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Original Article

A Rare Cause of Pulmonary Hypertension in Patients With Renal Transplant: High-Flow Arteriovenous Fistula

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ABSTRACT

Objective: Renal transplant is the most effective form of renal replacement therapy. Most of the patients with renal transplant have a history of hemodialysis before transplantation. Therefore, most have arterıovenous fistulas (AVF). Persistent, high flow AVF, which is a rare cause of pulmonary hypertension, should not be overlooked in patients who develop pulmonary hypertension after transplantation.

Methods: In our study, we retrospectively presented our renal transplant patients who newly developed pulmonary hypertension and followed up in our center. We performed fistula closure in our patients with high-flow AVF, which is one of the rare causes of pulmonary hypertension. We recorded our renal (creatinine, glomerular filtration rate, albuminuria, proteinuria), cardiac (ejection fraction) and pulmonary function (pulmonary pressure) data in the 1st and 3rd month follow-ups after the AVF closure procedure.

Results: We observed improvement in cardiac, renal and pulmonary functions of our patients. While creatinine, proteinuria, albuminuria, and pulmonary artery pressure values decreased after AVF closure; GFR and ejection fraction increased. Changes were statistically significant (p values <0.001)

Conclusion: Pulmonary hypertension may develop in renal transplant patients. High-flow fistula is a rare cause of pulmonary hypertension. The presence of high-flow fistula should be kept in mind among the causes of pulmonary hypertension in patients with renal transplantation. Nephrologists should keep in mind the presence of high-flow AVF in patients with newly developing symptoms of pulmonary hypertension.

INTRODUCTION

Kidney transplantation (KT) is the preferred treatment option and provides a significant survival advantage in patients with end-stage kidney disease (ESKD).[1] A large proportion of patients are being treated with hemodialysis (HD) until transplantation. Arteriovenous fistulas (AVF) are the most preferred access in hemodialysis.[1] For most patients, the AV access is maintained after KT in view of the potential risk of losing allograft function and the future need to restart HD. In current clinical practice, the AV access is ligated in the vast minority of transplant recipients as reported in a study about a cohort of 167,000 patients in which only 4.6% of patients underwent AV access ligation after KT.[1] The presence of persistent arteriovenous fistula in patients with KT has effects on the pulmonary and cardiovascular systems. The hemodynamic effects after AVF creation include decreased peripheral resistance and thus increased cardiac output. Because of this continuous hyperdynamic circulation, both left ventricular mass and pulmonary artery pressure increase. In some patients, the effective cardiac output decreases, leading to insufficient systemic perfusion.[2]

Most of the studies in hemodialysis and kidney transplant patients are concerned with the development of fistula-associated pulmonary hypertension (PAH), often caused by high pulmonary blood flow and/or increased pulmonary vascular resistance.[2-4] PAH is generally more frequent in patients on hemodialysis (31.6%) compared with patients on peritoneal dialysis (8.3%) or after kidney transplantation (5%). Remodeling of the pulmonary vascular system seems to be reversible after renal transplantation. This remodeling may be blocked or PAH may even deteriorate in patients with high-flow fistulas.[1] It is controversial whether fistula ligation or reconstruction should be performed in transplant recipients with pulmonary hypertension. There is no consensus on this issue. Clarkson et al.[5] and Kabitz et al.[6] showed that elevated systolic pulmonary artery

pressure can be corrected immediately after fistula ligation. Vanderweckene et al.[7] showed that persistent functional AVF was associated with decreased renal clearance and increased risk of graft loss in renal recipients. On the other hand, some researchers have discussed that prolonged persistent AVF is not at risk for cardiac function in renal transplant recipients.[8-10] Reviewing this controversial issue, Einollahi et al.[11] reported that more prospective data are needed on the long-term effects of fistula ligation on morbidity and mortality in kidney transplant patients.

The aim of our study is to examine the effects of post-transplant AV fistula ligation in our patients with pulmonary hypertension on the symptoms, kidney functions, pulmonary artery pressures, and ejection fractions of our patients.

MATERIALS AND METHODS

We retrospectively reviewed the files of our renal transplant recipients between December 2008 and December 2022. We evaluated 15 patients with pulmonary hypertension of unknown etiology who had dyspnea in their post-transplant follow-up. Our patients were in the hemodialysis program before renal transplantation and had persistent AVF. They were admitted to our outpatient clinics with dyspnea, increased creatinine levels, and unexplained pulmonary edema at different times after transplantation. All kidney transplant patients had no previous pulmonary hypertension and heart failure, and all of them had a fistula with a brachial arterial flow rate of at least 1,200 mL/min. We recorded clinical demographic data [age, gender, body weight, height, body mass index (BMI)], presence of hypertension and diabetes mellitus, RRT characteristics (type, duration), the flow rates and diameters of the fistulas. We also recorded serum creatinine, estimated glomerular filtration rate (eGFR) values, albuminuria, proteinuria, the left ventricle ejection fraction (LVEF), and systolic pulmonary artery pressure (sPAP) values before AVF surgical closure (T0), one month (M1), and 3 months (M3) after surgery. Ethics committee approval of our study was obtained from the ethics committee of Dr. Lütfi Kırdar City Hospital with the number 2023/514/247/7. Written informed consent was obtained from all patients. Statistical Analysis Descriptive statistics were presented as mean ± standard deviation for normally distributed variables or median with interquartile range (IQR) for non-normally distributed continuous variables. Categorical variables were expressed with frequency and percentages (%). Normal distribution of data was assessed by using the Shapiro-Wilk test. The Friedman test was performed to examine statistical differences between baseline, first, and last measurement for serum creatinine, eGFR, albuminuria, proteinuria, PAP, and ejection fraction. The differences between repeated measurements during follow-up were illustrated with a box plot by using the boxplot function in RStudio (v.4.0.2). All statistical analysis was two-tailed, and p values <0.05 were considered statistically significant. All statistical analyses were performed by SPSS software version 21 (Chicago, IL).

Table 1. Patients characteristics

	Patients (n=15)
Age	45.93±15.36
Sex, Male	10 (66.7)
Hypertension	15 (100)
Diabetes	4 (26.7)
Type of kidney transplantatıon (live/deceased)	11(73.3)/4(26.7)
Time after fistula craetıon, mo	109.33±60.99
Time after transplantatıon, mo	76,3±49.15
Fistula flow, ml/dak	2632±1436.51
Fistula diameter, mm	5.1 (4.6–6.2)
Body mass index	26.46±3.20
Hemoglobin, gr/dl	11.99±0.84
Systolic blood pressure	136 (126–140)
Diastolic blood pressure	82.6±10.29
Heart rate, beats/min	80.5±6.5

RESULTS

Clinical demographic and laboratory characteristics of our patients are presented in Table 1. Five of our patients were female and ten were male. The median age was 45.9±15.36 years. AVFs were in all patients located on the forearm. Eleven patients had living-donor kidney transplantations, four patients had deceased-donor kidney transplantations. Fifteen patients had hypertension and four patients had diabetes. The complaints of our patients were swelling of

Table 2. Comparıson of values before and after of AVF closure procedure

	Before AVF closure valeus	After AVF closure valeus (first month)	After AVF closure valeus (third month)	P values
Serum kreatinin, mg/dl	1.4 (1.2-1.9)	1.2 (0.9-1.3)	1.1 (0.9-1.2)	<0.0011,2
Proteinuria, mg/day	284 (159-934)	154 (81-650)	180 (68-350)	<0.0011,2
Albuminuria, mg/day	110 (62-299)	61 (14-130)	68 (18-102)	<0.0011,2
eGFR ml/dk	66 (51-88)	72 (56-96)	70 (62-96)	<0.0011,2
PAB mmHg	35 (30-40)	20 (18-22)	18 (16-20)	<0.0011,2
Ejection fractions, %	35 (30-40)	60 (55-60)	65 (60-66)	<0.0011,2

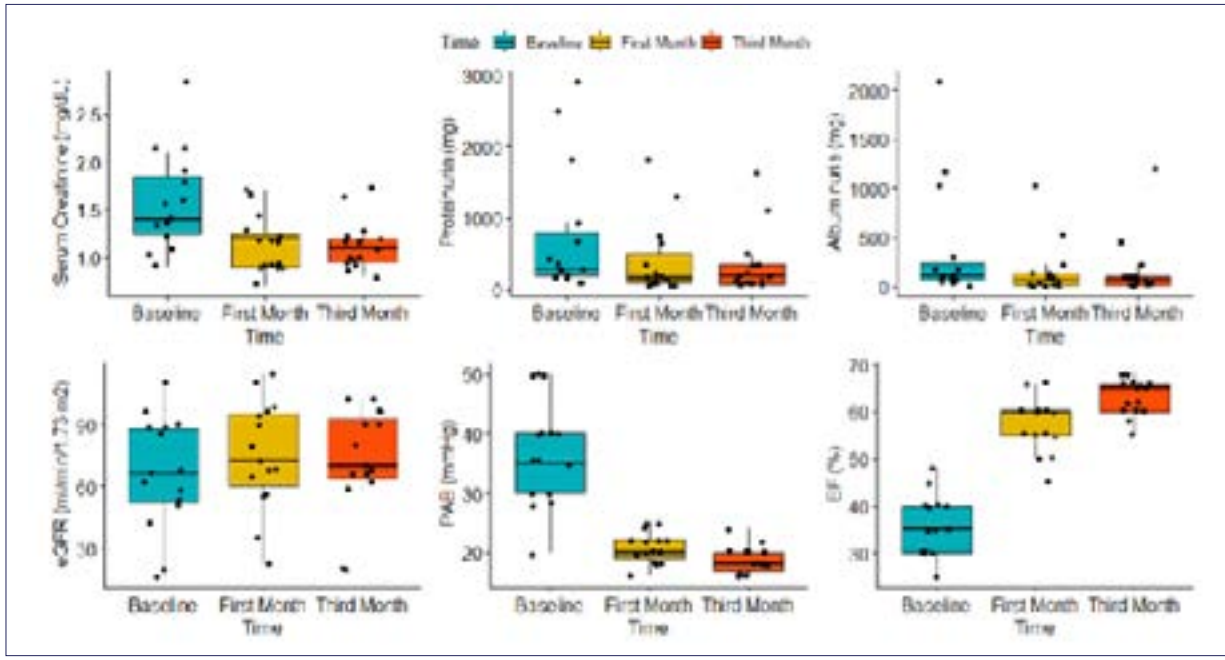

Figure 1. Serum creatinine, proteinüri, albuminuri, pulmonary arter pressure values decreased after closing AVF fistulas. Ejection fraction and EGFR values increaed after closing AVF fistulas.

the legs, shortness of breath, and decreased effort capacity. No signs of rejection were detected. Transthoracic echocardiography showed signs of heart failure, and a significant increase in pulmonary artery pressures. Flow velocity was found to be high in the fistula in Doppler ultrasonography. The median fistula flow rate was 2632 mL/min. After the AVF fistulas were closed, the complaints of our patients decreased. Comparison of data before and after the AVF (arterio-venous fistula) closure procedure are presented in Table 2. After the AVF closure procedure, the serum creatinine, albuminuria, proteinuria, ejection fraction, and PAP values significantly decreased compared to the values obtained before the AVF closure procedure ($p<0.001$). The values between the 1st month and the 3rd month are not statistically significant. Changes in serum creatinine, eGFR, proteinuria, albuminuria, sPAP, LVEF values of our patients are shown in Figure 1. The differences between repeated measurements during follow-up were illustrated with a box plot.

DISCUSSION

In our study, we presented the findings obtained before and after AVF surgical closure in our renal transplant patients. Our 1st and 3rd-month results were statistically significant compared to results obtained before AVF surgical closure. While there was an increase in eGFR and ejection fractions, we found a decrease in creatinine, proteinuria, albuminuria, and pulmonary artery pressures.

Persistent AVF is one of the rare causes that can cause pulmonary hypertension and can cause steal syndrome, edema, cosmetic defects, and heart failure. There is no clear consensus on the management of persistent fistulas after successful kidney transplantation. Although the general opinion is that persistent fistulas that are symptomatic should be closed, there is great variation in routine clinical management.[7] There are retrospective data showing that the closure of previously performed fistulas prevents the formation of high-output heart failure up to 25%. In a study by Abedini et al.[3] in 2013, systolic PAP was found to be higher in hemodialysis patients compared to previous peritoneal dialysis or kidney transplant patients, and it was shown to decrease after kidney transplantation. Based on these retrospective data, in 2020 Hetz et al.[12] conducted a prospective, randomized, controlled trial evaluating the potential benefit of ligature for high-flow AV fistulas. In this study, it was shown that the load on the right and left heart systems is reduced after fistula ligation. Several studies have shown a decrease in the left ventricle (LV) volume after AVF closure procedure. Patients referred for fistula closure are generally those who develop symptomatic heart failure.[5] Most studies in renal transplant patients have shown that AVF closure regresses LV hypertrophy, especially in symptomatic patients.[13-19]

In a randomized controlled study planned by Hertz et al.[20] in 2020 with 28 renal transplant patients with AVF, it was commented that prophylactic fistula closure might prevent heart failure.

Our study has some limitations. The small number of patients is the main limitation of the study. Secondly, asymptomatic patients were not included in the study.

Conclusion

AVF closure in symptomatic renal transplant recipients is associated with improved renal and cardiac functions. AVF flow should be evaluated in renal transplant patients who

develop symptoms of pulmonary hypertension. Further studies with larger samples, including both symptomatic and asymptomatic kidney transplant patients, are needed to assess the long-term clinical outcomes of AVF surgical closure.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 12.04.2023, Decision No: 2023/514/247/7).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.Y.; Design: S.Y.; Supervision: S.Y.; Fundings: S.Y.; Materials: S.Y.; Data: S.Y.; Analysis: S.Y.; Literature search: S.Y.; Writing: S.Y.; Critical revision: S.Y.

Conflict of Interest

None declared.

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Böbrek Nakilli Hastalarda Pulmoner Hipertansiyonun Nadir Bir Sebebi: Yüksek Akımlı Arteriyovenöz Fistül

Amaç: Renal transplantasyon, günümüzde renal replasman tedavisinin en etkili şeklidir. Böbrek nakli olan hastaların çoğunda nakil öncesi hemodiyaliz öyküsü vardır. Bu nedenle hastaların çoğunda hemodiyaliz giriş yolu olan arteriyovenöz fistül (AVF) mevcuttur. Pulmoner hipertansiyonun nadir bir nedeni olan persistan yüksek akımlı AVF, transplantasyon sonrasında pulmoner hipertansiyon gelişen hastalarda göz ardı edilmemelidir.

Gereç ve Yöntem: Çalışmamızda merkezimizde takip edilen ve nakil sonrası yeni pulmoner hipertansiyon gelişen renal transplant hastalarımızı retrospektif olarak sunduk. Pulmoner hipertansiyonun nadir nedenlerinden biri olan yüksek akımlı AVF'li hastalarımıza fistül kapatma işlemi gerçekleştirdik. İşlem sonrası 1. ay ve 3. ay takiplerde renal (kreatinin, glomeruler filtrasyon hızı (GFR), albumünüri, proteinüri), kardiyak (ejeksiyon fraksiyonu) ve pulmoner fonksiyon (pulmoner basınç) verilerimizi kaydettik. Takiplerde hastalarımızın renal kardıyoloji k ve pulmoner fonksiyonlarında iyileşme gözlemledik.

Bulgular: Takiplerde hastalarımızın renal kardıyoloji ve pulmoner fonksiyonlarında iyileşme gözlemledik.

İşlem sonrası 1. ay ve 3. ay takiplerde renal (kreatinin, glomeruler filtrasyon hızı, albumünüri, peroteinüri), kardiyak (ejeksiyon fraksiyonu) ve pulmoner fonksiyon (pulmoner basınç) verilerimiz: AVF Kapatma işleminden sonra kreatin, proteinüri, albüminüri ve pulmoner arter basınç değerleri azalırken; GFR ve ejeksiyon fraksiyonu arttı. Değişiklikler istatistiksel olarak anlamlıydı (p değerleri <0.001)

Sonuç: Renal transplantlı hastalarda pulmoner hipertansiyon gelişebilir. Yüksek akımlı fistül pulmoner hipertansiyonun nadir nedenlerindendir. Renal nakilli hastalarda hastalarda pulmoner hipertansiyon sespleri arasında yüksek akımlı fistül varlığı akılda tutulmalıdır. Nefrologlar, yeni gelişen pulmoner hipertansiyon semptomları olan hastalarda yüksek akımlı AVF'nin varlığını akılda tutmalıdırlar.

Anahtar Sözcükler: Pulmoner hipertansiyon; renal transplant; yüksek akımlı arteriyovenöz fistül.