Should we ligate arteriovenous fistulas in asymptomatic patients after kidney transplantation?

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Running title: Cardiovascular effects of AVF ligation

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When Brescia and Cimino first described a series of successful autogenous arteriovenous fistulas (AVF) creations for hemodialysis (HD) in 1966[1], they quickly recognized the ensuing increased cardiac output as the major disadvantage of the new technique. They considered it clinically insignificant and this was probably true in their cohort of young dialysis patients (mean age 43 years), none of which had end stage renal disease (ESRD) caused by diabetes or vascular disease. Over time, however, there have been significant changes in the demographics of the prevalent HD population, with trends toward increasing age and comorbidity, including impaired baseline cardiac function.

Left ventricular hypertrophy (LVH) is primarily an adaptive remodelling process as a response to increased cardiac workload aiming to minimize ventricular wall stress and is almost universal in new dialysis patients. The development, severity, and persistence of LVH are strongly associated with cardiovascular (CV) events and mortality risk in chronic kidney disease (CKD), especially in patients in the highest tertiles of change in LV mass treated with conventional HD[2]. Despite its detrimental effects when present, the impact of LVH regression on mortality remains uncertain. An elegant multifactorial interventional study by London *et al*[3] has demonstrated that a 10% decrease in LV mass translated into a 28% decrease in mortality risk from cardiovascular causes over a 5-year period. Contrary to these results, Foley et al[4] found that improvements in LV mass over a 1-year period after initiation of dialysis were associated with a subsequent reduced likelihood of cardiac failure but not with mortality risk.

NATURAL HISTORY OF LV MASS CHANGE AFTER AVF CREATION AND AFTER KIDNEY TRANSPLANTATION

The hemodynamic effects following AVF creation include decreased peripheral resistance and thus increased cardiac output, which initially does not lead to symptoms of congestive (or high-output) cardiac failure. As the fistula increases in size, the increased blood volume results to increased right atrial, pulmonary artery, and LV end-diastolic volumes until the myocardium decompensates, the LV dilates, the ejection fraction declines, and the patient

has symptoms of cardiac failure. Myocardial ischemia caused by an imbalance between subendocardial oxygen supply and increased oxygen demand as a result of increased cardiac output has also been implicated in the development of deleterious cardiac effects[5]. Using cardiac magnetic resonance (CMR) imaging, Dundon et al[6] showed a mean increase of 25% in cardiac output, 12.7% in LV mass and 21% in LV end-systolic volumes 6 months after AVF creation. These changes add a significant burden to the pre-existing LV hypertrophy, dilatation and dysfunction caused by the underlying uremic cardiomyopathy as CKD progresses.

On the other hand, re-establishment of renal function following kidney transplantation and avoidance of the pronounced intravascular volume shifts occurring during thrice-weekly hemodialysis therapy consistently reduces LVH[7]. More interestingly, regression of LVH continues beyond the first year after renal transplantation, reaching a nadir at the second year and persisting thereafter[8]. Kidney transplant (KT) recipients have lower CV death risk compared with patients on the transplant waiting list[9], suggesting that the progression of CV disease can be ameliorated by restoring renal function with a transplant.

AVF LIGATION IN KIDNEY TRANSPLANT RECIPIENTS

In this issue of *Circulation*, Rao and colleagues present a randomized controlled trial of 54 KT recipients equally randomized to AVF ligation or no intervention. All patients had a kidney transplant implanted at least 1 year prior (median 7.5-9 years), stable graft function, and underwent CMR at baseline and at 6 months (REFERENCE TO THE IN PRESS PAPER).

This was a well-conducted collaborative study with high standards in methodology. They have used CMR imaging which is widely considered to be the “gold standard” technique for the assessment of LV dimensions because it accurately defines mass, volume, and pattern of LVH (concentric, eccentric, or asymmetric) independently of geometric assumptions.

The key primary finding was a 15% reduction in LV mass in the AVF ligation group associated with a decrease in cardiac output. There was approximately 20% decrease in LV and atrial sizes and also a reduction in NT-pro BNP levels. No significant changes were documented in LV ejection

fraction, pulmonary artery velocity, blood pressure and estimated glomerular filtration rate (eGFR). Eight patients had minor complications following fistula ligation (6 had thrombosis and 2 had local infection). The authors advocate that these findings may have significant implications, given that a single intervention has the potential to provide substantial CV benefits.

The findings from Rao *et al* certainly are provocative, and they reflect the scarcity of knowledge and guidance in this particular field. They are hypothesis generating and, as the authors properly state, not definitive. Nevertheless, several important considerations must be addressed before widespread dissemination of the proposed approach.

These data significantly expand previously reported observational studies investigating the cardiac effects of AVF closure post-KT. Studies of the renal transplant population[10, 11] show that closure of the fistula results in significant reductions in both LV end-diastolic diameter and LV mass. Nevertheless, AVF closure does not restore a normal LV geometry and the reduction in LV mass is a result of the reduction in LV end-diastolic volume rather than a decrease in wall thickness[12].

NOT ALL AVF ARE EQUAL

Many unknowns remain and several of those key questions are highlighted by the authors. First, this study was not adequately powered to detect differences in cardiovascular and survival outcomes. Whether the decrease in LV mass and reversal of LVH following AVF closure imparts a protective effect and changes the trajectory of patient outcomes is still a matter to be resolved. Second, a risk stratification using surrogate markers such as fistula blood flow (Qa) measurements or the fistula site (i.e. upper arm compared with forearm AVF) has not be applied. Traditionally, patients with a Qa greater than 2L/min or an upper arm AVF are at increased risk for the development of cardiac failure[13] and perhaps would benefit more from fistula closure. Third, thoughtful consideration of the benefit of AVF ligation against the risk of losing a dialysis access site, especially in patients that will potentially return to HD during their lifetime should be applied. No doubt, preservation of the AVF or a flow reduction procedure may be preferable to fistula closure for younger patients. And finally when is the best time to ligate an AVF following

successful KT? It may be that the benefit on cardiovascular or even graft outcomes is greater if the fistula is ligated 3 to 6 months post-KT presuming stable graft function.

WHERE DO WE GO FROM HERE?

The added CV risk following AVF creation in patients with CKD, who already have excessive CV disease burden, is difficult to quantify. Even more so, the CV risk reduction attributed to AVF closure after successful kidney transplantation, where both events have a perceived favourable effect in cardiac indices, is even harder to examine. Notably, current guidelines in post-operative care in the kidney transplant recipient make no recommendations on management of a redundant AVF[14]. Studies such as the one from Rao and colleagues are a necessary step in the right direction.

The interplay of various factors contributing to LVH during a renal patient's timeline from the development of CKD to progression to ESRD requiring dialysis and transplantation dictates that a more holistic approach targeting all potential contributors starting early in CKD should be adopted. As part of this strategy fistula closure should be reserved for stable kidney transplant recipients with symptoms of overt cardiac failure or pulmonary hypertension and access-related complications (mainly aneurysm formation with risk of rupture, steal syndrome, infection or high Qa). For the rest, an individualized patient-centered approach which will include patients' preferences and beliefs is deemed more appropriate. The pros and cons of AVF ligation are summarized in Figure 1.

In the wake of this admirable work from Rao and colleagues, AVF closure post-KT has a role for selected patients. The adoption of this approach must be weighed against its generalizability to diverse transplant populations, the lack of definitive hard clinical end-points, and potentially high implementation costs. Future longitudinal studies focused on cardiovascular and survival outcomes with appropriate stratification and long-term follow-up will shed more light in this important controversy.

Conflict of Interest Disclosures

None

Legend

Figure 1

Theoretical advantages and disadvantages of AVF ligation

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