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Does renal transplantation actually improve heart rate variability?

İsmail Ateş, Zeynettin Kaya*, Tolegen Yegemberdiyev, Havva Asuman Yavuz, Alper Demirbaş, Ahmet Genç

Department of Cardiology, Faculty of Medicine, Medical Park Hospital, Antalya, Turkey

Abstract

Objectives: The End-Stage Renal Disease (ESRD) patients have high mortality rates despite the modern pharmacological and renal replacement therapies. Heart Rate Variability (HRV) is one of the markers of autonomic nervous system activity. The negative prognostic effect of the deteriorated HRV was clearly shown in several diseases. In our study, we have examined the effect of renal transplantation on HRV in ESRD patients.

Methods: 50 consecutive (12 females, 38 males) patients who underwent renal transplantation enrolled in the study. 24-hour Holter Electrocardiography (ECG) monitoring was done in all patients before and at the end of the third month of the transplantation in order to evaluate HRV. Time-domain HRV analyses were performed by using the recordings of the Holter ECG monitoring. Furthermore, transthoracic echocardiography was done before and early period after the transplantation, and the left ventricular mass index was compared.

Results: The average age was 42.38 ± 13.45. Hypertension was the most frequent comorbid disease (74%). The decrease in all HRV parameters (mNN, SDNN, SDANN, RMSSD, SDNN index) was observed on evaluation at the end of the third month of the transplantation compared with the pre-transplant values, but this difference was not important. In addition, it has been observed that a statistically significant decrease in the left ventricular mass index on evaluation at the end of the third month of the transplantation when compared to the pre-transplantation period (137.99 ± 47.11 *vs.* 126.85 ± 45.29, P=0.01).

Conclusions: The downward trends of HRV values can be one of the markers of increased cardiovascular risk in early post-transplantation period in patients with ESRD.

Keywords: End-stage renal disease, Renal transplantation, Heart rate variability, Left ventricular hypertrophy.

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Introduction

Chronic Kidney Disease (CKD) is defined as the deterioration of the renal fluid-solute balance as a result of the decrease in Glomerular Filtration Rate (GFR) as well as the chronic and progressive failure in the metabolic-endocrine functions of the kidneys [1]. CKD is public health problem health problem throughout the world [2]. The incidence of the CKD has been increasing each year due to high prevalence of Hypertension (HT) and Diabetes Mellitus (DM), the prolonged survival of the patients under treatment [2]. According to the USA findings, CKD prevalence was reported as 11% [3]. This frequency increases with aging, and it reaches up to 39.4% [4].

The most important causes of the morbidity and mortality among the CKD patients are the cardiovascular diseases [5]. End-Stage Renal Disease (ESRD) patients have high mortality rates even though they get modern pharmacological and renal replacement therapies [5]. Mortality rate of haemodialysis patients is 10-30 times higher compared with normal population even after adjustment for traditional risk factors such as gender, race and DM [6]. The most effective treatment is renal transplantation in ESRD. Quality of life and survival rate of the patients of ESRD improve after a successful renal transplantation [7].

Heart Rate Variability (HRV) is one of the important analysis methods, and it is an easy, cost-effective and non-invasive technique in determining the autonomic activity [8]. Decreased HRV is an indicator of the depressed vagal activity that is closely associated with ventricular arrhythmias and pathogenesis of sudden cardiac death [8]. Therefore, the evaluation of autonomic dysfunction with HRV is important in both the risk analysis and the treatment plan. HRV is used for the risk assessment of sudden cardiac death in several diseases such as heart failure, coronary artery disease, stroke, HT, Left Ventricular (LV) hypertrophy and ESRD [9-15].

There are several studies related to the HRV in ESRD patients but there is not enough data about the changes in HRV after renal transplantation [16]. The studies cannot explain the increased cardiovascular risk in the early period upon

transplantation [17]. In our study, we aimed to examine the effect of transplantation on HRV in ESRD patients.

Methods

Between April 2010 and October 2012, 50 consecutive patients (12 females, 38 males) who underwent renal transplantation enrolled into the study. Age, gender, concomitant diseases, pulse rates, demographic and clinical characteristics such as systolic and diastolic blood pressure of all patients were recorded. Fasting blood glucose, renal function tests, liver function tests, uric acid, calcium, phosphorus, fasting lipid profile, complete blood count, CRP levels of all patients were measured and evaluated before transplantation. Body mass index was calculated by using the 'weight/height^2' formula after the height (m) and weight (kg) measurements. GFR was calculated by using Cockcroft-Gault formula [18].

The patients who had atrial fibrillation in electrocardiogram, sinus node dysfunction, second-degree or complete atrioventricular block, acute myocardial infarction within the last 6 months, unstable angina pectoris, acute myocarditis, active chronic obstructive pulmonary disease, chronic liver disease, malignancies, severe valve regurgitation or stenosis detected on echocardiography were excluded from the study. Besides, the patients who were not willing to participate were also excluded from the study.

Echocardiography measurements were performed before and at the end of the third month of the transplantation. Measurements were done by using 2-4 MHz phase transducer with GE-Vivid S3 Cardio Ultrasound (GE Healthcare, UK) accompanied by electrocardiography ECG). The evaluations were done according to the criteria of the American Society of Echocardiography by using standard apical 2-4 and 5 spaces in the left lateral decubitus position, and the parasternal long-short axis images [19]. The LV end-diastolic diameter, end-systolic diameter and wall thickness were calculated by using the parasternal long axis view. LV ejection fraction was calculated, and the average value was obtained in the apical 2- and 4-chamber images by using "modified Simpson's method" [20]. LV mass of the patients were calculated by using Devereux formula [21]. LV mass indexes were calculated by dividing the LV mass to surface area of the body [22].

24-hour Holter ECG recordings were performed for all the patients before and after the transplantation by using the Schiller ECG Holter Monitoring System (SCHILLER AG, Switzerland) in order to evaluate the HRV. First, the recordings were analysed manually in order to exclude the artifacts. Then, automatically time-domain measurements were made. Time-domain analyses are the calculations that are based on the statistical measurements on the R-R intervals [9]. After determining the entire QRS complex in continuous electrocardiographic recordings, the spacings between adjacent QRS complexes (NN) were determined. In the study, mNN (Mean NN Interval), SDNN (The Standard Deviation Of NN Intervals), SDANN (Standard Deviation of the Average NN Intervals of 5-Minute Segments on the Recording), SDNN index (the average of the standard deviation of NN intervals), and rMSSD (square root of the difference between the mating intervals and the consecutive RR intervals) were calculated by evaluating the time-domain analysis [9].

Statistical analysis

The analysis was performed by using SPPS Statistical Software (version 15.0 for Windows; Chicago, IL). All data were shown as mean ± standard deviation. Continuous variables were expressed as mean ± SD and categorical variables as percentage. Normal distribution of the data was evaluated using the Kolmogorov Smirnov test. Differences of the continuous variables were compared between two groups using Student's t test or Mann-Whitney U test, depending on their distribution characteristics. Difference between the categorical variables was evaluated using chi-square test. Pearson's correlation test was used to evaluate the linear relationship between the parametric variables. $p<0.05$ was considered statistically significant.

Results

In our study, the findings of the 38 (76%) male and 12 (24%) female patients who underwent renal transplantation were evaluated. The average age was 42.38 ± 13.45. HT was the most frequent (74%) comorbid disease of the patients with ESRD. DM was observed only in 3 patients (6%). The mean creatine value was 8.02 ± 2.87 and the mean GFR was 13.28 ± 5.78. The pre-transplantation clinical characteristics of the patients can be seen in Table 1.

HRV parameters were compared before and after transplantation. All HRV parameters were observed to be decreased at the end of the third month compared with pre-transplantation period as shown in Table 2. But this difference was not statistically significant.

Echocardiographic findings were compared. Prevalence of LV hypertrophy was 62% before the transplantation and declined to 46% after the transplantation. LV end-diastolic diameter (48.52 ± 5.59 *vs.* 47.44 ± 4.96, P=0.01), LV end-systolic diameter (31.56 ± 6.12 *vs.* 30.54 ± 5.42, P=0.01) and LV mass index (137.99 ± 47.11 *vs.* 126.85 ± 45.29, P=0.01) were found to be decreased significantly at the end of the third month of the transplantation when compared to the findings obtained in the pre-transplantation period. There was no significant difference between the other echocardiographic parameters as shown in Table 3.

There was no statistically significant association between the echocardiographic measurements and HRV parameters according to the correlation analyses.

Table 1. *Demographic and clinical characteristics of the patients.*

		N	Mean ± SD
Age	(years)	50	42.38 ± 13.45
Body mass index	(kg/m^2)	50	24.48 ± 4.79

Systolic blood pressure	(mmHg)	46	131.52 ± 26.58
Diastolic Blood Pressure	(mmHg)	46	79.13 ± 11.51
Pulse rate	(bpm)	46	80.89 ± 8.35
Glucose	(mg/dl)	50	94.61 ± 29.81
Creatinine	(mg/dl)	50	8.02 ± 2.87
GFR	(ml/min)	49	13.28 ± 5.78
Uric acid	(mg/dl)	50	5.96 ± 1.51
Total protein	(g/dl)	50	7.44 ± .84
Albumin	(g/dl)	50	4.21 ± .58
ALT	IU/L	50	19.37 ± 11.69
AST	IU/L	50	16.02 ± 8.05
GGT	IU/L	50	33.17 ± 36.29
LDH	IU/L	50	196.78 ± 45.13
ALP	IU/L	49	105.14 ± 52.018
Total bilirubin	(mg/dl)	50	0.93 ± 3.62
Total cholesterol	(mg/dl)	50	177.55 ± 70.35
HDL	(mg/dl)	50	156.84 ± 784.85
LDL	(mg/dl)	50	91.46 ± 49.05
Triglyceride	(mg/dl)	49	181.32 ± 132.19
Na	mmol/L	50	139.07 ± 2.76
K	mmol/L	50	5.22 ± 1.06
Ca	mmol/L	50	9.12 ± 0.81
P	mmol/L	50	5.60 ± 1.57
Sedimentation	mm/hr	50	39.86 ± 23.55
C-Reactive Protein	(mg/dl)	50	0.81 ± 1.21
Hb	(g/dl)	50	11.43 ± 2.29
PLT × 1000	(n)	50	235.24 ± 72.01
WBC × 1000	(n)	50	7.53 ± 2.09

GFR: Glomerular Filtration Rate; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; WBC: White Blood Cell Count; BMI: Body Mass Index; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; ALP: Alkaline Phosphatase; PLT: Platelet Count; Hb: Haemoglobin; K: Potassium; Ca: Calcium; P: Phosphorus.

Table 2. *Heart rate variability parameters before and at the end of the third month after the transplantation.*

	Before Transplantation Mean ± SD	After Transplantation Mean ± SD	P
mNN	769.12 ± 101.11	761.44 ± 116.00	0.55
SDNN	80.84 ± 18.80	79.13 ± 20.94	0.39
SDANN	69.53 ± 18.84	67.00 ± 22.54	0.22
SDNN index	46.48 ± 19.30	43.70 ± 19.67	0.15
rMSSD	37.25 ± 27.17	34.65 ± 24.14	0.16

mNN: Mean NN interval; SDNN: The Standard Deviation of NN Intervals, SDANN: Standard Deviation of the Average NN Intervals of 5-minute Segments on the Recording; SDNN index: The Average of the Standard Deviation of NN Intervals; rMSSD: Square Root of the Difference between the Mating Intervals and the Consecutive RR Intervals.

Table 3. *Echocardiographic measurements before and at the end of the third month after the transplantation.*

	N	Before transplantation (Mean ± SD)	After transplantation (Mean ± SD)	P
LVEDD	50	48.52 ± 5.59	47.44 ± 4.96	0.01*
LVESD	50	31.56 ± 6.12	30.54 ± 5.42	0.01*
IVST	50	11.45 ± 1.84	11.30 ± 1.74	0.08
PWT	50	13.29 ± 1.91	13.29 ± 1.81	0.15
LVMI	50	137.99 ± 47.11	126.85 ± 45.29	0.01*
FS	50	35.24 ± 6.78	35.54 ± 6.36	0.57
LAD	50	36.82 ± 5.50	37.04 ± 5.34	0.31

LVEDD: Left Ventricle End Diastolic Diameter; LVESD: Left Ventricle End Systolic Diameter; IVST: Left Ventricle Interventricular Septum End Diastolic Thickness; PWT: Left Ventricle Posterior Wall End Diastolic Thickness; LVMI: Left Ventricle Mass Index; FS: Left Ventricle Fractional Shortening; LAD: Left Atrium Diameter.

Discussion

In our study, there was a downward trend in the HRV values in the early period upon transplantation. However, this difference was not statistically significant. On the other hand, LV mass index that is one of the criteria of LV hypertrophy significantly decreased in the early period after the transplantation.

There are two components of the autonomic nervous system including sympathetic and parasympathetic nervous systems. The balance between sympathetic and parasympathetic systems is necessary to maintain vital functions [23-25]. Fluctuations occur between consecutive heartbeats as a result of changes in the autonomic system [23-25]. HRV is the variability in the heart rate determined in a certain period of time [25]. HRV was studied for the first time by Wolf et al., They have stated that the patients who were diagnosed with myocardial infarction and who had marked sinus arrhythmia (high HRV) showed lower hospital mortality rates compared to others [26].

Healthy individuals show low sympathetic discharge during the resting status and they have high HRV [25]. HRV measurements can be divided to two groups: time-domain and frequency based measurements [23]. Both methods have not yet been shown to be superior to each other [23]. Short-term recordings are sufficient in order to perform the frequency based measurements whereas the time-domain analyses can only be done by using long-term recordings such as ECG Holter monitoring [23]. The intervals between adjacent QRS complexes (NN) and the instantaneous heart rate are primarily determined in time-domain measurements. Then, the parameters such as Mean NN (mNN), SDNN, SDANN,

rMSSD, SDNN are calculated. SDNN is the simplest parameter, and it is determined as the standard deviation of the NN intervals. It gives information about all components of HRV. SDANN is the standard deviation of the average NN intervals of a 5-minute segment of recordings, and it gives information about long-term HRV components. rMSSD gives information about short-term HRV components. rMSSD method is more preferred because it has better statistical features [23].

The negative prognostic effect of low HRV in many diseases has clearly been shown [10,11,14,27,28]. Suppression of HRV after myocardial infarction reflects the reduction in vagal activity, the dominance in sympathetic activity and the electrical instability [10,15]. Boskovic et al., performed a study with post-infarction patients. They showed that SDNN and mNN were significantly lower in patients who died and they suggested that SDNN was one of the independent predictors for all-cause mortality [10]. Similarly, it has been reported that the decreased HRV is the strong indicator of the cardiac mortality, sudden death and arrhythmic events in patients diagnosed with heart failure. Fauchier et al., performed a study with patients with non-ischemic heart failure. They have determined that HRV was one of the independent risk factors for sudden cardiac death and major arrhythmic events. Furthermore, Fauchier et al., reported that SDNN 100 msn could be used as the cut-off value in the risk classification [29].

End-stage renal disease is defined as a GFR is lower than 15 ml/minute, and patients need the renal replacement therapies such as dialysis and kidney transplantation [30]. Coronary artery disease is the leading cause of the increased mortality in early periods of CKD [5]. It has been shown that each 10 ml/minute decrease in GFR was indicated to be the 32% increases in risk of myocardial infarction [31]. LV hypertrophy, coronary calcification, heart failure, electrolyte imbalances were mentioned as the reasons of arrhythmic events and sudden cardiac death in ESRD patients [5].

Deterioration of HRV in patients with ESRD was shown in many studies [16,32-35]. Vita et al., performed a study with 30 ESRD patients undergoing haemodialysis and they have found autonomic dysfunction in 53% of patients by HRV [32]. In another study, it has been reported that HRV values were lower in ESRD patients who did not start the dialysis compared with the patients undergoing haemodialysis or peritoneal dialysis [16]. However, there was no consensus regarding the alterations in HRV values during the haemodialysis process [33-36]. Consistent with these studies, Hayano et al., stated that HRV was the independent predictive indicator of the mortality and sudden cardiac death in ESRD patients [37].

Cardiovascular risks decrease with the renal transplantation (annual fatal and/or nonfatal cardiovascular event risk is 3.5-5%). Nonetheless, cardiovascular risk is still high when compared with general population [38]. Studies on patients who underwent renal transplantation indicated that HRV increased in the early period [39-41]. These results were contradictory with outcomes of the large trial was done in 60141 renal transplanted patients [17]. The study showed that the cardiovascular risk after transplantation reached to the highest level in the early period particularly in the first three months [17]. In our study, HRV parameters were evaluated before and after the transplantation in the early period. The HRV values obtained after the transplantation were not significantly different compared with the values obtained before the transplantation. As a matter of fact, the values slightly decreased upon transplantation. In the early period both before and after the transplantation, SDNN value was lower than the cut-off value (<100 msn) that was implied as the indicator of the cardiovascular risk mentioned in the previous studies. According to our results, HRV can be evaluated as the indicator of the high cardiovascular risk despite the restored renal functions after the transplantation.

It has been known that the prevalence of traditional cardiovascular risk factors increased in renal transplanted patients. Besides, it has also been stated that the presence of pre-transplantation cardiovascular disease was the strong indicator of the post-transplantation [42]. Meanwhile, these patients are also faced with the additional risks due to the chronic renal disease and dialysis [43]. Furthermore, it has been reported that the immunosuppressive agents that are used in order to prevent the graft rejection and acute rejection attacks also increase the cardiovascular risk in the renal transplanted patients [44,45]. When all these taken into consideration, it can be explained why HRV values were not significantly altered in the early period in our study.

LV hypertrophy is frequently observed in patients with CKD related to anaemia; uraemia and HT depending on the chronic volume overload [46]. The frequency of the LV hypertrophy in ESRD patients was reported as 74% [46]. Upon renal transplantation, the decrease in the LV hypertrophy and regression in the LV mass index were showed in many studies. Montanaro et al., have observed that the prevalence of the LV hypertrophy was shown to be decreased from 78% to 44% after the two years of follow-up in the renal transplanted patients [47]. Similarly, Dounousi et al., have detected that there was a decrease in LV mass index in ESRD patients after renal transplantation [48]. Consistent with previous studies, we have detected the decrease in both LV mass index and LV hypertrophy. These changes can be explained with better blood pressure control, improvement in renal function, and decrease in volume and pressure overload in the early period of renal transplantation.

Limitations

Performing the study with comparatively low number of patients can be the limitation of our study. Besides, there was no finding regarding to the association between the HRV and the long-term cardiovascular risks because there were no long-term follow-up results. In our study, we have shown that there was a decrease in the HRV in renal transplanted patients compared with the pre-transplantation period. Since there was an inconsistency with other studies, our results should be supported by the prospective long-term follow-up studies with the higher number of patients.

Conclusions

There were downward trends of HRV values at the end of the third month of the transplantation. This finding can be the indicator of the comparatively increased risk of cardiovascular risk in the early period upon renal transplantation.

Acknowledgements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975i as revised in 2008. The study was approved by the local review and ethic board. Patients were comprehensively informed about the study, and their verbal and written consents were obtained.

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*Correspondence to

Zeynettin Kaya

Department of Cardiology

Faculty of Medicine

Mevlana University

Turkey