Long-Term Impact of Arteriovenous Fistula Ligation on Cardiac Structure and Function in Kidney Transplant Recipients: A 5-Year Follow-Up Observational Cohort Study

Tania Salehi,1,2 Nicholas J. Montarello,2,3 Nishant Juneja,3 Michael B. Stokes,3 Daniel J. Scherer,3 Kerry F. Williams,3 David King,1 Ewan Macaulay,1 Christine H. Russell,1 Santosh A. Olakkengil,1 Robert P. Carroll,1,2 Randall J. Faull,1,2 Karen S.L. Teo,2,3 Stephen P. McDonald,1,2 Matthew I. Worthley,4,5 Patrick T. Coates,1,2 and Nitesh N. Rao1,2

Abstract

Background The long-term effects of arteriovenous fistula (AVF) ligation on cardiovascular structure following kidney transplantation remain uncertain. A prospective randomized, controlled trial (RCT) examined the effect of AVF ligation at 6 months on cardiovascular magnetic resonance imaging (CMR)–derived parameters in 27 kidney transplant recipients compared with 27 controls. A mean decrease in left ventricular mass (LVM) of 22.1 g (95% CI, 15.0 to 29.1) was observed compared with an increase of 1.2 g (95% CI, 2.4 to 7.2) in the control group (P < 0.001). We conducted a long-term follow-up observational cohort study in the treated cohort to determine the evolution of CMR-derived parameters compared with those documented at 6 months post-AVF ligation.

Methods We performed CMR at long-term follow-up in the AVF ligation observational cohort from our original RCT published in 2019. Results were compared with CMR at 6 months postintervention. The coprimary end point was the change in CMR-derived LVM and LVM index at long-term follow-up from imaging at 6 months postindex procedure.

Results At a median of 5.1 years (interquartile range, 4.7–5.5 years), 17 patients in the AVF ligation group were studied with repeat CMR with a median duration to follow-up imaging of 5.1 years (IQR, 4.7–5.5 years). Statistically significant further reductions in LVM (−217.6 ± 23.0 g, P = 0.006) and LVM index (−10.0 ± 13.0 g/m², P = 0.006) were documented.

Conclusions The benefit of AVF ligation on LVM and LVM index regression appears to persist long term. This has the potential to lead to a significant reduction in cardiovascular mortality.

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Introduction

Kidney transplantation results in both an improvement in the quality of life and survival of patients with ESKD (1,2), and it is, therefore, the preferred treatment pathway for this disease entity. Remarkably, there are no guidelines to suggest whether an arteriovenous fistula (AVF) should be ligated following kidney transplantation when it is no longer clinically required (3–7).

Cardiovascular disease remains a significant cause of death after kidney transplantation (8–10), with maladaptive cardiac remodeling, particularly increased left ventricular mass (LVM), strongly associated with...
adverse cardiovascular outcomes in this cohort of patients (11–13). A permanent AVF creates a continuing, hemodynamically significant left-to-right shunt with documented blood flow rates on average between 1 and 2 L/min (14,15). Although the recognition that this may lead to a desirable fall in BP has controversially resulted in AVF creation as a treatment strategy for refractory hypertension (16), concerns relate to the documented ill effects of a permanent AVF. Not only has this been shown to increase LVM but also, left ventricular (LV) wall thickness and ventricular and atrial dimensions, leading to pathologic chamber dilation and reduced cardiac output (17,18). Despite the potential effect that these changes may have on cardiac structure and both cardiovascular morbidity and mortality, there has been a paucity of robust clinical data evaluating the cardiovascular effect of AVF ligation following successful kidney transplantation. The first prospective randomized, controlled trial (RCT) to examine the effect of AVF ligation on cardiovascular magnetic resonance imaging (CMR)–derived LVM in kidney transplant recipients was published by Rao et al. (19) in 2019. In this study, 54 kidney transplant recipients were randomized by our group in a 1:1 ratio to either AVF ligation or observation, with all participants evaluated with CMR at baseline and again at 6 months postliigation. The cohort of patients who had their AVFs ligated had a mean decrease in LVM of 22.1 g (95% confidence interval [95% CI], 15.0 to 29.1) between interval scans, compared with the control group in which a small increase in LVM of 1.2 g (95% CI, −4.8 to 7.2) was observed (P<0.001). The cohort of patients undergoing AVF ligation also demonstrated significant decreases in LV end diastolic and end systolic volumes, biatrial volumes, N-terminal prohormone brain natriuretic peptide (NT-proBNP), and cardiac output compared with controls (P<0.01).

The aim of this study was to determine if the improvements in cardiac parameters, particularly LVM, noted at 6 months post-AVF ligation are sustained. We, therefore, conducted a 5-year follow-up CMR observational study in the original cohort of AVF-ligated participants, looking at the evolution of the aforementioned CMR-derived parameters. Although the non-AVF ligation cohort was also followed with regard to similar parameters, they did not undergo CMR.

Materials and Methods

Study Population

In 2020, we conducted a retrospective review of outpatient kidney transplant recipients who formed part of the original prospective RCT (between 2013 and 2017) conducted by Rao et al. (19), which included both AVF ligation and nonligated cohorts and was published in 2019.

A total of 54 kidney transplant recipients were included in the study: 27 patients who had their AVFs ligated and 27 patients who did not. All patients had CMR at baseline and 6 months postintervention. Follow-up with 5-year CMR was not performed in the control group due to funding constraints and the fact that a large proportion of this cohort proceeded to have AVF ligation during the 5-year period on the basis of perceived clinical benefit from the study conducted by Rao et al (19). However, the demographics and clinical characteristics between the control and treated cohorts were similar with regard to age, sex, body mass index, diabetes status, hypertensive status, smoking status, history of ischemic heart disease, peripheral vascular disease, previous stroke, and pharmacology, allowing for long-term clinical outcomes to be compared between the two cohorts (Table 1).

Study Procedures

All participants from the AVF-ligated cohort were invited to undertake another CMR with a 1.5-T scanner (Siemens Magnetom Avanto; Siemens AG, Erlangen, Germany) utilizing a standardized protocol, consistent with our previous study (Supplemental Appendix). In order to limit bias, analyses of the CMR-derived parameters were performed offline by two cardiologists trained in CMR reporting.

Modified Borg dyspnea scale following a brisk walk and serum NT-proBNP were measured at the time of 5-year follow-up CMR.

Outcomes

The coprimary end point in the treated arm was the change in CMR-derived LVM and LVM index at long-term follow-up compared with the 6-month scans from the index procedure. Secondary CMR-derived end points in the AVF-ligated cohort included changes in LV systolic and end diastolic volumes, left and right atrial areas, left ventricular ejection fraction (LVEF), cardiac output, and cardiac index at long-term follow-up compared to the 6-month scans from the index procedure.

The key secondary clinical outcomes included all-cause mortality, cardiovascular mortality, nonfatal myocardial infarction (MI), and nonfatal stroke. Additional clinical outcomes included hospitalizations for cardiovascular-related disease, evaluation of BP trends, serum creatinine measurements, and transition to dialysis. All demographic and clinical outcome data were collected from Central Adelaide Local Health Network (CALHN) electronic medical records.

Statistical Analyses

Descriptive statistics were expressed as mean and SD for continuous variables, and percentages were reported for categorical variables. Independent sample t tests were conducted to determine the differences in baseline characteristics between the original AVF ligation group and the control group at long-term follow-up.

The Δ in CMR-determined cardiac parameters between 6-month postintervention scans and long-term follow-up was evaluated. The Δ in measurements was individually calculated for each participant. The 6-month versus 5-year results were compared with the use of a paired t test. Analyses were undertaken through StataCorp (Stata Statistical Software: Release 15; StataCorp LLC, College Station, TX). Two-sided tests were performed for all analyses, and the level of significance was set at P<0.05.

The trial protocol was approved by the institutional ethics committee (CALHN reference no. 12353). Written informed consent was obtained from all participants. The authors assume responsibility for accuracy and completeness of the data and analyses. All statistical analyses were performed independently by the authors and a statistician based at the Australia and New Zealand Dialysis and Transplant Registry in the South Australian Health and Medical Research...
Institute. The data to support the findings of this study are available from the corresponding author on reasonable request.

Results

During the study period of 2013–2017, 27 patients with kidney transplants had their AVF ligated. At follow-up of this cohort in 2020, two patients had died from malignancy, two patients were lost to follow-up, five patients did not wish to participate with follow-up CMR study, and one patient was unable to participate due to having an magnetic resonance imaging-incompatible pacemaker in situ. Seventeen patients from the original AVF ligation group, therefore, underwent repeat CMR at approximately 5 years postligation. There were no statistically significant differences in the baseline clinical characteristics between the AVF-ligated cohort that participated in the study and those that did not (Supplemental Appendix).

The median duration from ligation of AVF to the 6-month CMR scan in our original study was 6.7 months (interquartile range, 4.7–7.3 months) in the intervention group. Upon long-term follow-up of the 17 patients, the median duration between the 6-month post-AVF ligation and long-term follow-up CMR scan was 5.1 years (interquartile range, 4.7–5.5 years).

The changes in CMR-derived cardiac parameters, serum creatinine, and BP between the interval scans for the 17 participants are documented in Table 2. At 5 years post-AVF ligation, there were statistically significant reductions in LVM (−17.6±23.0 g/m², P=0.006), LVM index (−10.0±13.0 g/m², P=0.006), and left atrial volume index (−4.9±9.4 ml/m², P=0.05) compared with the 6-month post-AVF ligation CMR study. Figure 1 exhibits the change in LVM and LVM index in our cohort from baseline to long-term follow-up.

Our secondary CMR analyses demonstrated a significant increase in LV end systolic volume (11.3±20.0 ml, P=0.03) associated with a reduction in LVEF (−7.5%±10.3%, P=0.009). Two patients demonstrated a decline in LVEF from 79% to 49% and from 78% to 58%, respectively, with no regional wall motion abnormalities to suggest ischemia. One patient was noted to have new mid- to distal interoseptal hypokinesis consistent with an ischemic cardiomyopathy, with a fall in LVEF from 73% to 55%. Other cardiac parameters, including LV end diastolic volume, LV cardiac output, LV cardiac index, left atrial volume, and right atrial area, remained consistent throughout the interval period.

In the 17 patients undergoing CMR, serum creatinine remained stable between interval scans; however, significant rises in both systolic (17.2±21.5 mm Hg, P=0.005) and diastolic (10.9±12.1 mm Hg, P=0.002) BP were noted at 5 years. NT-proBNP (normal reference range <125 ng/L) was measured at the time of the 5-year CMR scan in ten of the participants, with a mean level of 964 ng/L (±1961.5). This was compared with a mean NT-proBNP level of 164.4 ng/L (±147.3) in 14 participants at 6 months post-AVF ligation. The mean modified Borg dyspnea scale following a brisk walk at long-term follow-up was 3.8 (±1.9), compared with 3.8 (±0.9) in 17 patients at 6 months postintervention.

Long-term clinical outcomes in the control and AVF ligation cohorts from our original study are demonstrated in

| Table 1. Five-year cohort baseline characteristics |
|-----------------------------------------------|
| Characteristics                  | Control Group, N=22 | Arteriovenous Fistula Ligation Group, N=23 | P Value |
|-----------------------------------------------|
| Age, yr                             | 64.1±9.3            | 64.3±12.1                                         | 0.23 |
| Men, no. (%)                         | 16 (72.7)           | 14 (60.9)                                          | 0.42 |
| BMI, kg/m²                           | 28.8±5.5            | 28.0±4.2                                          | 0.22 |
| Diabetes (%)                         | 6 (27.3)            | 9 (39.1)                                           | 0.42 |
| Hypertension (%)                     | 18 (81.8)           | 23 (100)                                           | 0.05 |
| Smoking status (%)                   | 1 (4.5)             | 2 (8.7)                                            | 0.64 |
| IHD (%)                             | 3 (13.6)            | 6 (26.1)                                           | 0.33 |
| PVD (%)                             | 0 (0.0)             | 1 (4.3)                                            | 0.51 |
| Stroke (%)                          | 0 (0.0)             | 1 (4.3)                                            | 0.51 |
| **Immunosuppressive medication (%)** |                                    |                                                   |       |
| CNI                                 | 16 (72.7)           | 14 (60.9)                                          | 0.40 |
| Mycophenolate                       | 16 (69.6)           | 16 (69.6)                                          | 0.82 |
| Azathioprine                        | 3 (13.6)            | 4 (17.4)                                           | 0.73 |
| Prednisolone                        | 16 (69.6)           | 23 (100)                                           | 0.007|
| mTOR inhibitors                     | 6 (27.3)            | 7 (30.4)                                           | 0.82 |
| **Cardiovascular medication (%)**    |                                    |                                                   |       |
| ACEi/ARB                            | 11 (50)             | 14 (60.9)                                          | 0.27 |
| β-blocker                           | 15 (68.2)           | 14 (60.9)                                          | 0.61 |
| CCB                                | 12 (54.5)           | 5 (21.7)                                           | 0.02 |
| Diuretic                           | 4 (18.2)            | 3 (13.0)                                           | 0.63 |
| Antiplatelet therapy                | 5 (22.7)            | 5 (21.7)                                           | 0.94 |
| Statin                             | 10 (45.5)           | 12 (52.2)                                          | 0.65 |

Plus-minus values are means ± SD. BMI, body mass index; IHD, ischemic heart disease; PVD, peripheral vascular disease; CNI, calcineurin inhibitor; mTOR, mechanistic target of rapamycin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.
Table 2. Results

| End Points                    | Baseline       | 6-mo Follow-Up | Long-Term Follow-Up | Δa | P Valueb |
|-------------------------------|----------------|----------------|---------------------|----|----------|
| LV mass, g                    | 145.7±30.5     | 124.0±31.1     | 106.4±29.6          | −17.6±23.0 | 0.006    |
| LV mass index, g/m²           | 77.8±14.9      | 66.1±15.2      | 56.1±10.3           | −10.0±13.0 | 0.006    |
| LV end diastolic volume, ml   | 152.6±53.8     | 127.5±48.3     | 135.5±41.5          | 8.0±24.7   | 0.20     |
| LV end systolic volume, ml    | 51.4±24.3      | 42.4±30.9      | 53.7±20.3           | 11.3±20.0  | 0.03     |
| LV ejection fraction, %       | 69.9±9.7       | 68.1±11.8      | 60.6±8.0            | −7.5±10.3  | 0.009    |
| LV cardiac output, L/min      | 6.8±2.3        | 5.7±1.4        | 5.2±1.5             | −0.5±1.4   | 0.14     |
| LV cardiac index, L/min⁻¹·m⁻² | 3.9±0.7        | 3.1±0.6        | 2.7±0.6             | −0.4±0.8   | 0.05     |
| LA volume, ml                 | 93.2±26.8      | 76.4±28.0      | 67.8±26.9           | −8.6±17.0  | 0.05     |
| LA volume index, ml/m²        | 49.1±9.9       | 40.2±12.0      | 35.3±10.9           | −4.9±9.4   | 0.05     |
| RA area, cm²                  | 22.2±5.2       | 20.2±5.7       | 18.5±6.0            | −1.8±4.5   | 0.13     |
| Serum creatinine, μmol/L      | 117.0±56.5     | 107.2±51.5     | 112.8±50.2          | 5.6±29.8   | 0.45     |

BP, mm Hg

Systolic 125.4±13.5 125.8±8.3 143.0±20.7 17.2±21.5 0.005
Diastolic 74.5±7.8 74.5±8.0 85.4±9.0 10.9±12.1 0.002

Plus-minus values are means ± SD. LV, left ventricle; LA, left atrium; RA, right atrium.

A Comparison of cardiac parameters at 6-month and long-term follow-up.

Table 3. Long-term clinical outcomes

| Clinical Outcomes             | Control Group, N=22 | Arteriovenous Fistula Ligation Group, N=23 | P Value |
|-------------------------------|---------------------|-------------------------------------------|---------|
| MI events (%)                 | 1 (4.5)             | 0 (0.0)                                   | 0.30    |
| Cardiac hospitalizations (%)  | 1 (4.5)             | 1 (4.3)                                   | 0.97    |
| Systolic BP, mm Hg            | 134.1±17.2          | 141.2±18.9                                | 0.20    |
| Diastolic BP, mm Hg           | 76.7±9.1            | 83.7±8.6                                  | 0.01    |
| Serum Cr                      | 117.0±35.9          | 123.1±56.7                                | 0.67    |
| Transition to dialysis (%)    | 2 (9.1)             | 1 (4.3)                                   | 0.52    |

Plus-minus values are means ± SD. MI, myocardial infarction; Cr, creatinine.
Serum creatinine remained stable within both groups over the 5-year follow-up and was not significantly different between groups ($P=0.67$). Two patients from the control group returned to dialysis compared with no patients in the AVF ligation cohort who underwent a 5-year CMR and one patient in the AVF ligation cohort who did not have a 5-year CMR performed ($P=0.52$). Thirteen of the patients from the control group (48.1%) underwent AVF ligation over the follow-up period.

**Discussion**

Cardiovascular disease remains a major cause of mortality in kidney transplant recipients with a functioning allograft (12,20,21). There is a clear relationship between left ventricular hypertrophy (LVH) and cardiovascular mortality in both the general and kidney transplant populations (11,22). The etiology of LVH in ESKD is multifactorial and includes the presence of a persistent high cardiac output state due to the existence of an AVF. Although LVH tends to improve following kidney transplantation, complete regression of preexisting LVH does not occur, and in part, this may be due to factors including persistent hemodynamic effects of maintaining AVF access (23). The sequelaes and long-term effects of AVF closure on cardiac parameters in this cohort of patients remain unclear. A prospective study demonstrated a reduction in LVM index and LV end diastolic diameter following AVF ligation in stable kidney transplant recipients, with the effect predominantly observed in patients with persistent LV dilation following transplantation (24). A meta-analysis performed on studies prior to January 2019 demonstrated that AVF closure improved both echocardiographic-derived cardiac morphology and renal graft function, with lower serum creatinine levels documented (25). Our previous prospective RCT demonstrated a clinically important and statistically significant reduction of LV myocardial mass following ligation of patent AVF in kidney transplant recipients with stable renal function (19). We also reported a statistically significant post-AVF ligation decrease in other CMR-derived cardiac parameters, including LV end diastolic and end systolic volumes, bivarial volumes, and cardiac output, but not LVEF when compared with controls (18). The 5-year follow-up data in this study cohort demonstrated that the initial improvements in cardiac parameters noted at 6 months following AVF ligation were generally maintained. Noteworthy, there was further statistically significant regression of LVM and LVM index at 5 years in our nonrandomized analysis. However, a decline in LVEF was observed across the cohort, with the deterioration predominantly driven by a decline in LVEF in three patients. The basis for the fall in LVEF is unclear but could in part be attributable to an exacerbation of hypertension following fistula ligation.

A rise in BP, particularly diastolic BP, has previously been reported following AVF closure (26). Although BP elevation was not observed at 6 months post-AVF ligation in our cohort, our follow-up data demonstrated a significant rise in both systolic and diastolic BPs. This is likely attributed to the long-term consequences of chronic immunosuppressive therapy in transplantation and more specifically, the use of glucocorticoid therapy and calcineurin inhibitors (27,28). This highlights the importance of close BP monitoring over the intermediate and long-term in this cohort of patients. Peer-reviewed data regarding the potential threat to kidney function following AVF closure in kidney transplant recipients has been conflicting (29,30). Our study has not demonstrated any negative effect of AVF ligation on long-term kidney allograft function as reflected by the stability of serum creatinine results or the need to return to dialysis.

Our study showed no increase in all-cause mortality in the control group compared with the AVF ligation cohort over the 5 years and no statistically significant difference in cardiovascular death, nonfatal stroke, nonfatal MI, or hospitalization for a cardiac cause.

A major limitation of this study, however, was its small sample size. We were unable to follow ten of the 27 patients in the AVF ligation group. However, we believe that the similarity of characteristics between this subgroup and those who proceeded to 5-year CMR allows for meaningful interpretation of findings across the entire AVF-ligated cohort. Additionally, there was no control group for comparison of CMR parameters. This arrangement leads itself to a significant risk of bias, in particular selection bias. Future large-scale randomized, prospective studies powered for clinical outcomes are required before the routine systematic ligation of AVF after successful kidney transplantation can be advocated.

This long-term follow-up study of patients undergoing AVF ligation after successful allograft kidney transplantation demonstrates continuing benefit with further regression of LVM and LVH and maintenance of the improvement in other CMR-derived cardiac parameters seen within 6 months of intervention. This may be important particularly given the effect of LVH and increase in LVM on cardiovascular mortality. This was not reflected in clinical outcome data in our small study. Neither was the decline in LVEF, which is of concern and requires further investigation.

**Disclosures**

R. Carroll reports consultancy agreements with HANSA Biopharma and research funding from Bristol Myers Squibb. P. Coates reports scientific advisor or membership with Transplantation Society of Australia & New Zealand. R. Faulk reports scientific advisor or membership with the Polycystic Kidney Disease Australia Scientific Advisory Board. S. McDonald reports research funding from Atel- lass and Baxter, honoraria from Nippro, and scientific advisor or membership with Fresenius Kidney Care Australia as a national clinical advisory committee member. All remaining authors have nothing to disclose.

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**Author Contributions**

P.T. Coates, D. King, E. Macaulay, S.A. Olakkengil, N.N. Rao, C.H. Russell, T. Salehi, M.B. Stokes, and M.I. Worthley conceptualized the study; N. Juneja, S.P. McDonald, N.J. Montarello, and T. Salehi were responsible for data curation; N.J. Montarello, D.J. Scherer, M.B. Stokes, K.S.L. Teo, and K.F. Williams were responsible for investigation; N.J. Montarello, T. Salehi, and
K.S.L. Teo were responsible for formal analysis; T. Salehi was responsible for methodology; K.F. Williams was responsible for project administration; K.S.L. Teo was responsible for resources; S.P. McDonald was responsible for software; P.T. Coates and N.N. Rao were responsible for funding acquisition; R.P. Carroll, P.T. Coates, R.J. Fauli, N.N. Rao, D.J. Scherer, M.B. Stokes, and M.I. Worthley provided supervision; N.J. Montarello, N.N. Rao, and T. Salehi wrote the original draft; and R.P. Carroll, P.T. Coates, R.J. Fauli, N.J. Montarello, N.N. Rao, T. Salehi, and M.I. Worthley reviewed and edited the manuscript.

Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000692021/.../DSupplemental.

Supplemental Appendix. Baseline characteristics.

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