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The impact of functioning hemodialysis arteriovenous accesses on renal graft perfusion: Results of a pilot study

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Abstract

Introduction: After a kidney transplant, it is unknown whether the maintenance of a functioning hemodialysis arteriovenous access could have deleterious effects on renal grafts. We hypothesize that maintaining an arteriovenous access can deviate a significant proportion of the cardiac output from the renal graft. The aim of this study was to investigate whether a temporary closure of the arteriovenous access could lead to an increase in graft perfusion.

Methods: We conducted a study in 17 kidney-transplanted patients with a functioning arteriovenous access. We evaluated, at baseline and 30 s after compression of the arteriovenous access (access flow occlusion), the hemodynamic parameters and the renal resistive index of the graft by Doppler ultrasound.

Results: After arteriovenous access occlusion 82.4% (n = 14) of the patients had a decrease in resistive index. All patients had a decrease in heart rate (67 vs 58 bpm, $p < 0.001$) and 14 (82.4%) had an increase in mean blood pressure (98.3 vs 101.7 mm Hg, $p = 0.044$). There was a significant decrease in the resistive index (ΔRI) after the access occlusion (0.68 vs 0.64, $p = 0.030$). We found a negative correlation in Qa ($r^2 = -0.55$, $p = 0.022$) with the ΔRI, and Qa was an independent predictor of ΔRI in a model adjusted to pre-occlusion resistive index.

Conclusion: Our results showed that temporary occlusion of an arteriovenous access causes a significant decline in renal graft resistive index and this decline is higher with the occlusion of accesses with higher Qa. These results suggest that the maintenance of arteriovenous accesses, mainly those with higher Qa, can decrease renal graft perfusion.

Keywords

Arteriovenous accesses, renal transplantation, graft perfusion

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Introduction

The management of arteriovenous (AV) accesses in patients who underwent successful kidney transplantation (KT) is a topic of ongoing debate. Although AV accesses are associated with the best outcomes in dialysis patients and still are the access of choice for the majority of patients, there are growing concerns about their potential long-term systemic toxicity.

There are few studies evaluating the impact of maintaining an AV access on graft function. These studies are mostly retrospective and have conflicting results.[1–5] Weekers et al.[1] described a faster allograft glomerular

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filtration rate (GFR) decline after arteriovenous fistula (AVF) closure. On the contrary, Vajdic et al.[2] found better graft function and better graft survival, 1 and 5 years after transplantation, respectively, in patients who closed the AVF after transplantation. Sheashaa et al.,[3] Unger et al.,[4] and Cridlig et al.[5] did not find any difference in allograft function and/or allograft survival between patients with and without a functioning AV access.

Immediately after the AV access occlusion, there is a shift of blood from the access to the remaining vascular tree, which causes some compensatory responses via the baroreceptor–vagal nerve axis.[6] These compensatory responses lead to an increase in blood pressure (BP) and a decrease in heart rates (HRs).[7]

Given that the kidneys are extremely sensitive to changes in the BP and blood volume, it is acceptable to consider that the occlusion of an AV access can lead to changes in the graft vasculature.[8]

A successful KT improves the impaired autonomic functions characteristic of chronic kidney disease, namely, the baroreceptor system.[9] Consequently, a more pronounced hemodynamic change with the access occlusion can be expected in transplanted patients compared to that observed in those under dialysis.[10]

We hypothesized that the maintenance of a functioning AV access after KT can reduce the renal allograft perfusion in two ways. First, deviating a significant proportion of the cardiac output from the systemic circulation, and consequently from the renal graft artery, causing a "graft steal syndrome-like." Second, the functional and structural cardiac adaptations secondary to the AV access[11] can exacerbate the changes in the systemic circulation caused by the AV access, leading to a "cardio-renal graft syndrome-like."

We used the resistive index (RI) measured by Doppler ultrasound as a dynamic marker for the intrarenal vasculature adaptations during the access compression because it has been used as a tool for studying the renal microcirculation and it is widely used in KT patients. It is a non-invasive procedure and has a low cost.[12]

The aim of this study was to investigate whether a temporary closure of an AV access in kidney-transplanted patients could lead to an increase in graft perfusion.

Materials and methods

Inclusion and exclusion criteria

We conducted an experimental study in kidney-transplanted patients with a functioning AV access. A total of 17 patients were randomly selected for the study. The inclusion criteria were patients older than 18 years who received a single kidney at least 9 months before and had a stable allograft function (at least two GFR measures over the past 3 months higher than 30 mL/min). GFR was calculated according to the chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

We excluded all the patients with signs or symptoms of congestive heart failure, heart arrhythmia, biopsy-proven acute rejection episodes or chronic graft dysfunction, renal artery stenosis, hydronephrosis, perirenal fluid collections, or other anatomical abnormalities of the graft presents in any radiologic examination available in the patient records or discovered during our study.

Measurements

The AV access flow (Qa) measurement was performed in the AV access feeding artery with Doppler ultrasound, by the same interventional nephrologist with experience in vascular ultrasound. Three measurements were performed and the mean value was used in the statistical analysis.

The renal RI was determined by Doppler ultrasound by a well-trained radiologist of the radiology department of our hospital. We used a pulsed Doppler sonography with a 3- to 4-MHz convex probe (LOGIQ E9). The interlobar arteries were visualized in duplex color mode and the peak systolic velocity (Vmax) and the minimal diastolic velocity (Vmin) were determined. The RI was calculated with the following formula: ((peak systolic velocity − end diastolic velocity)/peak systolic velocity).

In each moment of the study, that is, before and during the access occlusion, three measurements of the RI were done at three places in the kidney (lower pole, between poles, and upper pole). The mean values of the three measurements at each time were considered for statistical analysis.

Study protocol

After a period of 5 min in the supine position, patient's hemodynamic parameters (HR and BP), Qa, and graft RI were measured. After these baseline measurements, and with the patient in the same position, the AV access was manually compressed for 30 s. The access was examined by palpation and auscultation, to ensure the absence of a thrill and bruit, confirming the complete stop of the access blood flow. After 30 s of compression, and keeping the AV access blocked, the hemodynamic parameters (HR and BP) and the RI measurements were repeated.

The baseline (with the AV access functioning) RI and the hemodynamic parameters were compared with the same parameters measured during the access occlusion.

All demographic data, including the detailed transplant medical history, and laboratory results (creatinine and estimated glomerular filtration rate (eGFR)) were collected from the clinical report.

The protocol of the study was approved by the local ethics committee. All participants enrolled in the study gave informed consent.

Statistical analysis. Variables are expressed as frequencies for categorical variables and median values with interquartile range (IQR) for continuous variables non-normally distributed and ordinal variables.

Table 1. Baseline Characteristics of the Patients.

Variables	Patients (n = 17)
Age (years)	56 (42–59)
Gender, male	9 (52.9)
Race, Black	5 (29.4)
Diabetes	2 (11.8)
Hypertension	12 (70.6)
Donor, deceased	16 (94.1)
Transplant vintage (months)	14 (10–37)
eGFR (mL/min)	51 (47–57)
Access type	
Fistula	16 (94.1)
Graft	1 (5.9)
Access location	
Proximal	10 (58.8)
Distal	7 (41.2)
Access blood flow (Qa) (L/min)	2.3 (1.3–2.5)
ESRD, causes	
FSGF	5 (29.4)
Chronic GN	3 (17.7)
ADPKD	3 (17.7)
ANCA vasculitis	1 (5.9)
Nephroangiosclerosis	1 (5.9)
Unknown	4 (23.5)
Immunosuppression regimen	
PDN + CNI + MMF	15 (88.2)
PDN + mTORi + CNI	2 (11.8)
Hypotensive drugs	
RAAS inhibitors	9 (52.9)
Calcium channel blockers	9 (52.9)
Beta-blockers	3 (17.7)
α_2-adrenergic agonists	2 (11.8)

eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; FSGF: focal segmental glomerulosclerosis; GN: glomerulonephritis; ADPKD: autosomal-dominant polycystic kidney disease; CNI: calcineurin inhibitor; mTORi: mTOR inhibitors; RAAS inhibitors: renin–angiotensin–aldosterone system inhibitors.

Comparison of the variables before and during the access compression was performed using the Wilcoxon signed rank test. Spearman correlation was also used for univariable analysis. Linear regression analysis was used for multivariable analysis.

The sensitivity and specificity of Qa values in identifying the patients with a significant drop in the RI after AV access occlusion was assessed by a receiver operating characteristic (ROC) curve analysis.

For all comparisons, a $p < 0.05$ was considered statistically significant. Statistical analysis was performed with Stata® software version 14.2.

Results

A total of 17 patients were enrolled in the study, 9 were male (53%), with a median age of 56 years, and 2 (11.8%) were diabetics. Median KT vintage was 14 months (IQR 10–37), 16 (94%) had a deceased donor and median eGFR was 51 mL/min. From the 17 patients, 16 (94.1%) had an AVF and 10 (58.8%) had an access in a proximal position. The median measured Qa was 2.3 L/min, and 53% (n = 9) of the patients had a Qa >2 L/min. The Qa measurements were reproducible and precise—we found a mean variability between the three different Qa measurements in each patient of 0.22 L/min. Table 1 summarizes the baseline demographic characteristics of the enrolled patients.

All the patients slowed their HR during the access compression (67 (IQR 62–83) vs 58 (56–66), $p < 0.001$) with an average drop of 9 bpm (Figure 1). During the access compression, there was a statistically significant increase in the mean arterial pressure (MAP) and a decrease in the diastolic blood pressure (DBP) (Figure 1). There was not a statistically significant change in the systolic blood pressure (SBP) (136 (IQR 124–150) vs 134 (IQR 129–150), $p = 0.097$) or pulse pressure (60 (IQR 46–69) vs 61 (41–68), $p = 0.403$) with access compression.

In 82.4% (n = 14) of the patients, there was a decrease in RI during AV occlusion. The median pre-occlusion RI was 0.68 (0.63–0.74) and decreased to 0.64 (0.62–0.67) during occlusion. A Wilcoxon signed rank test showed that this drop was statistically significant ($p = 0.030$, $z = -2.250$) (Figure 1).

The variation of the RI with access compression (ΔRI) was negatively correlated with the Qa ($r = -0.55$, $p = 0.023$) and with pre-occlusion RI of the graft ($r = -0.57$, $p = 0.048$). In multivariable analysis (linear regression) adjusted to pre-occlusion RI, Qa remained an independent predictor of ΔRI (Figure 2). We tested whether a quadratic model fitted this relationship better than a linear regression; however, the quadratic model did not achieve statistical significance ($F(3, 13) = 3.11$; $p = 0.06$; $R^2 = 0.42$). No significant correlation was found between ΔRI and other studied variables, including age, transplant vintage, eGFR, baseline SBP, DBP, MAP, or HR.

The ROC curve analysis showed that Qa values ⩾2.4 L/min predicted the occurrence of an RI drop of at least 0.06 points (sensitivity 83.3%, specificity 81.8%, area under the curve (AUC) 0.773) (Figure 3). The ROC curve used to determine which Qa value could predict a drop in graft RI ($\Delta RI < 0$) was not statistically significant.

In univariable analysis, there were no significant differences in the baseline characteristics (age, gender, race, prevalence of diabetes mellitus (DM) or hypertension (HTN), BP drugs used, immunosuppression therapy, AV access type and location, and deceased vs living KT) between patients in whom RI dropped and in whom it did not drop.

It was not planned in the original protocol of the study to measure the hemodynamic and RI after the access was re-opened. We updated the protocol and also measured, in the last three patients, the BP, HR, and RI 30 s after the

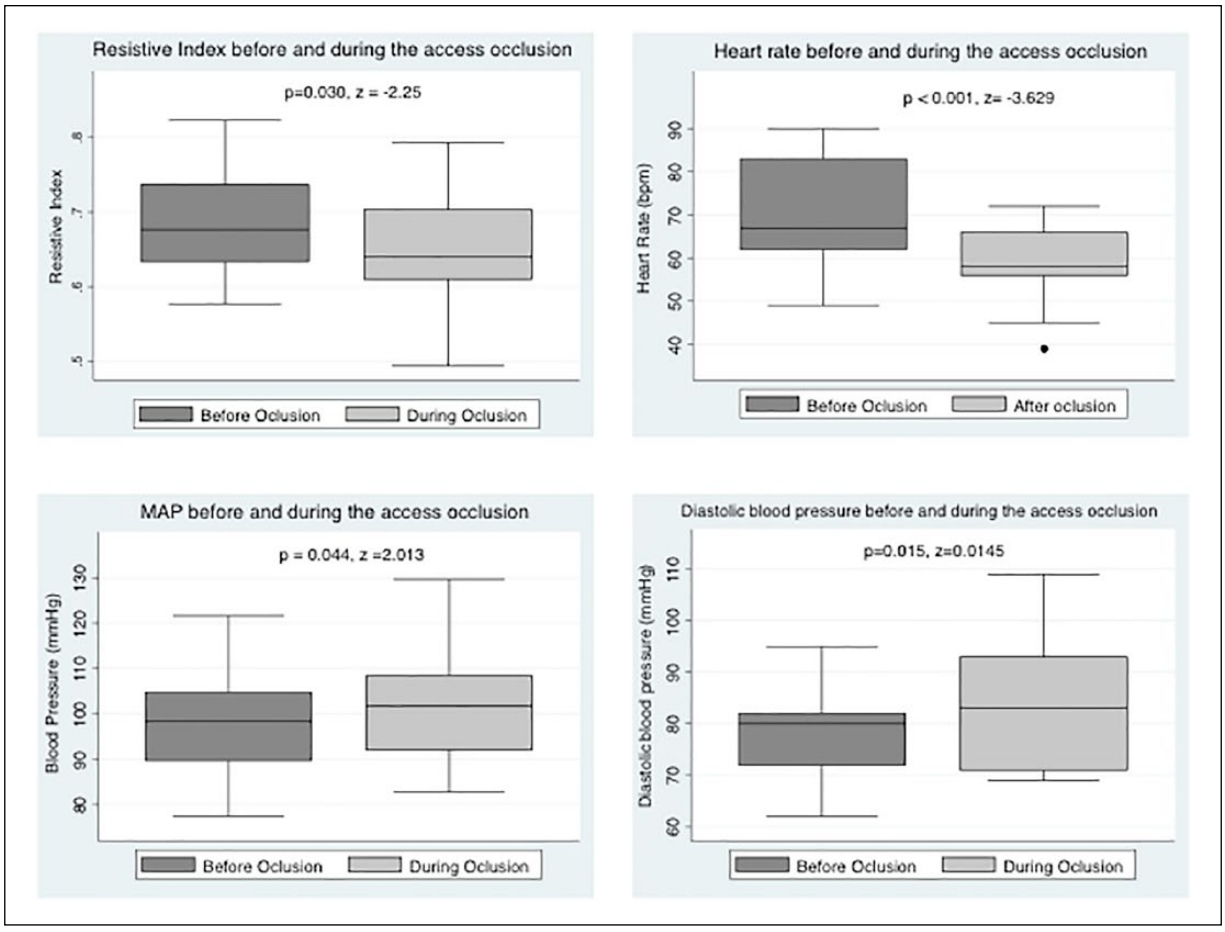

Figure 1. Graphs of the RI, HR, DBP, and MAP before and during access occlusion.

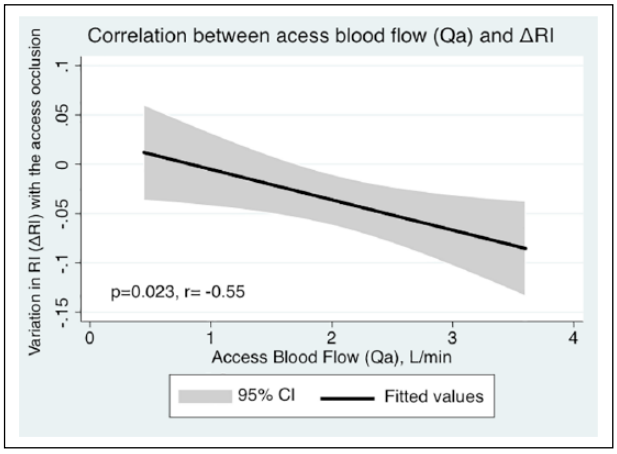

Figure 2. Graph of the access blood flow and ΔRI. The dark line shows point estimate for linear regression adjusted to the pre-occlusion RI. Gray area denotes 95% CI.

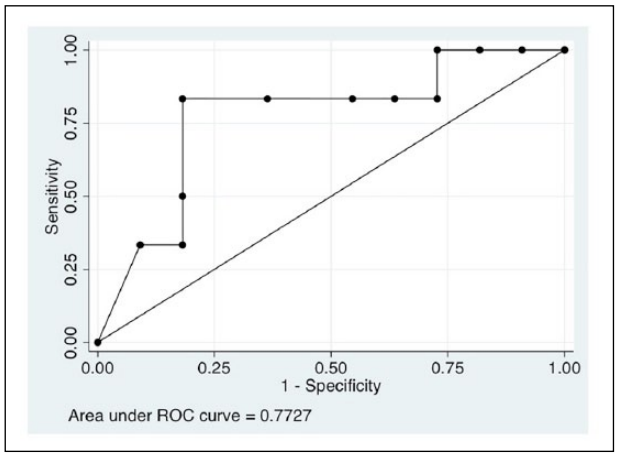

Figure 3. ROC curve analysis—Studding the sensitivity and specificity of Qa values in identifying the patients with a significant decrease in the RI (ΔRI < −0.06) after AV.

access was re-opened. In those patients, MAP (101 vs 99.5, p=0.67), HR (70 vs 69, p=0.89), and RI (0.71 vs 0.73, p=0.63) returned to the baseline values after the re-establishment of the blood flow.

Discussion

This study showed that the temporary occlusion of an AV access in KT patients causes, in the great majority of the

patients, a significant decline in the renal graft RI. The observed drop in graft RI is higher with the occlusion of AV accesses with higher Qa.

As previously described in KT and non-KT patients, we observed a rapid decrease in HR and an increase in MAP with access compression. The clinical relevance of this hemodynamic response is still unknown. However, some authors suggested that the range of this response could reflect the toxicity of AV access on the patient's systemic circulation.[7,9]

Apart from the HR drop, we observed a significant increase in MAP, mainly as a consequence of the DBP increase. It can be observed from the formula used to calculate the RI (peak systolic velocity − end diastolic velocity)/peak systolic velocity) that for an unchanged peak systolic velocity, the increase in the end diastolic velocity causes a drop in the RI, which is in accordance with our findings—a drop in the RI associated with an increased DBP with an unchanged SBP.

An increased renal RI has been described in many diseases such as hemorrhagic shock,[13] renal artery stenosis (RAS),[12] hepato-renal syndrome,[14,15] cardio-renal syndrome,[14] acute kidney injury associated with hypovolemia, sepsis, or multiple organ failure. These diseases have in common the occurrence of hemodynamic changes that cause kidney hypoperfusion. Our results showed that the occlusion of an AV access causes a drop in the RI and corroborates our hypothesis that an AV access can deviate a significant blood volume from the kidney, causing graft hypoperfusion—a "graft steal syndrome-like."

The average drop in RI observed after AV access occlusion was 0.04. Several studies determined that a side-to-side difference in RI of 0.05 is a specific marker of severe unilateral RAS in non-KT patients.[16] The drop in the graft RI we observed is similar to this cut-off used for the diagnosis of RAS, which suggests that small changes in the RI can reflect a clinically significant change in the renal perfusion, especially in patients with a solitary kidney as the KT patients.

Although the preservation of the renal perfusion determines the appropriate organ tissue oxygenation, both the reduction and increase in renal perfusion can lead to a decrease in renal tissue oxygenation and fibrosis.[17] The kidney denervation in the grafts could impair the intrarenal hemodynamic response to the cardiovascular and renal perfusion changes.[17] Future studies are needed to clarify the clinical impact of this increase in graft function and survival.

It was verified in previous studies with KT patients that the acute compression of accesses with higher Qa causes more relevant systemic hemodynamic changes, even if they are not linearly related. For patients with AV accesses with Qa greater than 2–2.5 L/min, there is a cardiovascular exhaustion and the hemodynamic adaptations reach their "maximum."[6] These findings corroborate the study results of Basile et al. about cardiac events in patients under hemodialysis with high-flow AVF (they found that Qa value $\geq$2.0 L/min predicts high-output heart failure).[18] We found a Qa cut-off value $\geq$2.4 L/min as a predictor for a significant drop in the RI ($\Delta RI < -0.06$) during AV access occlusion. We recognize that this model is possibly overfitting the data, so this result should be tested in a bigger sample. However, these three Qa values are very similar, suggesting that accesses with Qa higher than 2–2.5 L/min could be associated with AV accesses' systemic toxicities, such as renal graft hypoperfusion.

In this study, we investigated the acute effects of AV access occlusion in intrarenal vascular changes. Another study showed that the acute hemodynamic effects during traumatic AVFs compression were compared with long-term effects of AV access ligation (the decrease in cardiac output observed during the acute compression is similar to the decrease in the cardiac output observed long term after the AV access ligation).[7] These results suggest that the acute hemodynamic effect observed with AV access occlusion could be an adequate predictor of long-term hemodynamic effects of AV access occlusion.[10] Future studies are needed to investigate whether the acute RI reduction described is a long-term reduction and whether this acute change in the RI could help the physician to predict which patients may benefit more from the access ligation.

In addition to the RI drop, some experimental works described other immediate renal adaptations after an AV occlusion/creation.[19] One of the most important observations (in traumatic AVFs) was that after an AV communication is occluded, there is an abrupt increase in the renal excretion of sodium and the creation of an AV communication has the opposite effect (renal retention of salt).[19] This study did not find acute changes in renal clearance after an AV communication occlusion.[19] These observations in conjunction with the described decreasing serum brain natriuretic peptide (BNP) after AVF occlusion support the theory that when an AV access is occluded, the vascular tree is filled with a greater volume of blood, which causes multisystemic compensatory responses in kidney function (salt excretion), kidney hemodynamics (drop in the intrarenal RI), in heart function (drop in the HR and stroke volume), and hemodynamic changes (increase in BP).

Our study has some limitations: it has a small sample size; it is not a blind study (during the measurements the investigators always knew the access blood flow status, which may have influenced some measurements); renal Doppler RI determination is dependent on the operator expertise and the ability to select an equivalent interlobar artery at each measurement; the focal measurement of the RI in the interlobar arteries may not reflect the heterogeneous intrarenal vascular changes of the entire kidney and future research works are needed to study whether the observed RI decrease is clinically relevant; we could not stop the hypotensive drugs during the study, which could have impacted the changes in the hemodynamic and graft perfusion parameters.

In conclusion, our results suggest that the systemic hemodynamic changes associated with the temporary occlusion of an AV access in KT patients can increase the graft perfusion. The impact of the access occlusion on the graft perfusion is higher with the compression of accesses with higher Qa. A Qa cut-off value ⩾2.4 L/min can be used to predict which patients will have a significant increase in the graft perfusion with the access compression. These results and its consequences in the graft should be studied in prospective randomized studies.

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Declaration of conflicting interests

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