Renal transplantation normalizes baroreflex sensitivity through improvement in central arterial stiffness

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ABSTRACT

Background. In end-stage renal disease (ESRD) patients, the most common cause of mortality and morbidity are cardiovascular events. This could be attributed to the impaired baroreflex function observed in this group of patients. The effect of renal transplantation (RT) on the baroreflex sensitivity (BRS) in ESRD patients has been inadequately addressed. Therefore, we investigated baroreflex function and its relation to arterial stiffness indices and cardiovascular variability parameters (heart rate and blood pressure variability—HRV and BPV) in ESRD patients before and after transplantation to decipher the underlying mechanism of attenuated BRS in ESRD patients.

Methods. We studied 23 ESRD patients (mean age; 36 years) prospectively before and at 3 and 6 months after RT. Baroreflex function was determined by spontaneous method (sequence and spectral indices). Short-term HRV and BPV were assessed using power spectrum analysis of RR intervals and systolic blood pressure by frequency domain analysis. Arterial stiffness indices were assessed by carotid-femoral pulse-wave velocity (PWV), augmentation index (AI) and central pulse pressure using Sphygmocor Vx device (AtCor Medical, Australia).

Results. RT was associated with the normalization of BRS by 6 months. Arterial stiffness indices, such as AI and central pulse pressure, showed a significant reduction as early as 3 months after RT. PWV and frequency domain measures of HRV after RT did not show statistically significant changes except the LF/HF ratio which had a significant increase at 6 months when compared with baseline. Systolic BPV total power showed a significant reduction by 3 months after RT.

Conclusions. Our data suggest that RT normalizes BRS in ESRD patients by 6 months which follows the improvement in the AI and central pulse pressure.

INTRODUCTION

Cardiovascular events are the most common cause of morbidity and mortality in end-stage renal disease (ESRD) patients [1]. This reported high incidence of cardiovascular events is attributed to hypertension [2], vascular stiffening [3] and cardiovascular autonomic dysfunction [4].

Baroreflex sensitivity (BRS) is an important marker of overall integrity of cardiovascular autonomic control and is an established independent predictor of mortality in ESRD patients [5]. Baroreflex function is found to be severely impaired in the patients of ESRD [6–8] and this deterioration in BRS has been shown to be related to the high incidence of intradialytic hypotension [9]. Impaired BRS could be attributed to chronic hypertension, large arterial stiffness and autonomic neuropathy in ESRD patients.

Renal transplantation (RT) has been shown to improve the baroreflex function in two cross-sectional study designs [7, 8]. The improvement in BRS after nocturnal dialysis was shown...
to be correlated with the improvement in total arterial compliance [10].

Literature on the efficacy of RT as a treatment modality in renal failure for reversal of impaired BRS is inadequate and the probable mechanism underlying this improvement has not been studied.

The present study was prospectively designed to investigate the time course of changes in BRS 3 and 6 months after RT in ESRD patients and to decipher the underlying mechanism of changes in BRS; changes in the arterial stiffness and wave reflections, blood pressure variability (BPV) and heart rate variability (HRV) were also evaluated in ESRD patients before and after RT.

MATERIALS AND METHODS

Patients

The study was conducted in 31 patients with ESRD slated for RT at the All India Institute of Medical Sciences (AIIMS), New Delhi. Assessment of the haemodynamic and clinical parameters prior to and a follow-up at 3 and 6 months after RT was done. Four patients had mortality before the second follow-up [acute myocardial infarction (1), acute rejection of transplanted kidney (1) and unknown (2)]. Four patients were lost to follow-up. Twenty-three patients were tested and followed up further at 3 and 6 months. The period of patient recruitment and data collection lasted for approximately one and a half years from June 2010 to November 2011. The study was approved by the ethics committee for research in humans AIIMS (IESC/T-85/1.4.10).

ESRD patients were diagnosed in the Department of Nephrology, AIIMS, and the testing of vascular parameters was done in the Autonomic and Vascular Function Laboratory, Department of Physiology. Inclusion criteria of the study included patients aged between 18 and 70 years, ESRD patients scheduled for RT in AIIMS, a functioning kidney 3 months following transplantation, the ability to obtain reliable haemodynamic measurements, absence of primary cardiovascular and autonomic disorders and the ability to obtain an informed consent. Informed consent was obtained from each patient after full explanation of the purpose, nature and risk of all procedures used. The study sample was composed of 23 ESRD patients who were on haemodialysis. The mean age of the patients was 36 years and all were non-smokers. All patients had living donors. All patients received a standardized immunosuppressive regimen that included tacrolimus, mycophenolate mofetil and corticosteroids. All patients were on an antihypertensive regimen which included amlodipine, metoprolol, prazocin and clonidine (Table 1). The percentage of patients without blood pressure (BP) control changed from 47 to 17% at 3 months and 8.6% at 6 months after transplantation. There were no significant changes in the antihypertensive taken 3 and 6 months after transplantation.

Measurements

Before the experimental protocol, subjects refrained from food and caffeine consumption for a 4-h period. All recordings were done in controlled ambient temperature. Subjects were given 15 min of supine rest before assessment of haemodynamic parameters. The measurements of BRS, HRV, BPV and arterial stiffness indices were performed at the same visit—3 days before transplantation, at 3 and 6 months in morning hours.

Short-term variability in blood pressure and inter-beat intervals and baroreflex sensitivity (BRS) determination

Arterial pressure was measured beat-to-beat non-invasively with finger photoplethysmography using Finometer® model 2 (FMS, Finapres Medical Systems, the Netherlands) based on the volume clamp method of Penaz along with Lead II ECG for 5 min under spontaneous breathing by patients. After visually inspecting the data for waveform aberrations and ensuring good quality data, recordings are stopped and saved with the appropriate annotations.

Signal analysis and extraction of parameters

All signals recorded and saved were analysed offline using the Nevrokard HRV and BPV analysis software for extraction and calculation of the frequency domain parameters along with the derivation of spontaneous BRS.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)a</td>
<td>35.9 ± 9.3</td>
</tr>
<tr>
<td>Male:female (n)</td>
<td>22:1</td>
</tr>
<tr>
<td>CKD duration (years)b</td>
<td>4 (2–6)</td>
</tr>
<tr>
<td>Dialysis vintage (months)b</td>
<td>24 (12–36)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>Nil</td>
</tr>
<tr>
<td>Probable ESRD aetiology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis (CGN)</td>
<td>15 (65.2)</td>
</tr>
<tr>
<td>Chronic interstitial nephritis (CIN)</td>
<td>2 (8.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (8.6)</td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
<td>2 (8.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (8.6)</td>
</tr>
<tr>
<td>Patients on antihypertensive drugs, n (%)</td>
<td></td>
</tr>
<tr>
<td>One drug</td>
<td>13 (56.6)</td>
</tr>
<tr>
<td>Two drugs</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>Three drugs</td>
<td>1 (4.3)</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; ESRD, end-stage renal disease; n, number.

a The values are expressed in mean ± SD.
b The values are expressed in median (inter-quartile range).
Baroreflex sensitivity. BRS was quantified by sequence and spectral methods as described earlier [11, 12]. Criteria used for the identification of the sequences were (i) RR variation >5 ms, (ii) BP changes >0.5 mmHg, (iii) sequences >3 beats and (iv) sequences correlation coefficient >0.85. The slope of regression line between RR interval and systolic blood pressure gives estimates of the BRS. In the spectral method, analysis of RR interval and simultaneously recorded beat-to-beat blood pressure was done. Thus, baroreflex gain was computed by dividing the amplitude of RR oscillations in low-frequency (LF) band (0.04–0.15 Hz) and high-frequency (HF) band (0.15–0.4 Hz) by the amplitude of corresponding oscillations in BP. A Hanning window was used and magnitude of squared coherence (K^2) function between the BP and RR interval was computed for the calculation of gain in the transfer function in each frequency band. The coherence between the RR interval and beat-to-beat BP was assessed by cross-spectral analysis. The α-index (gain in relationship between the RR intervals and beat-to-beat BP) was calculated only when the K^2 between the RRI spectrum and the BP spectrum >0.5. α-LF is K^2 function between pressure and RR interval in LF band, whereas α-HF is K^2 function between the BP and RR interval in an HF band. Both α-LF and α-HF are expressed as ms/mmHg.

Heart rate variability and blood pressure variability. HRV and BPV parameters were assessed by the spectral method using frequency domain analysis.

Frequency domain analysis of heart rate variability
From the original electrocardiographic signal, the interval between successive R waves was computed (RRI). The RR-tachogram was further analysed by power spectral density (PSD) analysis of the RR sequences. The PSD was calculated using fast Fourier transformation (FFT) using Hanning window in the three frequency bands such as very low-frequency (VLF; frequency 0.001–0.04 Hz), LF (frequency 0.04–0.15 Hz) and HF (frequency 0.15–0.40 Hz). The measurement of VLF, LF, HF power components was made in absolute values of power (ms^2) [13]. The powers were further normalized to account for changes in the total power of the HRV.

Frequency domain analysis of blood pressure variability
Spectral analysis of fluctuations in BP was performed offline. The output was calculated in mmHg^2. The PSD was calculated using FFT using Hanning window in the three frequency bands such as VLF (frequency 0.001–0.04 Hz), LF (frequency 0.04–0.15 Hz) and HF (frequency 0.15–0.40 Hz). PSDs were plotted in mmHg^2/Hz for BPV [14, 15].

Measures of arterial stiffness
Arterial stiffness was quantified using direct measures—carotid-femoral pulse-wave velocity (c–f PWV)—and indirect surrogate measures—augmentation index (AI) and central pulse pressure [16–18]. C-f PWV and central pulse-wave analysis were measured a few days before surgery and 3 months after renal transplantation. After 10 min of rest in the supine position, the brachial artery BP was recorded twice consecutively, with a 1-min interval between each measurement, with a mercury sphygmomanometer using the auscultatory method with phases I and V of the Korotkoff sounds as guides to the SBP and DBP, respectively. The average of the two measurements of BP taken at 1 min interval was used as brachial systolic BP and diastolic BP. All haemodynamic measurements were done on the opposite side of an arteriovenous fistula if present.

The c–f PWV was determined using the SphygmoCor Vx device (AtCor Medical, Australia) [16, 18]. The proximal distance was measured from the suprasternal notch to the carotid artery and the distal distance from the suprasternal notch to the umbilicus and from umbilicus to the femoral artery. The distance was calculated as the proximal distance subtracted from the distal distance. The tonometer probe was placed at the right carotid and femoral arterial sites subsequently. Using an ECG-gated signal and anthropometric distances, the PWV was derived using methodology previously described and validated. The foot-to-foot method was used where time elapsed between the onset of pulse wave at carotid and femoral arteries was calculated. The value was averaged for 10 cardiac cycles to obtain the mean time difference. PWV was then calculated using the mean time difference and the arterial path length between the two recording sites. If the standard deviation of a measurement was >15% of the mean PWV value, the study was repeated. Quality control parameters included: (i) easy identification of foot of the wave, (ii) minimum three pairs of data to calculate the result, (iii) standard deviation (ms) for the two sites <6% of mean time. The c–f PWV was recorded once during the follow-up visit for most of the patients.

The peripheral pulse-wave profile was obtained by placing tonometer over the radial artery using the SphygmoCor Vx pulse-wave analysis system (AtCor Medical, Australia). The Central BP was derived using radial artery pulse-wave analysis and brachial systolic BP and diastolic BP [19].

Statistical analysis
Each parameter was tested for distribution of the data based on standard normality tests (D’Agostino-Pearson omnibus normality test and Shapiro–Wilks test). In case the data distribution was ‘Gaussian’, parametric tests were applied; and for non-Gaussian distribution, appropriate non-parametric tests were applied. The following tests were used: repeated-measures ANOVA with Tukey’s post hoc multiple comparison test for normally distributed data and the Kruskal–Wallis test with Dunn’s post hoc multiple comparison for non-Gaussian distribution. As HRV parameters showed non-normal distributions, they were normalized by logarithmic transformation. The association between changes in central haemodynamics with changes in BRS was determined by Spearman correlation analysis. Stepwise multiple regression analysis was performed to identify independent predictors of improvement in BRS. The level of statistical significance was set at P < 0.05. All statistical analyses were performed using GraphPad Prism Version 5.00 for Windows (GraphPad Software, Inc., USA) and multiple regression analysis using MedCalc Version 12.2.1.0 (MedCalc Software, Belgium).
RESULTS

The study was conducted in 23 ESRD patients and parameters were assessed before RT and a follow-up at 3 and 6 months after transplantation.

Table 1 shows the baseline demographic and clinical characteristics of the ESRD patients. The patients included 22 males and a single female. All the patients were on an anti-hypertensive regimen with 56.6% on one drug, 39.1% on two drugs and 4.3% on three drugs. All patients were on haemodialysis with a median duration of 24 months. In our study, the most common aetiology of ESRD was chronic glomerulonephritis (presumed), which is in concordance with the available literature in India [20].

Biochemical profile of patients before, 3 and 6 months after renal transplantation

After successful RT, patients had a dramatic improvement in the estimated glomerular filtration rate (GFR) as early as 3 months, which plateau thereafter with no further improvement at 6 months when compared with 3 months (Table 2). A similar pattern was observed in the other biochemical parameters—haemoglobin and calcium phosphate product in patients where the haemoglobin levels significantly increased by 3 months and calcium phosphate product decreased by 3 months and no further statistically significant changes by 6 months. Serum cholesterol and albumin had no statistically significant changes even after 6 months post-transplantation. Hence, after successful RT, estimated GFR stabilizes as early as 3 months with improvement in anaemia and abnormal mineral metabolism in these patients.

Clinical profile of patients before, 3 and 6 months after renal transplantation

The clinical profile of the patients that included body mass index, heart rate and brachial blood pressure parameters did not show significant changes by 3 and 6 months after RT (Table 3). After RT, the conventional parameters (brachial BP and heart rate) used to assess the cardiovascular risk did not show statistically significant changes by 6 months.

Baroreflex sensitivity parameters at baseline, 3 and 6 months after renal transplantation

BRS as assessed by the sequence method showed a significant increase by 6 months when compared with baseline and 3-month post-transplantation. While the BRS assessed by the spectral method showed a statistically significant increase in α-LF by 6-month post-transplantation when compared with baseline. Thus, BRS after RT had a significant improvement only by 6 months (Table 4).

Arterial stiffness parameters at baseline, 3 and 6 months after renal transplantation

The arterial stiffness parameters of patients after RT are depicted in Table 5. AI and central pulse pressure show a significant improvement by 3 months and further improvement at 6 months. The decline in both indices continued 6 months after RT, while no statistically significant changes were observed in PWV and central systolic, diastolic and mean blood pressures.

Association of improvement in baroreflex sensitivity with changes in arterial stiffness indices and biochemical parameters

The improvement in BRS showed a significant association with changes in AI (r = −0.3751; P = 0.0007, Figure 1). On

<p>| Table 2. The biochemical profile of patients before, 3 and 6 months after renal transplantation |
|---------------------------------|-----------------------------|--------------------------|-------|
| Biochemical parameters         | Time after renal transplantation | P-value |       |</p>
<table>
<thead>
<tr>
<th></th>
<th>Before (n = 23)</th>
<th>3 months (n = 23)</th>
<th>6 months (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (mmol/L)</td>
<td>5.9 (5.5–6.2)d</td>
<td>6.5 (6.2–7.6)d</td>
<td>7.4 (6.3–8.6)d</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>3.2 ± 0.7</td>
<td>3.1 ± 1.0</td>
<td>3.7 ± 1.4</td>
</tr>
<tr>
<td>Estimated GFR (mL/min/1.73 m²)</td>
<td>&lt;5</td>
<td>66.0 ± 24.0</td>
<td>70.1 ± 22.3</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>40 (40–45)d</td>
<td>44 (40–47)d</td>
<td>40 (40–46)d</td>
</tr>
<tr>
<td>Calcium phosphate product (mmol²/L²)</td>
<td>4.7 (4.1–5.8)d</td>
<td>1.4 (1.2–2.6)d</td>
<td>1.4 (1.2–2.6)d</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD—repeated-measures ANOVA with Tukey’s post hoc multiple comparison test. GFR, glomerular filtration rate; NS, not significant.

*Comparison of before and 3 months after RT.

Comparison of before and 6 months after RT.

Comparison of 3 months and 6 months after RT.

Values are expressed as median with inter-quartile range (first quartile – third quartile)—Kruskal–Wallis test with Dunns post hoc multiple comparison test.
multiple regression analysis, only 16% of changes in BRS could be explained by the model consisting of delta changes in the AI and haemoglobin as independent predictors ($R^2$-adjusted: $-0.1685$).

**Frequency domain measures of heart rate variability at baseline, 3 and 6 months after renal transplantation**

The frequency domain measures of HRV after RT did not show statistically significant changes except the LF/HF ratio which had a significant increase at 6 months when compared with baseline (Table 6).

**Frequency domain measures of blood pressure variability parameters at baseline, 3 and 6 months after renal transplantation**

The parameters of BPV (Table 7) showed a significant decline in total power and LF domain measures in absolute units by 3 months which continued further till 6 months, whereas the HF component in absolute units had a significant improvement by 3 and 6 months when compared with baseline but no further improvement between 3- and 6-months post-transplantation. LF and HF power in normalized units had a significant improvement only by 6 months when compared with baseline.
with baseline with no significant changes at 3 months. The favourable effect of RT in decreasing the total power of BPV is seen as early as 3 months.

**Timeline of changes in the cardiovascular profile of patients after renal transplantation**

The time course of changes in the multiple cardiovascular parameters (systolic BRS by the sequence method, systolic BPV and HRV in the LF band and indirect measures of arterial stiffness indices) after RT is represented in Figure 2. Total power of BPV, AI and central pulse pressure had a significant decline by 3 months when compared with baseline. Along with total power of BPV, AI and central pulse pressure, BRS had a significant improvement by 6 months when compared with baseline, while from 3 to 6 months, total power of BPV, AI, central pulse pressure and BRS had further significant improvement.

**DISCUSSION**

ESRD patients slated for RT were recruited in the present study, and their baroreflex function along with cardiovascular variability and arterial stiffness parameters were evaluated before RT, as well as at 3 and 6 months after successful transplantation. Results of the study show a significant increase in the BRS and decrease in spectral indices of BPV—total power, LF and HF component obtained in a supine position. There was a trend toward increase in LF component of HRV, with a significant improvement in the LF/HF ratio at 6 months. The central pulse pressure and AI decreased while no statistically significant changes were observed in PWV after RT.

RT in patients with ESRD led to an expected improvement in the GFR, haemoglobin and mineral metabolism. These changes were evident at 3 months after transplantation with no further improvements at 6 months. The BRS, however, showed

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**Table 5. Arterial stiffness indices of patients before, 3 and 6 months after renal transplantation**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time after renal transplantation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before (n = 23)</td>
<td>3 months (n = 23)</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>8.65 ± 2.02</td>
<td>8.62 ± 3.23 NS</td>
</tr>
<tr>
<td>AI (%)</td>
<td>27.7 ± 11.3</td>
<td>17.1 ± 9.0 P &lt; 0.05</td>
</tr>
</tbody>
</table>

**Central BP**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Time after renal transplantation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>114.0 ± 21.6</td>
<td>106.6 ± 17.5 NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72.3 ± 11.0</td>
<td>72.4 ± 11.0 NS</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>41.7 ± 13.9</td>
<td>33.0 ± 11.1 P &lt; 0.05</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>89.6 ± 15.6</td>
<td>86.8 ± 12.7 NS</td>
</tr>
</tbody>
</table>

Repeated-measures ANOVA with Tukey’s post hoc multiple comparison test. Values are expressed as mean ± SD.

NS, not significant.

aComparison of before and 3 months after RT.
bComparison of before and 6 months after RT.
cComparison of 3 and 6 months after RT.
Rubinger et al. [8] and Studinger et al. [7] have reported that BRS is better in ESRD patients who have undergone transplantation when compared with those who were on haemodialysis although these results were obtained in a cross-sectional design. The comparison between haemodialysis and renal transplantation patients could be misleading without the knowledge of the actual BRS before transplantation in the same patient group. However, in a

### Table 6. HRV of patients before, 3 and 6 months after renal transplantation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before (n = 23)</th>
<th>3 months (n = 23)</th>
<th>6 months (n = 23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF power (ms²)</td>
<td>40.8 (20.3–123)</td>
<td>64.0 (19–144) NS</td>
<td>128.9 (52.7–210.8)</td>
<td>NSb NSc NS</td>
</tr>
<tr>
<td>HF power (ms²)</td>
<td>57.8 (35.7–66.9)</td>
<td>27.9 (19.9–68.7) NSa</td>
<td>33.1 (13.7–54.8)</td>
<td>NSb NSc NS</td>
</tr>
<tr>
<td>Total power (TP) (ms²)</td>
<td>315.0 (144.7–477)</td>
<td>384.0 (207.6–586) NSa</td>
<td>459.1 (215.1–783)</td>
<td>NSb NSc NS</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>0.54 (0.36–1.34)</td>
<td>1.8 (0.71–5.30) NS</td>
<td>2.28 (0.39–3.51)</td>
<td>NSa 0.0486</td>
</tr>
<tr>
<td>Log(LF/HF ratio)</td>
<td>0.7 ± 0.6</td>
<td>1.3 ± 0.8 NSa</td>
<td>1.7 ± 0.7</td>
<td>P &lt; 0.05b NSc 0.0058</td>
</tr>
<tr>
<td>LF power (normalized units)</td>
<td>33.1 (25.2–52.8)</td>
<td>27.9 (19.9–68.7) NSa</td>
<td>33.1 (13.7–54.8)</td>
<td>NSa 0.0270</td>
</tr>
<tr>
<td>HF power (normalized units)</td>
<td>44.3 (21.1–97.1)</td>
<td>27.9 (19.9–68.7) NSa</td>
<td>33.1 (13.7–54.8)</td>
<td>NSa 0.0008</td>
</tr>
</tbody>
</table>

Values are expressed as median with inter-quartile range (first quartile – third quartile). Kruskal–Wallis test with Dunns post hoc multiple comparison test. NS, not significant.

- aComparison of before and 3 months after RT.
- bComparison of before and 6 months after RT.
- cComparison of 3 and 6 months after RT.
- dMean ± SEM—back transformation of log-transformed data. Repeated-measures ANOVA with Tukey’s post hoc multiple comparison test.

### Table 7. Systolic BPV of patients before, 3 and 6 months after renal transplantation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before (n = 23)</th>
<th>3 months (n = 23)</th>
<th>6 months (n = 23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF systolic BP power spectrum (mmHg²/Hz)</td>
<td>123.1 (110–140)</td>
<td>90.3 (71–120.9) P &lt; 0.05a</td>
<td>70 (50.1–82.4) P &lt; 0.05a &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HF systolic BP power spectrum (mmHg²/Hz)</td>
<td>9.0 (7.6–9.8)</td>
<td>5.2 (3.9–8.1) P &lt; 0.05a</td>
<td>4.6 (3.0–6.1) P &lt; 0.05a &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Total power (mmHg²/Hz)</td>
<td>134.0 (118.7–149.5)</td>
<td>100.4 (78.6–127.1) P &lt; 0.05a</td>
<td>72 (58.3–92.8) P &lt; 0.05a &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>LF power (normalized units)</td>
<td>140.9 (87.9–327.7)</td>
<td>100.0 (62.0–213.7) NSa</td>
<td>62.0 (50–144) P &lt; 0.05b NSc 0.0270</td>
<td></td>
</tr>
<tr>
<td>HF power (normalized units)</td>
<td>36.0 (20.8–52.7)</td>
<td>22.7 (13.5–32.3) NSa</td>
<td>16.0 (11.3–25.6) P &lt; 0.05b NSc 0.0008</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as median with inter-quartile range (first quartile – third quartile). Kruskal–Wallis test with Dunns post hoc multiple comparison test. NS, not significant; BP, blood pressure.

- aComparison of before and 3 months after RT.
- bComparison of before and 6 months after RT.
- cComparison of 3 and 6 months after RT.
subgroup of ESRD patients, who were followed-up after transplantation, Agarwal et al. [6] found similar results after 6-month post-transplantation, whereas Rubinger et al. [8] reported no change in their baroreflex function. This is in contrast to the results of the present study. Probable reasons for this disparity could be the smaller sample size of 16 in their study and a variable duration of follow-up after RT.

Baroreceptors play an important function of buffering the spontaneous BPV by varying the heart rate. Improvement in BRS dampens the blood pressure oscillations by increasing the HRV in the LF (0.1 Hz) band [21]. In the present study, the total power of BPV decreased at 3 months with a further decline at 6 months after RT, while the LF and HF (normalized units) of BPV showed a significant decrease at 6 months when compared with baseline. These findings were in close agreement with the results obtained by Rubinger et al. [8] in 16 ESRD patients which were studied up to 1 year after transplantation.

There was a significant improvement in the LF/HF ratio by 6 months. This is probably due to an increased LF component (though not significant). The LF band comprises the 0.1 Hz baroreflex-dependent oscillations in the heart rate which buffer the blood pressure changes in the same frequency range [22]. In supine rest conditions, the oscillation of RR at LF is almost entirely accounted for by a baroreflex mechanism, since it is not produced in the absence of a 0.1 Hz pressure oscillation [23]. LF component comprises both sympathetic and parasympathetic components [13]. The recent available literature suggests that the LF band reflects baroreflex-mediated oscillations [15, 24]. A recent study by Moak et al. [25] found significant correlation between the cardiac BRS with LF power of HRV \((r = 0.73)\), whereas no correlation between LF power and sympathetic innervations was not significant. Several investigators have reported an increase in total power of HRV after RT [26, 27]. We did not find a significant rise in
HRV, which may indicate that 5-min HRV may not be as sensitive as 24-h HRV which was used in these studies.

In the present study, the AI and central pulse pressure decreased significantly, whereas the decrease in PWV was not significant. However, the quantum of change in the PWV was ~0.5 m/s, which is similar to that observed in earlier studies [28, 29] but the level of significance could not be achieved probably due to small sample size.

AI and central pulse pressure are indirect indices of arterial stiffness as they are also affected by the magnitude of wave reflections [30]. The reduction in these parameters could probably be due to improvement in large artery compliance [16, 17]. The trend toward reduction in PWV with improvement in AI and central pulse pressure probably indicates toward improvement in central arterial stiffness, which itself is an important determinant of BRS [31, 32]. Our results are consistent with the observations by Ignace et al. [29] and Covic et al. [28] who found improvement in the AI by 3 months and a year after RT. Wilkinson et al. [19] and previous study from our laboratory [33] have shown that the AI is a composite marker of central arterial stiffness and vascular tone.

To further investigate whether the improvement in BRS was due to the reduction in arterial stiffness after successful RT, we looked for the correlation between changes in vascular function parameters and changes in BRS in ESRD patients. On univariate correlation analysis, it was observed that, delta changes in BRS had a strong and significant negative correlation with the delta change in the AI, although on multiple regression analysis, only 16% of changes in BRS could be estimated by the model comprising changes in AI and haemoglobin levels (R²-adjusted = 0.1685). These findings cannot be extrapolated to a direct cause–effect relationship between improvement in BRS and vascular functions in ESRD patients after renal transplantation. However, in the light of evidence from epidemiological studies correlating the baroreflex function with arterial stiffness indices [31, 32], it can be stated that, reduction in stiffness indices precedes and hastens the improvement in BRS.

The most salient finding of our study is that RT normalizes BRS in ESRD patients by 6 months probably due to the improvement in the central arterial stiffness. To the best of our knowledge, this is the first study where there has been a comprehensive assessment of autonomic and vascular function parameters of patients—BRS, HRV and BPV along with arterial stiffness indices simultaneously in a prospective study design.

On the basis of the results of the current study and other reported literature, we propose a model for the improvement in baroreflex function after RT (Figures 2 and 3). RT results in an improvement in mineral metabolism [34] and the removal of uraemic toxins [35]. This results in a decrease in vascular stiffness indices [28, 29]. The amelioration in the arterial compliance in the barosensitive regions contributes to the increase in BRS [6] and thus the blood pressure fluctuations are reduced (decrease in BPV) [8] by better heart rate responses (increase in HRV) [26, 27].

In conclusion, in the present study, we provide evidence of the efficacy of RT as a treatment modality in normalization of BRS along with improvement in cardiovascular variability parameters and arterial stiffness indices which itself is an important determinant of BRS.


**CONFLICT OF INTEREST STATEMENT**

None declared.

NDT ERA-EDTA OLA has selected this publication for Blog commentary by its faculty in view of its quality and potential educational value.

Kaur and colleagues in India report on the normalization on the baroreflex sensitivity of hemodialysed patients after successful kidney transplantation (by 6 months).(1) More than a decade ago, it was already shown such improvement (2). However in the present work, measurements were realized in a prospective and longitudinal way just before and after 3 and 6 months of living donor kidney transplantation in 23 young patients (mean age of 36 years) compared to themselves. In the same vein, arterial stiffness indices like augmentation index and central pulse pressure were improved whereas no modification was observed in other parameters (carotid femoral pulse wave velocity and heart rate variability). This improvement in some arterial stiffness indices and baroreflex sensitivity could participate in the lower morbidity and mortality risk noted in kidney graft recipient population in comparison to patients still under dialysis treatment.

The NDT ERA-EDTA OLA readers may be interested to learn more from the authors of this very interesting article about:

(1) Mean age of the patients included was relatively low and almost all compared to themselves patients (except one) were male. Do the authors think the same results could be applied to older or to female patients? It was shown that augmentation index increased with age until 55 and that this parameter was higher in females than in males

(2) The majority of the population (2/3) suffered from glomerulonephritis. Would the same results be expected from diabetic or hypertensive ESRD patients?

(3) The percentage of patients with excellent blood pressure control significantly increased after transplantation. Could this observation have played a role in the baroreflex sensitivity improvement noted in the study?

(4) This improvement of BRS only became significant by 6 months after the transplantation whereas the kidney function was quickly normalized after the surgery. How can we explain this delay? Is this the consequence of healing of large artery structural lesions secondary to endothelial function, oxidative stress and/or inflammation improvements?

(5) It is also known that interactions exist between the autonomic nervous system and the immune system (3). The control of the immune system by immunosuppressive drugs could perhaps play a role. In the current work, tacrolimus, a calcineurin inhibitor, was used. Could we expect the same data with cyclosporin a a potential activator of the sympathetic nervous system by baroreflex resetting (4)?

(6) In this order of idea, some indices of arterial stiffness (usually increased in ESRD) such as augmentation index and central pulse pressure decreased by 3 months after kidney transplantation. So the authors considered these earlier changes as one mechanism for the later increase in BRS but how can we explain that the pulse wave velocity did not significantly change during the same period? Is it also due to the young age of the population in the present study? Indeed, Mitchell et al (5) from the Framingham heart study, showed that Carotid-Femoral PWV was lower than Carotid-Radial PWV below the age of 50 but higher after 50y. The PWV values are besides relatively low and so more difficult to lower.

(7) Another explanation for the absence of PWV improvement could be that these young patients with relatively short dialysis vintage (2y) did not present important aortic calcifications. PWV was related to this complication in hemodialysis (6). Chesterton et al (7) moreover showed a relation between baroreflex sensitivity, vascular calcification and pulse wave velocity in hemodialysis patients. Would more calcified patients present similar evolution as in Kaur’s study after kidney transplantation?

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REFERENCES