The Effects of Arteriovenous Fistulas (AVF) on Patients’ Cardiac and Endothelial Function in Renal Transplant Recipients

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Abstract

Objectives: This was a cross-sectional study to demonstrate the effects of AVFs in renal transplant recipients on cardiac and endothelial functions of patients.

Methods: The patients were evaluated in three groups including working AVF, closing AVF, and never opening AVF. LVM and LVMI values were calculated from echocardiographic measurements. Brachial artery FMD (flow-mediated vascular dilation) measurements of 81 patients were performed using the high-resolution external B-mode USG method. At the end of two years, the LVM and LVMI values of 45 patients, were calculated from echocardiographic measurements and compared with baseline findings.

Results: In the group with open AVF, it was observed that LVM (244±72 [g]) to 222±56 [g], p=0.039) and LVMI (139±31 [g/m²] to 123±27 [g/m²], p=0.002) values decreased significantly after two years. In the brachial artery FMD analysis, when the group with open AVF was compared with the group with AVF closed, the FMD values of the group with open AVF were found to be statistically significantly lower (p=0.023).

Conclusion: The study concluded that while there was no significant effect of AVF on left ventricular hypertrophy, it was associated with endothelial dysfunction.

Keywords: Kidney transplantation, arteriovenous fistula, endothelial disfunction

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disease, chronic heart failure, peripheral vascular disease, diabetes, and chronic renal failure.\(^{[12]}\)

With high-resolution B-mode external vascular ultrasonography, the increase in lumen width due to the increased blood flow of the brachial artery and the endothelium's vasodilatation capacity can be measured.\(^{[13]}\) This study aimed to demonstrate the effects of AVFs on patients’ cardiac and endothelial functions in renal transplant recipients with transthoracic echocardiography and high-resolution B-mode external brachial artery USG.

**Methods**

Two hundred ten renal transplant recipients followed between January 2008 and December 2010 in the Transplantation Unit of Istanbul University, Istanbul Medical Faculty, Nephrology Department were included in the study. All patients between 18-65 years of age with a first renal transplantation were accepted. Exclusion criteria included COPD, diabetes mellitus, a history of cardiovascular disease, a creatinine clearance of <30 mL/min, primary pulmonary hypertension, and thyroid dysfunction. Ten patients were excluded due to the exclusion criteria–five of them had DM, and the other five had high creatinine during follow-up. In the study, a cross-sectional evaluation was planned for three patient groups: 93 (46.5%) with an open arteriovenous fistula, 70 (35%) with a closed arteriovenous fistula, and 37 (18.5%) with a never opened arteriovenous fistula. All patients’ age, gender, body mass index (BMI), smoking history, pre-transplant dialysis duration, donor type (living, cadaveric), arteriovenous fistula duration, and systolic and diastolic blood pressure were evaluated. The patients’ blood pressure was measured with a sphygmomanometer after at least 10 minutes of rest during outpatient clinic follow-ups. Patients with a systolic blood pressure above 140, a diastolic blood pressure above 90, and antihypertensive treatment were evaluated as hypertensive.

Echocardiographic examinations were performed using the Vivid 7 device and a 3 MHz probe, and the patients were placed in the left lateral decubitus position. Measurements were made with an echocardiograph of the left atrium diameter, right ventricle diameter, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPWT), ejection fraction (EF), and pulmonary artery pressure (PAP). Left ventricular mass (LVM) and left ventricular mass index (LVMI) were calculated using echocardiographic measurements. The left ventricular mass was calculated using the formula developed by Reichuk & Devereux and measured as follows: 1.04 [(diastolic LV diameter + septum thickness + LVP wall thickness) - 3(diastolic LV diameter)] - 13.6. The left ventricular mass index was calculated by dividing the left ventricular mass by the body surface area. For left ventricular hypertrophy, >134 g/m² in men and >110 g/m² in women were taken.

Brachial artery FMD (flow-mediated vascular dilation) measurements were performed on 81 patients whose consent was obtained after being informed about the study’s purpose and nature. FMD measurement was performed on the brachial artery using a 10 MHz probe with high-resolution USG from the patients’ arms without AV fistula. The linear probe was placed 3-7 cm above the antecubital fossa. Measurements were taken from the same place by keeping the arm in which the measurement was made constant and marked. At the end of the diastole, three measurements of the brachial artery’s inner diameter were made, and the average of the measurements was recorded. Forearm ischemia was created by holding the sphygmomanometer’s cuff for five minutes at 180-200 mmHg by wrapping it around the upper arm. Sixty seconds after the cuff was loosened, three measurements of the brachial artery diameter were made, and the average of the measurements was recorded. Thus, FMD occurring in response to reactive hyperemia was evaluated.

FMD values indicating EDD (endothelium-dependent dilation) and endothelial dysfunction were calculated according to the formula below:

\[
\text{FMD}\% = \frac{\text{mean diameter after hyperemic flow - basal diameter}}{\text{basal diameter}} \times 100
\]

The plan was to evaluate 50 patients in the study’s prospective arm to compare the basal LVM and LVMI values determined by an echocardiographic method with the LVM and LVMI values after two years of follow-up and to investigate whether the presence of AVF affected these values.

**Statistical Analysis**

Statistical analyses were performed using SPSS, Version 24.0. Normality analyses were performed using the Kolmogorov-Smirnov test. Quantitative and qualitative variables were given as mean±standard deviation and frequency and percentage, respectively. Pearson’s chi-square and independent samples t-tests were used to determine the main characteristic differences between patient groups. Baseline measurements of LVM and LVMI levels and measurements after two years were compared using an independent t-test. Two-sided tests were performed for all analyses, and a p<0.05 significance level was determined.

**Results**

The demographic characteristics of the patients are shown in Table 1. A total of 200 patients, who were informed about
the purpose and quality of the study and whose consent was obtained were included in the study, 124 (62%) male and 76 (38%) female. The study group consisted of three smaller groups: 93 (46.5%) patients with working AVF, 70 (35%) patients with closed AVF, and 37 (18.5%) patients with never opened AVF. The mean BMI was found as 24.4±4.4 kg/m$^2$. Before transplantation, 159 (79.5%) of the patients in the study were receiving hemodialysis, 26 (13%) were receiving peritoneal dialysis, and 15 (7.5%) had preemptive renal transplantation. The mean duration of the PreTx dialysis was 46±45 months (1-180 months). The mean number of AVF operations for those with AVF was 1.5±1 (1-6 operations), and the mean duration of AVF for those with open AVF was 73±59 months. After Tx, 25 of the patients whose AVF did not work was closed voluntarily, and the fistula of 45 patients stopped spontaneously. The main reasons for AVF closure were determined as an aneurysm (10 patients), cosmetic reason (nine patients), cardiac complaint (four patients) and fistula thrombosis (two patients). Of the 45 patients whose AVF stopped spontaneously, 24 had stopped during the transplantation operation, two during the post-transplant delivery, the others (n=19 patients) during the posttransplant period for unknown reasons. When the patients' demographic characteristics were evaluated, no significant difference was found in terms of age, gender, body mass index, duration of pretransplant dialysis, or smoking rates.

Hypertension was found in 123 (61.5%) of the patients, and hyperlipidemia was found in 83 (41.5%). When the patients in all three groups were evaluated in terms of hypertension, the use of antihypertensive therapy, systolic blood pressure, diastolic blood pressure, the presence of hyperlipidemia, and the use of statins, no statistically significant difference was found between them.

### Echocardiography Findings

Basal echocardiography findings are shown in Table 2. When the patients' echocardiographic findings were evaluated, no statistically significant difference was found between the groups in terms of EF, PAP, left atrium and right ventricle diameter, LVEDD, LVESD, IVST, LVM, and LVMI measurements.

Systolic dysfunction was detected in two patients, and 52 (30%) patients had diastolic dysfunction. There was no significant difference between the groups in terms of systolic and diastolic dysfunction. LVH was found in 51.6% (48/93) of patients with working AVF, 45.7% (32/70) of patients with closed AVF, and 43.2% (16/37) of patients with never opened AVF (p=0.737). FMD was measured by brachial artery USG in 81 patients to evaluate their endothelial functions. These patients were evaluated in three groups as AVF open (46 patients [56.8%]), AVF closed (23 patients [28.4%]), AVF never opened (12 patients [28.4%]). FMD values were found to be 8.0±6.1% in patients with open AVF, 12.2±5.9% in patients with closed AVF, and 10.4±5.7% in patients with never opened AVF group. When all groups were evaluated, the group's FMD values with open AVF were statistically significantly lower than the other groups (p=0.027). In the subgroup analysis, when the group with open AVF was compared with the group with closed AVF, the group's FMD values with open AVF were statistically significantly lower. (p=0.023) There was no statistically significant difference between the other groups.

<table>
<thead>
<tr>
<th>Table 1. The clinical and demographic characteristics of the patients</th>
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<tr>
<td><strong>Clinical and demographic characteristics</strong></td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Gender (male/female)</td>
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<tr>
<td>BMI (kg/m$^2$)</td>
</tr>
<tr>
<td>Smoking history (present/absent)</td>
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<tr>
<td>Dialysis duration (months)</td>
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<tr>
<td>Donor type (living, cadaveric)</td>
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<tr>
<td>Arteriovenous fistula duration (months)</td>
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<tr>
<td>Hypertension (present/absent)</td>
</tr>
<tr>
<td>Antihypertensive therapy (present/absent)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
</tr>
<tr>
<td>Hyperlipidemia (present/absent)</td>
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<tr>
<td>Statin therapy (present/absent)</td>
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</tbody>
</table>

AVF: Arteriovenous fistula; Tx: Transplantation; BMI: Body mass index; mmHg: millimetermercury.
During the study, 45 patients were prospectively evaluated. The demographic characteristics of these patients were similar to the study group. Control echocardiography of 45 patients enrolled in the prospective arm of the study was performed. These patients, 24 (53.3%) AVF open, 13 (28.9%) AVF closed, and 8 (17.8%) never opened AVF, were evaluated in three groups. The new LVM and LVMI findings of the patients in all three groups were compared with the LVM and LVMI findings two years ago. When all groups were evaluated, LVM (from 227±81 [g] to 218±53 [g]) (p=0.481) and LVMI (129±37 [g/m²] to 120±27 [g/m²]) values were observed to decrease significantly (p=0.065).

In the group with open AVF, it was observed that the LVM values decreased from 244±72 [g] to 222±56 [g], and the LVMI values decreased from 139±31 [g/m²] to 123±27 [g/m²]. At the end of two years, a statistically significant decrease was found in the LVM (p=0.039) and LVMI (p=0.002) in the group with open AVF.

LVM values increased from 180±61 [g] to 215±59 [g], and LVMI values increased from 106±29 [g/m²] to 120±29 [g/m²] in the group whose AVF was closed. At the end of two years, a statistically significant increase in LVM levels was detected in this group (p=0.037). There was also a significant increase in LVMI levels, but this increase did not reach a statistically significant level (p=0.203).

It was observed that LVM values decreased from 266±111 (g) to 215±44 (g), and LVMI values decreased from 146±51 (g/m²) to 114±28 (g/m²) in the group without AVF. However, this decrease did not reach a statistically significant level (p=0.345).

### Discussion

The risk of developing cardiovascular disease in patients with chronic renal disease is 10-20 times higher than in the average population. Cardiovascular diseases are the most significant causes of morbidity and mortality in patients with chronic renal disease, independent of other factors.[4]

Cardiovascular mortality increases, even in the very early stages of chronic kidney disease. After the development of end-stage renal disease, the only practical treatment approach is renal replacement therapies. Cardiovascular events are the most common cause of mortality in patients receiving dialysis treatment. Cardiovascular mortality after transplantation is high in patients who have undergone renal transplantation, which is the most exclusive treatment method of end-stage renal disease.[14]

Left ventricular hypertrophy is also an independent risk factor for cardiovascular mortality in end-stage renal disease patients.[15] Left ventricular mass index (LVMI) is calculated and used to evaluate left ventricular hypertrophy. Some studies have found that working arteriovenous fistula increases the development of left ventricular hypertrophy.[16, 17] In a study conducted by Iwashima et al., in ESRD patients, it was found that there was an increase of approximately 15% in cardiac output two weeks after AVF opening, an increase in cardiac contractility, and it was considered that this situation could contribute to the development of left ventricular hypertrophy.[18] In our study’s prospective arm, we calculated the baseline LVM and LVMI values to evaluate the effect of AVF on left ventricular hypertrophy and compared them with the values two years later. In the group with open AVF, it was observed that LVM (244±72 [g] to

### Table 2. Basal echocardiography findings of the patients

<table>
<thead>
<tr>
<th>Echocardiography findings</th>
<th>Tx patients with open AVF n=93</th>
<th>Tx patients with AVF closed n=70</th>
<th>Tx patients with never opened AVF n=37</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>62±5</td>
<td>63±6</td>
<td>63±7</td>
<td>0.471</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>26±8</td>
<td>24±7</td>
<td>24±6</td>
<td>0.712</td>
</tr>
<tr>
<td>left atrium diameter (mm)</td>
<td>35±7</td>
<td>33±4</td>
<td>33±5</td>
<td>0.124</td>
</tr>
<tr>
<td>right ventricle diameter (mm)</td>
<td>25±5</td>
<td>22±2</td>
<td>23±4</td>
<td>0.155</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>46±5</td>
<td>45±5</td>
<td>46±5</td>
<td>0.756</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>27±5</td>
<td>29±6</td>
<td>28±5</td>
<td>0.452</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>11±2</td>
<td>11±2</td>
<td>11±2</td>
<td>0.891</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>232±81</td>
<td>217±74</td>
<td>220±95</td>
<td>0.776</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>135±37</td>
<td>130±40</td>
<td>129±44</td>
<td>0.696</td>
</tr>
<tr>
<td>Systolic dysfunction (present/absent)</td>
<td>1/77</td>
<td>1/62</td>
<td>0/31</td>
<td>0.79</td>
</tr>
<tr>
<td>Diastolic dysfunction (present/absent)</td>
<td>24/54</td>
<td>23/40</td>
<td>5/26</td>
<td>0.128</td>
</tr>
</tbody>
</table>

AVF: Arteriovenous fistula; Tx: Transplantation; EF: ejection fraction; PAP: pulmonary artery pressure; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; IVST: interventricular septum thickness; LVM: left ventricular mass; LVMI: left ventricular mass index; g: gram; mm: millimeter; mmHg: millimeter mercury; m²: square meters.
222±56 (g), p=0.039) and LVM (139±31 (g/m²) to 123±27 (g/m²), p=0.002) values decreased significantly after two years. LVM (180±61 (g) to 215±59 (g), p=0.037) and LVM (106±29 (g/m²) to 120±29 (g/m²), p=0.203) levels increased in the group with closed AVF. In contrast to many previous studies, in our study, LVM values decreased statistically significantly at the end of two years in the group with open AVF.[20, 21] Although there was a statistically significant increase in LVM levels in the patient group with AVF closure and a significant increase in LVMI levels, these did not reach statistically significant levels due to the small number of patients. Neurohormonal changes such as vascular remodeling increased cardiac output, a secondary increase in atrial and brain natriuretic peptide levels, and a decrease in plasma renin activity in patients with open AV fistula cause a decrease in peripheral vascular resistance.[16-18] A significant decrease in the LVMI value in patients with open AVF may be associated with decreased afterload of the heart due to low peripheral resistance and consequently a decrease in the resistance that the heart must overcome during systole. On the contrary, in patients with closed AVF, increased peripheral resistance can be shown to cause the development of concentric hypertrophy in the left ventricle and, as a result, an increase in LVM and LVMI values.

Endothelial dysfunction is a condition in which endothelial cells undergo changes and cannot fulfill their functions due to decreased endothelial-dependent vasodilation resulting from a decrease in NO production in endothelial cells. [19] Endothelial dysfunction can be detected from the early stages of atherosclerosis.[20, 21] Therefore, it is accepted as a marker or even a precursor of cardiovascular morbidity and mortality in many diseases such as hypertension, coronary artery disease, chronic heart failure, peripheral vascular disease, diabetes, and chronic renal failure.[12, 22] Endothelial dysfunction can be evaluated by measuring flow-mediated vascular dilation (FMD) on the brachial artery with high-resolution USG. FMD is an endothelium-dependent process and occurs through the release of NO through potassium channels. Deterioration in response to the shearing effect is accepted as a sign of endothelial dysfunction. Therefore, FMD in the brachial artery can be used to indicate endothelial function.[23, 24]

The effect of arteriovenous fistulas on endothelial functions is not clear yet. To evaluate the effect of AVF on endothelial functions, FMD was measured by brachial USG in 81 patients within the scope of the study. Patients were evaluated in three groups as 46 (56.8%) patients with open AVF, 23 (28.4%) patients with closed AVF, and 12 (28.4%) patients with never opened AVF. The effect of arteriovenous fistulas on endothelial functions is not clear yet. To evaluate the effect of AVF on endothelial functions, FMD was measured by brachial USG in 81 patients within the scope of the study. Patients were evaluated in three groups as 46 (56.8%) patients with open AVF, 23 (28.4%) patients with closed AVF, and 12 (28.4%) patients with no AVF. When all groups were evaluated, the group’s FMD values with open AVF were found to be statistically significantly lower than the other groups. (p=0.027) In the subgroup analysis, when the group with open AVF was compared with the group with closed AVF, the group’s FMD values with open AVF were found to be statistically significantly lower (p=0.023). With these findings, it can be concluded that the presence of AVF negatively affects endothelial functions and contributes to cardiovascular morbidity and mortality in patients with chronic renal disease.

Conclusion

In our study, the direct relationship of open AVFs with left ventricular hypertrophy could not be demonstrated, but increased LVM and LVM, evaluated regarding increased peripheral resistance in the early period after AVF closure, were detected. It has been shown that AVF patency negatively affects endothelial functions secondary to hyperdynamic circulation.

Acknowledgments


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