. 0. 64, p = 0.8) and Δ MPI-RV (0.013 vs. 0.014, p = 0.9) compared to patients without pulmonary hypertension.

Table 5 Sensitivity and Specificity of AVF-Related Parameters for Predicting Worsening of RV Function.

	Sensitivity	Specificity
Qa ≥ 950 ml/min	73%	67%
Feeding artery diameter ≥ 4 mm at baseline	73%	67%
Arm AVF	75%	70%

Abbreviations: AVF, arteriovenous fistula; Qa, flow rate of the arteriovenous fistula; RV, right ventricle.

Discussion

The current study supports the contribution of AVF to RV remodelling and dysfunction in ESRD patients on

Table 3 Changes in Echocardiographic Measurements Based on Access Flow rate.

Variable	Qa > 950 ml/min. (n = 15)	Qa ≤ 950 ml/min. (n = 15)	P-value
Δ RVD_1, cm	0.3 (−0.7–1.05)	−0.02 (−0.77–0.33)	0.014
Δ RVD_2, cm	0.14 (−1.0–1.0)	−0.1 (−0.27–0.39)	0.29
Δ RVD_3, cm	0.25 (−1.0–1.18)	−0.1 (−1.6–0.33)	0.089
Δ mean PAP, mmHg	2 (−4–3)	3 (−1–5)	0.8
TDI of lateral tricuspid annulus			
Δ s′ wave, cm/sec	−0.3 (−6.8–3.3)	0.1 (−10–3.8)	0.7
Δ e′ wave, cm/sec	0.1 (−7.5–4.4)	−0.3 (−11–8)	0.6
Δ a′ wave, cm/se	−2.0 (−14–8.2)	−1.0 (−9.6–9.6)	0.6
Δ MPI-RV	0.12 (−0.2–0.26)	−0.03 (−0.3–0.2)	0.04
Δ LV end diastole volume index, ml/m^2	9.9 (2–19)	0.00(−14–13)	0.004
Δ LA volume index, ml/m^2	3 (0–4.1)	1(0–3.6)	0.016
Δ LVEF, %	1.0 (−7.2–17.7)	2.0 (−13.0–7.6)	0.39
Δ MPI-LV	0.08 (−0.3–0.35)	0.1 (−0.34–0.33)	0.77

Data are presented as median (range).
Abbreviations: LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; MPI-LV, myocardial performance index of the left ventricle; MPI-RV, myocardial performance index of the right ventricle; PAP, pulmonary artery pressure; Qa, flow rate of the arteriovenous fistula; RVD1, right ventricular diameters at basal level; RVD2, right ventricular diameters at the level of LV papillary muscles; RVD3, base-to-apex measurement of the right ventricle; TDI, tissue Doppler imaging.

Table 4 Univariate Predictors of Worsening of RV Function.

Variable	Δ MPI-RV > 0.015	Δ MPI-RV ≤ 0.015	P-value
Qa, ml/min	1079 (408–3208)	691 (228–2224)	0.04
Arm AVF	9 (60)	3 (20)	0.025
Feeding artery diameter at baseline, mm	4.1 (2.5–5.6)	3.0 (2.2–3.9)	0.013

Data are presented as median (range) or number (percent).
Abbreviations: AVF, arteriovenous fistula; MPI-RV, myocardial performance index of the right ventricle; Qa, flow rate of the arteriovenous fistula.

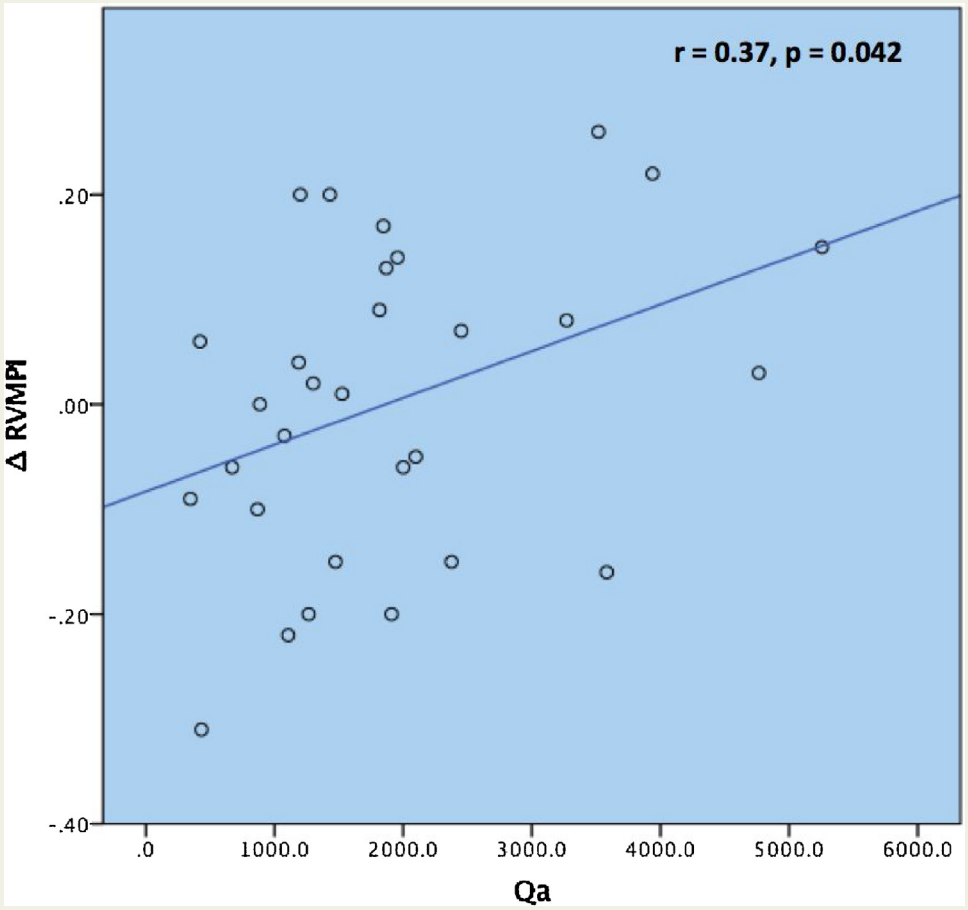

Figure 2 Correlation between change in myocardial performance index of the right ventricle (Δ MPI-RV) and AVF flow rate (Qa).
Abbreviations: AVF, atriovenous fistula; Δ MPI-RV, change in myocardial performance index of right ventricle.

haemodialysis. Based on AVF flow, patients with higher flow rates showed significant RV dilatation and worsening in RV function 6 months after AVF creation.

Available evidence is suggestive—but not conclusive—that AVF flow contributes to the development of RV dysfunction. In a recent study by Reddy et al., among 137 ESRD patients studied before AVF creation, RV dilatation and dysfunction was detected in 20% and 12% of patients, respectively. Over a median follow-up duration of 2.6 years after AVF creation, worsening RV dilation and dysfunction were observed in 37 and 34% of patients respectively [8]. In another study by Paneni et al., patients on long-term haemodialysis had higher prevalence of RV dysfunction (quantified as MPI > 0.53) compared to peritoneal dialysis patients (70% versus 34.6% $p < 0.001$) [7]. Importantly, presence of AVF was associated with RV dysfunction independent of age, gender, heart rate, duration of dialysis, dialysis adequacy and pulmonary pressure. In another magnetic resonance imaging study by Dundon et al., 6 months after creation of AVF there was significant increase in RV end diastolic volume (up to 18%) with no significant change in RV ejection fraction [15]. In the aforementioned studies, data on AVF flow was not available and therefore it could not be determined whether high AVF flow rates contributed to the increased risk of RV dilation and dysfunction. In the current study, the contribution of AVF to RV dysfunction is supported by the finding that (1) increasing AVF flow rate showed significant positive correlation with the magnitude of declining in RV function and (2) compared to patients with lower AVF flow rates, patients with higher flow rates showed significant RV dilatation and worsening in RV function after AVF creation.

Creating AVF is associated with chronic RV volume overload and excess RV wall stress. This is important since it has been previously shown that RV is more vulnerable to abnormal loading conditions and is more prone to developing fibrosis compared to the LV [16,17]. Other potential pathophysiological mechanisms include myocardial ischaemia [18], neurohormonal activation [6], and endothelial dysfunction [15]. It is unclear whether AVF creation plays a causal role in the development of RV dysfunction or is simply acting as a precipitating factor that unmasks a preexisting subtle RV dysfunction. This latter possibility is important since most dialysis patients are affected by one or more comorbid conditions that, by themselves, may induce or exacerbate RV dysfunction (eg, pulmonary hypertension, LV hypertrophy, and chronic obstructive airway disease). The current study may suggest a causal role through the finding that

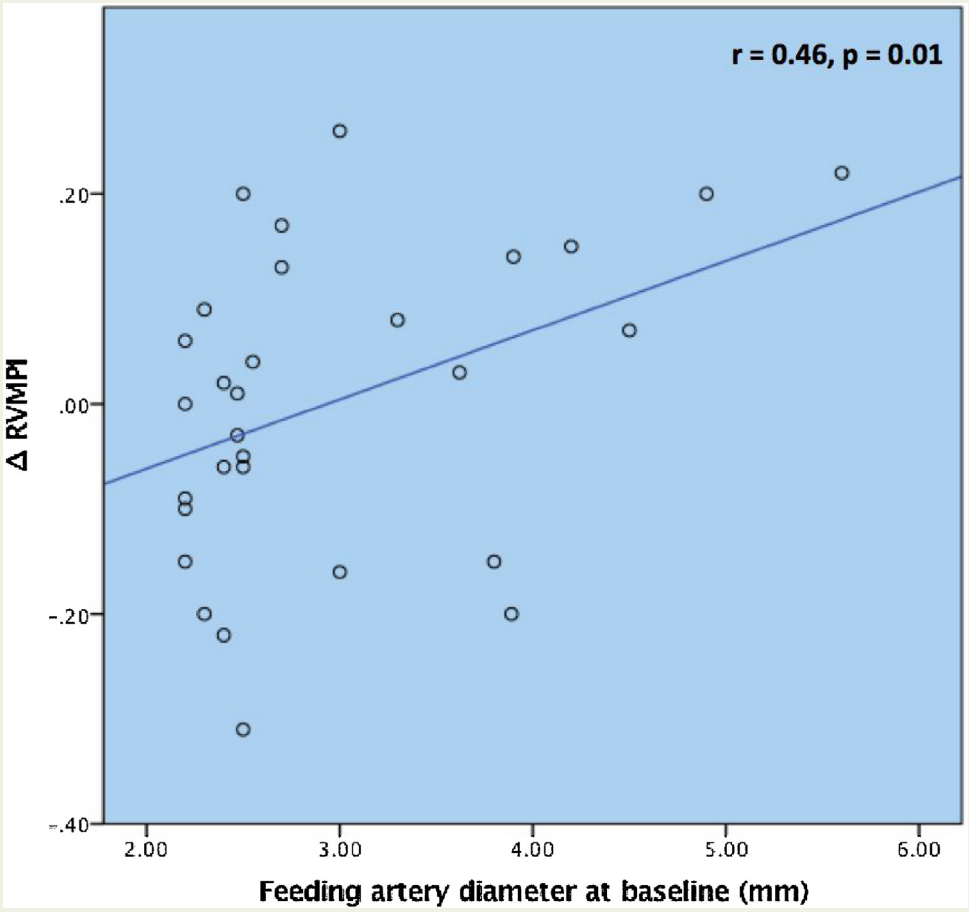

Figure 3 Correlation between change in myocardial performance index of the right ventricle (Δ MPI-RV) and feeding artery diameter at baseline.
Abbreviation: Δ MPI-RV, change in myocardial performance index of right ventricle.

preexisting RV dysfunction before AVF creation was not associated with increased risk of worsening of RV function. A large study with adjustment for variables known to affect RV function is required to explore the causal contribution of AVF to the development of RV remodelling.

To the best of our knowledge, the present study is the first to report the relation between specific AVF-related measurements and cardiac changes after AVF creation. In a study by Reddy et al., none of the studied clinical or echocardiographic variables was able to predict the development of RV dilatation or dysfunction after AVF creation [8] suggesting that AVF creation itself may be responsible for changes in RV size and function. In our study, among all tested variables, only three AVF-related variables that reflect excess access flow showed significant association with worsening of RV function. It is important to note that these variables are interrelated since AVF with higher flow tend to have large feeding arteries and to present in the upper arm.

In the current study AVF flow rate ≥950 ml/min showed modest ability to predict RV dysfunction. Generally, there is no definition of the ideal AVF flow rate; rates greater than 350 to 600 ml/min are recommended to avoid thrombosis and failure of fistula maturation [19,20] and rates ≥2 L/min were reported to be highly predictive for high-output cardiac failure [21]. In practice, giving special attention to AVF flow rate is particularly relevant in patients at higher risk for RV dysfunction (e.g. patients with pre-existing RV dysfunction, heart failure, or pulmonary hypertension); in these patients attention should be given to the location and size of dialysis access.

In our study the lack of correlation between MPI-RV and mean pulmonary artery pressure as well as the absence of significant difference in MPI-RV between patients with and without pulmonary hypertension argue against a major role for pulmonary hypertension in the development of RV dysfunction in patients with AVF. Likewise, in a study by Paneni et al., RV dysfunction in patients with AVF occurred independently of PASP [7]. In the study by Reddy et al., there was no significant difference in pulmonary artery pressure in patients with or without worsening of RV function ($p = 0.4$) and in patients with or without RV dilatation ($p = 0.9$) after AVF creation [8].

In our study, there was no association between AVF flow rate and pulmonary artery pressure. Prior studies reported

controversial findings; while some studies confirmed the presence of association between AVF flow rate and pulmonary artery pressure [22–24] other studies failed to show such association [25,26]. Before formulating a conclusion on the relation between pulmonary artery pressure and either RV dysfunction or AVF flow the following should be considered. First, although elevation of pulmonary artery pressure due to increase pulmonary flow resulting from AVF has been proposed as a mechanism of pulmonary hypertension in dialysis patients, the increased pulmonary flow alone would be physiologically incapable of increasing pulmonary artery pressure due to the compliant nature of the normal pulmonary vascular circulation [27]. Second, echocardiographic measurements of pulmonary artery pressure were reported to be inaccurate in patients with pulmonary hypertension [28,29] and are affected by several technical and haemodynamic factors. For example, many factors were reported to affect RV acceleration time including heart rate, cardiac output, and RV function [30]. Importantly, it has been shown that RV function can affect RV acceleration time with RV systolic dysfunction tending to lengthen the RV acceleration time [31]. Accordingly, right heart catheterisation remains the gold standard for the diagnosis of pulmonary hypertension. Third, the timing of the measurement of pulmonary artery pressure is important in patients receiving haemodialysis. A pre-dialysis measurement is likely to overestimate pulmonary pressure due to the fluid overload, whilst an immediate post-dialysis measurement may underestimate pulmonary pressure due to redistribution of fluid for several hours post-dialysis [27]. Consequently, large prospective studies using cardiac catheterisation for haemodynamic measurement with adjustment of volume status are needed to assess the relation between pulmonary artery haemodynamics and RV function as well as AVF flow.

The study is predominantly limited by the small number of patients recruited; this is attributed to the many exclusion criteria used to rule out many confounding variables that may affect RV function. In this study, AVF flow rate was quantified by CDU and not by the invasive dilution method which is known to be the best accurate method to measure the blood flow of a vascular access. Prior studies showed that the access flow rate measured by CDU correlates well with the flow rate measured by a dilution method [32]. Myocardial performance index was reported to be load dependent [33]. However, it was shown that MPI measured by pulsed-wave TDI, rather than conventional pulsed-wave Doppler, is not or only minimally affected by preload reduction in haemodialysis patients [34–36]. Pulsed TDI velocities were used in this study rather than the newer TDI derivatives of strain and strain rate. However, strain and strain rate indices may be less representative of global RV function. There was no data on volume removed in dialysis. The degree of systemic shunting and its influence on the RV may be modified by the degree of chronic blood volume control. However, patients in this study had completed three times per week dialysis sessions throughout the period of the study.

In conclusion, findings of this study suggest that higher AVF flow rates adversely affect RV function and predictors of worsening of RV function include: higher AVF flow rate; AVF in the arm; and large feeding artery. Given the potential impact of AVF on RV function, greater attention should be given to the location and size of dialysis access especially in patients at higher risk for RV dysfunction. Atriovenous fistula should be placed as distal as possible and vascular surgeons should be prudent in the selection of the size of AVF and feeding artery to control the degree of systemic shunting. Calculation of AVF flow by CDU may be considered in high risk patients as those with heart failure, pulmonary hypertension, or preexisting RV dysfunction. Patients with a high flow rates should be followed with serial echocardiography to watch for changes in the RV size and function. Future research that focusses on the underlying mechanisms and clinical consequences of AVF-related RV remodelling may give us insights into more favourable techniques of vascular access, methods of dialysis, or adjunctive therapy, that can help reduce the risk of heart failure and mortality seen in this patient population.

References

[1] Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. Lancet 2016;388:276–84.

[2] Hickson LJ, Negrotto SM, Onuigbo M, Scott CG, Rule AD, Norby SM, et al. Echocardiography criteria for structural heart disease in patients with end-stage renal disease initiating hemodialysis. J Am Coll Cardiol 2016;67:1173–82.

[3] McCullough PA. Why is chronic kidney disease the "spoiler" for cardiovascular outcome. J Am Coll Cardiol 2003;41:725–8.

[4] Yamamoto S, Kon V. Mechanisms for increased cardiovascular disease in chronic kidney dysfunction. Curr Opin Nephrol Hypertens 2009;18:181–8.

[5] London GM. Cardiovascular disease in chronic renal failure: pathophysiologic aspects. Semin Dial 2003;16:85–94.

[6] Iwashima Y, Horio T, Takami Y, Inenaga T, Nishikimi T, Takishita S, et al. Effects of the creation of arteriovenous fistula for hemodialysis on cardiac function and natriuretic peptide levels in CRF. Am J Kidney Dis 2002;40:974–82.

[7] Paneni F, Gregori M, Ciavarella GM, Sciarretta S, De Biase L, Marino L, et al. Right ventricular dysfunction in patients with end-stage renal disease. Am J Nephrol 2010;32:432–8.

[8] Reddy YNV, Obokata M, Dean PG, Melenovsky V, Nath KA, Borlaug BA. Long term cardiovascular changes following creation of arteriovenous fistula in patients with end stage renal disease. Eur Heart J 2017;38:1913–23.

[9] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

[10] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.

[11] Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984;70:657–62.

[12] Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation 1983;68:302–9.

[13] Beard JT, Newman JH, Loyd JE, Byrd BF. Doppler estimation of changes in pulmonary artery pressure during hypoxic breathing. J Am Soc Echocardiogr 1991;4:121–30.

[14] Tei C, Dujardin KS, Hodge DO, Bailey KR, McGoon MD, Tajik AJ, et al. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr 1996;9:838–47.
[15] Dundon BK, Torpey K, Nelson AJ, Wong DT, Duncan RF, Meredith IT, et al. The deleterious effects of arteriovenous fistula-creation on the cardiovascular system: a longitudinal magnetic resonance imaging study. Int J Nephrol Renovasc Dis 2014;7:337–45.
[16] Modesti PA, Vanni S, Bertolozzi I, Cecioni I, Lumachi C, Perna AM, et al. Different growth factor activation in the right and left ventricles in experimental volume overload. Hypertension 2004;43:101–8.
[17] Friedberg MK, Redington AN. Right versus left ventricular failure: differences, similarities, and interactions. Circulation 2014;129:1033–4410.
[18] Savage MT, Ferro CJ, Sassano A, Tomson CR. The impact of arteriovenous fistula formation on central hemodynamic pressures in chronic renal failure patients: a prospective study. Am J Kidney Dis 2002;40:753–9.
[19] Konner K, Nonnast-Daniel B, Ritz E. The arteriovenous fistula. J Am Soc Nephrol 2003;14:1669–80.
[20] National Kidney Foundation. K/DOQI clinical practice guidelines and clinical practice recommendations for vascularaccess 2006. Am J Kidney Dis 2006;48(Suppl. 1):S176–322.
[21] Basile C, Lomonte C, Vernaglione L, Casucci F, Antonelli M, Losurdo N. The relationship between the flow of arteriovenous fistula and cardiac output in haemodialysis patients. Nephrol Dial Transpl 2008;23:282–7.
[22] Havlucu Y, Kursat S, Ekmekci C, Celik P, Serter S, Bayturan O, et al. Pulmonary hypertension in patients with chronic renal failure. Respiration 2007;74:503–10.
[23] Yu TM, Chen YH, Hsu JY, Sun CS, Chuang YW, Chen CH, et al. Systemic inflammation is associated with pulmonary hypertension in patients undergoing haemodialysis. Nephrol Dial Transpl 2009;24:1946–51.
[24] Abdelwhab S, Elshinnawy S. Pulmonary hypertension in chronic renal failure patients. Am J Nephrol 2008;28:990–7.
[25] Acarturk G, Albayrak R, Melek M, Yuksel S, Uslan I, Atli H, et al. The relationship between arteriovenous fistula blood flow rate and pulmonary artery pressure in hemodialysis patients. Int Urol Nephrol 2008;40:509–13.
[26] Unal A, Tasdemir K, Oymak S, Duran M, Kocyigit I, Oguz F, et al. The long-term effects of arteriovenous fistula creation on the development of pulmonary hypertension in hemodialysis patients. Hemodial Int 2010;14:398–402.
[27] Kawar B, Ellam T, Jackson C, Kiely DG. Pulmonary hypertension in renal disease: epidemiology, potential mechanisms and implications. Am J Nephrol 2013;37:281–90.
[28] Rich JD, Shah SJ, Swamy RS, Kamp A, Rich S. Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice. Chest 2011;139:988–93.
[29] Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. Heart 2011;97:612–22.
[30] Chan KL, Currie PJ, Seward JB, Hagler DJ, Mair DD, Tajik AJ. Comparison of three Doppler ultrasound methods in the prediction of pulmonary artery pressure. J Am Coll Cardiol 1987;9:549–54.
[31] Stewart WJ, Jiang L, Mich R, Pandian N, Guerrero JL, Weyman AE. Variable effects of changes in flow rate through the aortic, pulmonary and mitral valves on valve area and flow velocity: impact on quantitative Doppler flow calculations. J Am Coll Cardiol 1985;6:653–62.
[32] May RE, Himmelfarb J, Yenicesu M, Knights S, Ikizler TA, Schulman G, et al. Predictive measures of vascular access thrombosis: a prospective study. Kidney Int 1997;52:1656–62.
[33] Cheung MM, Smallhorn JF, Redington AN, Vogel M. The effects of changes in loading conditions and modulation of inotropic state on the myocardial performance index. Comparison with conductance catheter measurements. Eur Heart J 2004;25:2238–42.
[34] Gerede DM, Turhan S, Kaya CT, Ozcan OU, Goksuluk H, Vurgun VK, et al. Effects of hemodialysis on Tei index: comparison between flow Doppler and tissue Doppler imaging. Echocardiography 2015;32:1520–6.
[35] Su HM, Lin TH, Voon WC, Chen HC, Lin FH, Kuo MC, et al. Impact of preload alterations by hemodialysis on the Tei index: comparison between pulsed flow and tissue Doppler analyses. Acta Cardiol 2007;62:25–30.
[36] Ozdemir K, Balci S, Duzenli MA, Can I, Yazici M, Aygul N, et al. Effect of preload and heart rate on the Doppler and tissue Doppler-derived myocardial performance index. Clin Cardiol 2007;30:342–8.