Nephrol Dial Transplant (2013) 28: 1294–1305
doi: 10.1093/ndt/gfs455
Advance Access publication 4 November 2012

ndt Nephrology Dialysis Transplantation

Original Articles

A randomized controlled trial of exercise training on cardiovascular and autonomic function among renal transplant recipients

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Keywords: baroreflex sensitivity, cardiac autonomic function, exercise training, heart-rate variability, renal transplantation

ABSTRACT

Background. There are conflicting data regarding the effects of renal transplantation (RT) on uraemic autonomic dysfunction. Moreover, no study has examined the impact of physical training on the cardiac autonomic function in RT patients. Thus, we studied the effects of exercise training on heart rate variability (HRV) and arterial baroreflex sensitivity (BRS), which are sensitive markers of cardiac autonomic outflow, in RT recipients.

Methods. Eleven patients (Exercise group—aged 52.1 ± 5.6 years) were studied before and after 6 months of exercise training. Twelve age- and sex- matched RT patients (Sedentary) and 12 healthy sedentary individuals (Healthy), who remained untrained, served as controls. At baseline and follow-up, all the subjects underwent cardiopulmonary exercise testing for the evaluation of peak oxygen consumption (VO_2peak), a tilt test for the evaluation of BRS and baroreflex effectiveness index (BEI) and an ambulatory 24-h Holter monitoring for time- and frequency-domain measures of HRV.

Results. In the exercise group, VO_2peak increased by 15.8% ($P < 0.05$) and all depressed HRV and BRS indices were significantly improved after training. Specifically, the standard deviation of all normal-to-normal (NN) intervals (SDNN) significantly increased by 92.5%, the root-mean-square of the differences between consecutive NN intervals by 45.4%, the percentage value of NN50 count by 58.2%, the high-frequency by 74.8% and low-frequency spectral power by 41.6%, BRS by 43.7% and BEI by 57.3%. None of the variables studied was altered over time in either control group.

Conclusions. The increased cardiorespiratory fitness by exercise training was associated with an improved BRS function and a modification of the sympathovagal control of HRV towards a persistent increase in parasympathetic tone. These alterations may lead to a better cardiovascular prognosis in RT recipients.

INTRODUCTION

The effects of successful renal transplantation (RT) on uraemic cardiac autonomic neuropathy are controversial. Several studies have reported that RT improves cardiac autonomic dysfunction, which is observed in the majority of dialysis patients and is associated with increased cardiovascular morbidity and mortality [1–7]. However, at a relatively early stage (1–3 months after RT), all autonomous nervous system (ANS) parameters were found to be similar to pre-RT levels [8, 9], while improvements were reported from 6 to 24 months after RT [1, 5, 6, 9, 10]. Hausberg *et al.* [11] have shown that RT recipients with diseased native kidneys are characterized by increased sympathetic nerve activity, at a level similar to that of dialysis patients. Additionally, calcineurin-dependent immunosuppressant cyclosporine withdrawal was not found to

be associated with a decrease in sympathetic outflow in renal allograft recipients [12]. On the other hand, although improvement in parasympathetic activity has been reported after RT [1], parasympathetic dysfunction was found to be common >1 year after RT [6, 13].

Analysis of heart rate variability (HRV) and baroreflex sensitivity (BRS) has emerged as a simple, non-invasive and highly reproducible method of evaluating the activity of the sympathetic and vagal components of the ANS. [7, 14]. They are also used in different clinical settings, as clinical tools for screening and identifying patients particularly at risk of cardiac mortality, since decreased global HRV and BRS are found to be strong predictors of increased all-cause cardiac and/or arrhythmic mortality in chronic kidney disease (CKD) patients [7, 15–17].

In several studies, it has been suggested that exercise training improves cardiac autonomic regulation in healthy subjects and also various patient populations, as in patients with coronary artery disease [18, 19], chronic heart failure [20], chronic obstructive pulmonary disease [21] and diabetes mellitus [22, 23]. In CKD patients undergoing maintenance haemodialysis (HD), exercise training was found to increase cardiac vagal activity and improve both HRV indices and BRS [24–26]. However, there is no study examining the effects of exercise training on cardiac autonomic modulation in RT recipients. We hypothesized that exercise training, which is a remarkable non-pharmacological intervention, can improve autonomic regulation of heart rate (HR) in RT patients and increase HRV and BRS indices, which are used as predictive markers of an increased risk of cardiac mortality in CKD. Thus, this study was designed to assess whether combined endurance and muscle strength exercise training can improve cardiac ANS function assessed by HRV and BRS in RT recipients.

MATERIALS AND METHODS

Study population

Thirty-three RT recipients with preserved native kidneys volunteered to participate in the study. Patients were included if they were aged between 18 and 60 years, were sedentary and non-smokers, had received their transplant at least a year previously and their transplant function was stable with serum creatinine level <1.8 mg/dL and moreover, they were not using drugs that were known to modify ANS, such as sympatholytic drugs. Patients with unstable hypertension, diabetes mellitus, amyloidosis, congestive heart failure, recent myocardial infarction, unstable angina or musculoskeletal abnormality were excluded. After a detailed medical examination, 24 patients were found to fulfil the aforementioned criteria (Figure 1). They were randomly assigned to either the exercise group (Exercise) or the sedentary patient control group (Sedentary). The groups were created by simple random allocation (drawing lots). Allocation sequence was concealed until intervention was assigned. All the patients had a functioning arterio-venous fistula and were on a stable medication regimen with antihypertensive drugs. Additionally, 12 normotensive age- and sex-matched healthy sedentary non-smoker volunteers were recruited (Healthy) and instructed to refrain from exercising during the study period. All the subjects gave written informed consent. The study protocol was approved by the Ethics Committee of Aristotle University. The trial was registered in the German Clinical Trials Register (DRKS00004287).

Study design

All recordings were obtained in the morning, between 9:00 and 10:00 am, in a quiet room after a 15-min period of rest.

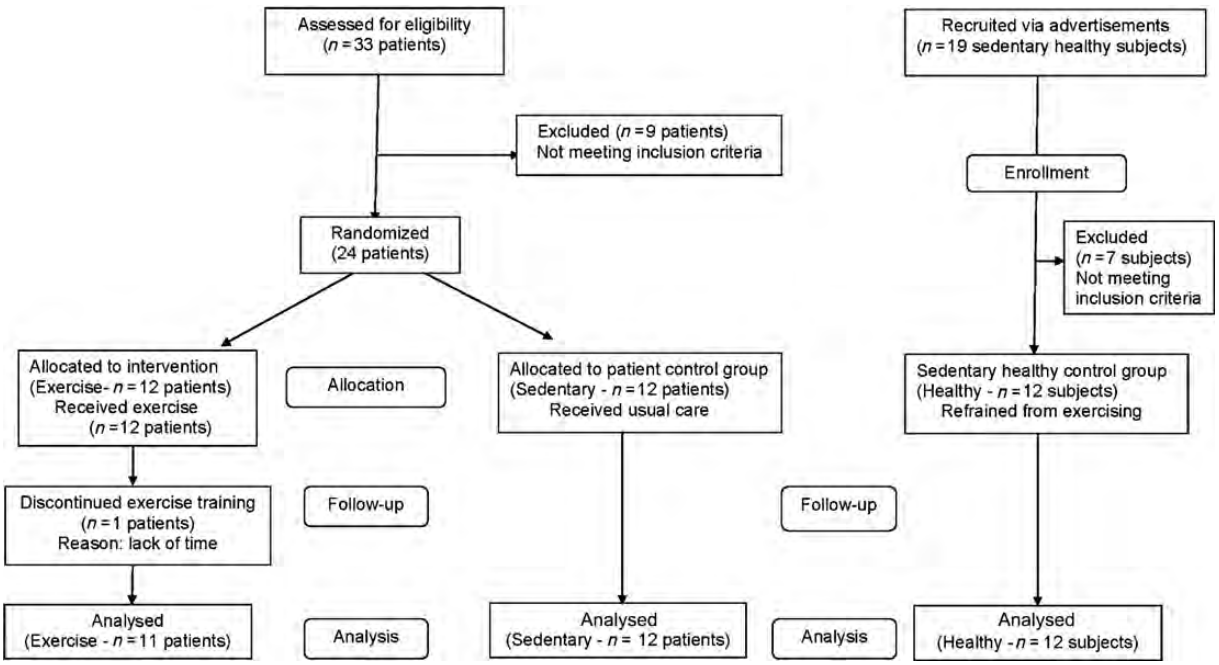

FIGURE 1: Flowchart of the participants.

The subjects were asked to refrain from alcohol and caffeine-containing beverages for at least 12 h and strenuous physical activity for 24 h before their examination. All tests were conducted and interpreted by the same cardiologist blinded to the identity of the subjects. At the beginning and end of the 6-month study, all the subjects underwent a clinical examination, resting electrocardiogram (ECG), head-up tilt testing for the evaluation of BRS, 24-h ECG monitoring for arrhythmia detection and HRV analysis and a cardio-pulmonary exercise testing. All medications were continued throughout the study and remained constant. After baseline measurements, the patients of the exercise group participated in a 6-month exercise training programme, while the subjects of the sedentary and healthy groups were asked to continue their usual sedentary lifestyle.

Exercise training programme

The patients of the exercise group followed a 6-month exercise training programme in a municipal gym consisting of four 60–90 min weekly sessions. Patients were included in the analysis if they had attended at least 80% of the training sessions. The exercise programme was primarily aerobic and performed under the responsibility of two exercise trainers specialized in physical rehabilitation. The patients' HR during training was continuously monitored (Polar FT1, Polar Electro Oy, Kempele, Finland) and their blood pressure (BP) was also measured every 15 min.

Each exercise session started with a 10-min warm-up and finished with a 10-min cool-down period with breathing and relaxation exercises. Each main training routine consisted of a 30–40 min aerobic exercise programme followed by 10–30 min of strengthening exercises for upper and lower extremity and abdominal muscles. The duration of each part was gradually increased over time according to each patient's ability and finally reached the maximum duration. The exercise intensity was prescribed on an individual basis, based on the exercise testing results, and was progressively increased. The target intensity was scheduled to be close to the anaerobic or ventilatory threshold (50–75% VO_2peak or 65–85% HRmax) to enhance cardiorespiratory fitness [27, 28].

The aerobic part included interval fitness training (stationary cycling, jogging, step-aerobic exercises, calisthenics and dancing). During the first 6 weeks of training, 8 stations (1 set, 12 repetitions at 70% of 1 repetition maximum (RM) for the abdominal, upper and lower limbs) were performed. The workload was gradually increased by increasing the repetitions and sets. The target was to reach two to three sets of 10–12 repetitions at 80% of 1 RM.

Measurements

Head-up tilt testing for BRS assessment. The Task Force Monitor 3040i device (CNSystem, Graz, Austria) was used for the BRS assessment. Beat-to-beat BP was recorded by finger plethysmography by means of a two-finger cuff and was corrected to oscillometric brachial BP. Moreover, stroke volume was measured by impedance cardiography and continuous ECG was monitored and analysed beat-to-beat [assessment of R–R intervals (RRI)]. BRS, which reflects the response in HR to a given reduction or elevation in BP, was measured in the supine position and following head-up tilt for sympathetic stimulation and was analysed by applying the sequence method. After a horizontal supine rest period of 5 min, the tilt table was inclined at 60° head-up position for 30 min. This tilt angle is recommended for activation of baroreflex [29]. BRS was assessed from the spontaneously occurring BP rises and falls which were accompanied by counter-regulatory RRI changes. A linear regression between systolic blood pressure (SBP) and RRI was applied to each individual sequence and the mean slope of the SBP/RRI relationship was calculated and taken as a measure of spontaneous BRS. Only regression lines with a squared correlation coefficient $r^2 > 0.85$ were accepted for analysis. The BRS was the average regression slope for all of the linear regressions plotted for accepted baroreflex sequences. Moreover, the baroreflex effectiveness index (BEI), which shows the frequency of concomitant changes in SBP and RRI and reflects the number of times the reflex is active, was estimated.

Holter monitoring and HRV assessment. For the 24-h Holter monitoring, the Burdick Vision Holter System from Cardiac Science (Bothell, Washington) was used. ECGs were recorded in all the subjects during normal daily activity via a 3-channel Burdick Vision 5L Recorder. All digital ECG information was stored on a removable flash memory card and analysed for the incidence of arrhythmias and ST-segment changes.

Moreover, the frequency- and time-domain analysis of HRV was done over the Holter monitoring. The normal and aberrant beats were distinguished automatically by the HRV software module. From the time domain measures, the following parameters were obtained: standard deviation of normal-to-normal (NN) interval (SDNN), which has been used to describe sympathovagal balance, as well as root-mean-square of successive NN interval differences (rMSSD) and percentage value of NN50 count (pNN50), which indicate vagal activity. From the frequency-domain analysis, the following indices were recorded: (i) the low-frequency (LF) components (0.04–0.15 Hz), which is generally considered a quantitative marker of sympathetic modulations, (ii) the high-frequency (HF) components (0.15–0.4 Hz) of the autoregressive power spectrum of the NN intervals, which is accepted as a relative index of cardiac vagal activity and (iii) their ratio (LF/HF), which has been used to describe sympathovagal balance [14].

Cardiopulmonary exercise testing. All of the subjects underwent a symptom-limited cardiopulmonary exercise testing, under continuous ECG monitoring, on a treadmill (Trackmaster TM-400, Carollton, TX) using the Bruce protocol. The HR, SBP and diastolic blood pressure (DBP) at rest, the end of each stage, peak exercise and during recovery were assessed.

During the tests, expired gases were collected with a face-mask and analysed on a breath-by-breath basis using the Med-Graphics Breeze Suite CPX Ultima ergospirometer device (Medical Graphics Coorporation, Minnesota). Before each test, the device was calibrated with standard calibration gases. Peak O_2 consumption (VO_2peak) was defined as the highest

Table 1. Clinical characteristics of the subjects who completed the study[a]

	Exercise ($n = 11$)	Sedentary ($n = 12$)	Healthy ($n = 12$)
Age (years)	52.1 ± 5.6	52.6 ± 5.4	52.3 ± 4.2
Male/female (n)	8/3	8/3	8/4
Height (cm)	166.9 ± 7.0	166.9 ± 6.6	168.6 ± 7.1
Weight (kg)	69.1 ± 5.0	69.3 ± 5.0	69.4 ± 5.2
Time on haemodialysis before trasplant (months)	43.2 ± 12.5	42.8 ± 12.4	—
Time after transplant (months)	22.0 ± 4.6	22.1 ± 4.0	—
Haemoglobin (g/dL)	12.7 ± 0.6	12.6 ± 0.6	13.3 ± 1.2
BUN (mg/dL)	22.2 ± 1.2	22.3 ± 1.3	19.5 ± 0.9
Serum creatinine (mg/dL)	1.2 ± 0.8	1.2 ± 1.0	1.1 ± 0.7

[a]Values expressed as mean ± SD unless otherwise noted.
BUN, blood urea nitrogen.

VO_2 obtained, characterized by a plateau of oxygen uptake despite further increases in effort. Obtained VO_2peak values were considered maximal when respiratory exchange ratio was greater than 1.10. Moreover, peak pulmonary ventilation (VEpeak) and peak treadmill tolerance time (ExTime) were assessed.

Sample size calculation. Sample size calculation was based on hypothesized differences between the exercise and sedentary group in BRS. On the basis of the results of an earlier study (25), we assumed that there will be an improvement in BRS of 1.4 ms/mmHg with a SD of 1.0 in the exercise group, whereas the sedentary group will show no change at the end of the study. Using a two-tailed test of significance with a 0.05 two-sided significance level, to achieve a power of 80%, it was estimated that a total of 10 subjects per group were required. The goal was to recruit 12 subjects into each group, assuming a 20% dropout rate.

Statistical analysis

Continuous variables were expressed as mean ± SD. The Kolmogorov–Smirnov test was used to test normality, a condition fulfilled by the data analysed. Changes in variables within the groups at baseline and the end of the study were evaluated by two-way analysis of variance (ANOVA), time and group being the independent variables. Moreover, within-group change from baseline was obtained by subtracting the final from the baseline values. A one-way ANOVA followed by Bonferroni *post hoc* test was used for between-group comparisons of change from baseline. Correlation coefficients were calculated by Pearson's analysis. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL), version 20.0 software for Windows. A two-tailed P-value of < 0.05 was considered statistically significant.

RESULTS

Study population

One patient of the exercise group dropped out during the study for non-medical reasons (Figure 1). Clinical features of the 23 patients who completed the 6-month study and the 12 healthy controls are shown in Table 1. There were no significant differences between the three groups, regarding their clinical data. Seventeen patients received kidneys from cadavers (8 from the exercise group) and 6 from living donors (3 from the exercise group). Immunosuppressive drug treatment consisted of corticosteroids in all of the patients, cyclosporine A and azathioprine in 14 (7 from each group) and tacrolimus and mycophenolate mofetil in 9 patients (4 from the exercise group). Sixteen transplant recipients (8 from each group) were receiving calcium channel blockers and 7 diuretics (3 from group A). Their serum ion concentrations were within the normal limits, ruling out a possible role in the test's outcome.

Baseline data

The results obtained from the cardiopulmonary exercise testing are presented in Table 2. At baseline, all tests were terminated because of volitional exhaustion. There was no statistically significant difference in HR, SBP and DBP either at rest or at peak effort between the three groups. Moreover, there was no statistically significant difference between the two patient groups (exercise and sedentary). On the contrary, in the exercise group, the ExTime and VO_2peak were lower by 9.8% ($P < 0.05$) and 11.5% ($P < 0.05$) respectively, while VEpeak was greater by 15.8% ($P < 0.05$) compared with healthy subjects.

Table 3 presents the results of the cardiac ANS testing. At baseline, there was no statistically significant difference in any HRV and BRS indices between group Exercise and Sedentary. However, the mean values of almost all the ANS indices in the exercise group were statistically significantly reduced compared with those in healthy, except HF, which was reduced by

Table 2. Mean baseline levels and mean changes from baseline to follow-up and between-group mean changes in the cardiorespiratory efficiency data[a]

	Groups			Between-group change					
	Exercise ($n = 11$)	Sedentary ($n = 12$)	Healthy ($n = 12$)	Exercise versus Sedentary		Exercise versus Healthy		Sedentary versus Healthy	
				Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value
HRrest (bpm)									
Baseline, mean ± SD	73.5 ± 5.8	72.4 ± 4.4	71.8 ± 6.9	−0.5 (−3.3, 2.3)	0.713	−0.9 (−3.7, 1.9)	0.504	−0.4 (−3.1, 2.3)	0.757
Mean change (95% CI)	−1.1 (−3.7, 1.6)	−0.6 (−2.7, 1.6)	−0.2 (−1.7, 1.4)						
SBPrest (mmHg)									
Baseline, mean ± SD	129.5 ± 7.2	128.8 ± 7.4	129.6 ± 6.9	−0.9 (−6.2, 4.5)	0.742	−0.9 (−6.2, 4.4)	0.740	−0.01 (−5.2, 5.2)	1.0
Mean change (95% CI)	−0.5 (−4.8, 3.9)	0.4 (−4.0, 4.8)	0.4 (−3.0, 3.9)						
DBPrest (mmHg)									
Baseline, mean ± SD	78.5 ± 6.0	77.4 ± 4.6	77.8 ± 6.2	−1.8 (−4.7, 1.0)	0.198	−0.5 (−3.3, 2.3)	0.725	1.3 (−1.4, 4.1)	0.334
Mean change (95% CI)	−0.9 (−3.4, 1.6)	0.9 (−0.9, 2.7)	−0.4 (−2.5, 1.7)						
HRmax (bpm)									
Baseline, mean ± SD	152.5 ± 18.0	151.3 ± 17.2	158.2 ± 12.2	10.3 (4.5, 16.0)	0.001	8.0 (2.3, 13.7)	0.007	−2.3 (−7.8, 3.3)	0.418
Mean change (95% CI)	9.2 (1.8, 16.6)	−1.1 (−3.3, 1.1)	1.2 (−0.9, 3.2)						

SBPmax (mmHg)									
Baseline, mean ± SD	163.8 ± 6.5	164.3 ± 6.4	165.2 ± 7.7	−0.8 (−7.2, 5.5)	0.787	−0.4 (−6.8, 5.9)	0.891	0.4 (−5.8, 6.6)	0.892
Mean change (95% CI)	−0.2 (−8.4, 8.0)	0.7 (−2.0, 3.3)	0.3 (−1.6, 2.1)						
DBPmax (mmHg)									
Baseline, mean ± SD	78.6 ± 5.0	78.6 ± 4.7	78.8 ± 4.8	−3.7 (−7.3, −0.5)	0.047	−2.4 (−6.0, 1.2)	0.182	1.3 (−2.3, 4.8)	0.477
Mean change (95% CI)	−4.1 (−8.3, 0.1)	−0.4 (−1.3, 0.5)	−1.7 (−4.1, 0.8)						
ExTime (min)									
Baseline, mean ± SD	9.2 ± 1.4	9.2 ± 1.2	10.2 ± 0.8	2.0 (1.6, 2.4)	<0.001	1.8 (1.4, 2.2)	<0.001	−0.2 (−0.6, 0.2)	0.382
Mean change (95% CI)	1.9 (1.4, 2.4)	−0.1 (−0.3, 0.1)	0.1 (−0.2, 0.3)						
VEmax (L/min)									
Baseline, mean ± SD	72.7 ± 15.9	69.4 ± 9.7	60.6 ± 4.5	−3.0 (−8.7, 2.8)	0.302	−2.7 (−8.5, 3.0)	0.341	3.0 (−2.8, 5.9)	0.302
Mean change (95% CI)	−3.0 (−10.5, 4.5)	−0.02 (−2.4, 2.4)	−0.3 (−1.8, 1.3)						
VO_2peak (mL/kg/min)									
Baseline, mean ± SD	27.8 ± 4.8	27.7 ± 4.5	31.4 ± 1.9	5.5 (3.5, 7.5)	<0.001	5.6 (3.6, 7.5)	<0.001	0.1 (−1.8, 2.0)	0.930
Mean change (95% CI)	5.4 (3.1, 7.7)	−0.1(−1.0, 0.8)	−0.2 (−1.3, 1.0)						

[a]Baseline results are presented as mean ± SD and changes from baseline to follow-up as means (95% CIs) HR, heart rate; SBP, systolic arterial blood pressure; DBP, diastolic arterial blood pressure; HRmax, maximal heart rate; SBPmax, maximal systolic arterial blood pressure; DBPmax, maximal diastolic arterial blood pressure; ExTime, maximal treadmill tolerance time; VE, pulmonary ventilation; VO_2peak, peak oxygen consumption.

Table 3. Mean baseline levels and mean changes from baseline to follow-up and between-group mean changes in the HRV analysis and BRS data[a]

	Groups			Between-group changes					
	Exercise ($n = 11$)	Sedentary ($n = 12$)	Healthy ($n = 12$)	Exercise versus Sedentary		Exercise versus Healthy		Sedentary versus Healthy	
				Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value
SDNN (ms)									
Baseline, mean ± SD	101.8 ± 20.4	101.8 ± 19.4	129.2 ± 9.7	95.2 (83.3, 107.1)	<0.001	96.0 (84.1, 107.9)	<0.001	0.8 (−10.8,12.5)	0.885
Mean change (95% CI)	94.2 (77.7, 110.7)	−1.0 (−3.4, 1.4)	−1.8 (−3.5, −0.2)						
rMSSD (ms)									
Baseline, mean ± SD	23.8 ± 6.0	23.8 ± 5.5	31.6 ± 3.8	11.1 (9.1, 13.0)	<0.001	10.8 (8.8, 12.7)	<0.001	−0.3 (−2.2, 1.6)	0.751
Mean change (95% CI)	10.9 (8.6, 13.1)	−0.2 (0.6, 0.2)	0.08 (−1.3, 1.4)						
pNN50 (%)									
Baseline, mean ± SD	7.9 ± 2.8	7.9 ± 2.7	10.5 ± 1.4	4.6 (2.8, 6.4)	<0.001	4.9 (3.1, 6.7)	<0.001	0.3 (−1.5, 2.0)	0.773
Mean change (95% CI)	4.5 (2.2, 6.9)	−0.8 (−0.6, 0.4)	−0.3 (−1.0, 0.3)						
HF (ms^2)									
Baseline, mean ± SD	185.1 ± 73.9	182.9 ± 68.6	226.7 ± 19.2	138.5 (108.8, 168.2)	<0.001	144.3 (114.5, 174.0)	<0.001	5.8 (−23.3, 34.8)	0.690
Mean change (95% CI)	138.4 (97.0, 179.9)	−0.08 (−2.8, 2.7)	−5.8 (−11.6, −0.1)						
LF (ms^2)									
Baseline, mean ± SD	598.4 ± 108.9	602.7 ± 104.8	815.0 ± 48.9	252.2 (188.4, 316.0)	<0.001	262.1 (198.3, 325.9)	<0.001	9.9 (−52.5, 72.3)	0.748
Mean change (95% CI)	248.8 (161.8, 335.7)	−3.4 (−10.8, 3.9)	−13.3 (−33.7, 7.0)						
LF/HF									
Baseline, mean ± SD	3.6 ± 1.0	3.7 ± 0.9	2.8 ± 0.5	−0.8 (−1.3, −0.3)	0.002	−0.9 (−1.4, −0.5)	<0.001	−0.1 (−0.6, 0.3)	0.565
Mean change (95% CI)	−0.8 (−1.4, −0.2)	0.01 (−0.1, 0.1)	0.2 (−0.03, 0.3)						

BRS (ms/mmHg)							
Baseline, mean ± SD	7.1 ± 2.1	7.0 ± 2.0	11.5 ± 1.8	3.1 (2.2, 4.0)	<0.001	3.0 (2.1, 3.9)	<0.001	−0.1 (−1.0, 0.8)
0.829								
Mean change (95% CI)		3.1 (2.0, 4.2)	−0.1 (−0.3, 0.3)	0.1 (−0.4, 0.6)				
BEI (%)								
Baseline, mean ± SD	52.9 ± 16.2	54.5 ± 13.4	71.3 ± 10.8	29.9 (21.6, 38.3)	<0.001	30.5 (22.1, 38.8)	<0.001	0.6 (−7.6, 8.7)
0.888								
Mean change (95% CI)		30.2 (18.6, 41.8)	0.3 (−1.3, 2.0)	−0.3 (−1.2, 0.7)				

[a]Baseline results are presented as mean ± SD and changes from baseline to follow-up as means (95% CIs).
SDNN, standard deviation of RR intervals; rMSSD, square root of the average of sum of squares of difference between adjacent filtered RR intervals; pNN50, percent of RR intervals differing >50 ms from the preceding RR; LF, low-frequency power; HF, high-frequency power; BRS, baroreflex sensitivity; BEI, baroreflex effectiveness index.

18.4% (NS). The LF/HF ratio was significantly increased by 22.2% ($P < 0.05$) in exercise compared with healthy.

Follow-up data

At the end of the study, significant improvements in the cardiorespiratory efficiency were noted only in the exercised 11 transplant recipients. In the exercise group, after the 6-month exercise training programme, the HRmax increased by 6% (from 152.5 ± 18.0 to 161.6 ± 22.8 bpm, $P < 0.001$), the average ExTime during the stress test by 20.7% (from 9.2 ± 1.4 to 11.1 ± 1.1 min, $P < 0.001$) and the VO_2peak by 15.8% (from 27.8 ± 4.8 to 32.2 ± 6.0 mL/kg/min, $P < 0.001$) compared with the baseline values. Analysis of the mean changes from baseline between the groups showed that the exercise group showed highly significant improvement in HRmax, VO_2peak and ExTime compared with the other two groups (Table 2).

Exercise training in RT patients significantly improved all the cardiac ANS indices measured (Table 3). Specifically, SDNN significantly increased by 92.5% (from 101.8 ± 20.4 to 196.0 ± 30.8, $P < 0.001$), rMSSD by 45.4% (from 23.8 ± 6.0 to 34.6 ± 4.8, $P < 0.001$), pNN50 by 58.2% (from 7.9 ± 2.8 to 12.5 ± 4.0, $P < 0.001$), HF by 74.8% (from 185.1 ± 73.9 to 323.5 ± 104.7, $P < 0.001$), LF by 41.6% (from 598.4 ± 108.9 to 847.2 ± 165.0, $P < 0.001$), BRS by 43.7% (from 7.1 ± 2.1 to 10.2 ± 3.3, $P < 0.001$) and BEI by 57.3% (from 52.9 ± 16.2 to 83.2 ± 16.5, $P < 0.001$) compared with the baseline values. Analysis of the mean changes from baseline between the groups showed that the exercise group had highly significant improvement in all the HRV and BRS indices compared with the other two groups (Table 3). At follow-up, the exercised transplants were found to have significantly increased SDNN by 48.6% ($P < 0.001$), rMSSD by 31.8% ($P < 0.001$), pNN50 by 37.6% ($P < 0.05$), HF by 43.5% ($P < 0.05$), LF by 29.3% ($P < 0.05$), BRS by 31.4% ($P < 0.05$) and BEI by 34.0% ($P < 0.05$) and decreased LF/HF by 32.1% ($P < 0.05$) compared with the sedentary group. Moreover, the exercise group showed SDNN increased by 35.1% ($P < 0.05$), pNN50 by 18.4% ($P < 0.05$), HF by 31.2% ($P < 0.05$) and BEI by 14.7% ($P < 0.05$) compared with the healthy group. No significant differences were found in the mean changes from baseline in the HRV and BRS indices between sedentary and healthy controls.

Pearson's analysis showed no significant correlation in the exercise group between age, time spent on HD prior to RT or the period after RT and cardiorespiratory efficiency and cardiac ANS indices measured at the beginning and the end of the study. Specifically, at baseline, in the exercise group, there was a positive correlation between ExTime and SDNN ($r = 0.731$, $P < 0.05$), rMSSD ($r = 0.605$, $P < 0.05$), pNN50 ($r = 0.747$, $P < 0.001$) and BRS ($r = 0.614$, $P < 0.05$), as well as between VO_2peak and SDNN ($r = 0.839$, $P < 0.001$), rMSSD ($r = 0.886$, $P < 0.001$), pNN50 ($r = 0.874$, $P < 0.001$), HF ($r = 0.760$, $P < 0.001$) and BRS ($r = 0.683$, $P < 0.05$). Moreover, at follow-up, in the exercise group, there was a positive correlation between ExTime and SDNN ($r = 0.701$, $P < 0.05$), rMSSD ($r = 0.735$, $P < 0.05$), pNN50 ($r = 0.783$, $P < 0.001$) and BRS ($r = 0.666$, $P < 0.05$), as well as between VO_2peak and SDNN ($r = 0.690$, $P < 0.05$), rMSSD ($r = 0.768$, $P < 0.001$), pNN50 ($r = 0.805$, $P < 0.001$), BRS ($r = 0.692$, $P < 0.05$) and

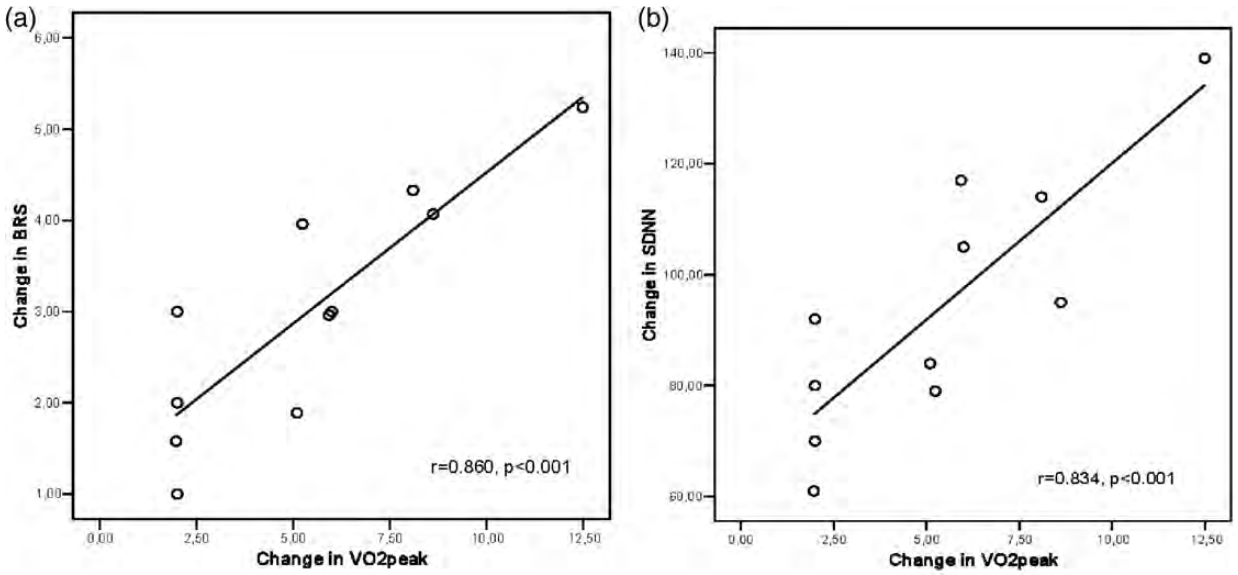

FIGURE 2: Scatter plots showing the correlations between the change from baseline to follow-up in VO_2peak and the change from baseline to follow-up in (**a**) BRS and (**b**) SDNN in the Exercise group. VO_2peak, peak oxygen consumption; SDNN, standard deviation of RR intervals; BRS, baroreflex sensitivity.

BEI ($r = 0.605$, $P < 0.05$). Significant correlations also exist between mean change from baseline to follow-up in VO_2peak and mean change from baseline in SDNN and BRS in the same group (Figure 2).

DISCUSSION

The results show that renal transplant recipients almost 2 years after successful transplantation still had depressed HRV and BRS and effectiveness indices. Following a 6-month exercise training programme, there was an eventual improvement in all the cardiac ANS parameters in association with the enhanced cardiorespiratory efficiency.

It is suggested that uraemic autonomic dysfunction is a result of humoral factors reversed by successful RT [3]. Moreover, RT is found to reduce sympathetic overactivity and improve uraemic cardiac sympathetic neuropathy mainly by removing the renal afferent nerves [8]. Many studies have demonstrated that normalization of kidney function ameliorates cardiac autonomic neuropathy at about 6 months after transplantion [2, 9]. However, it is suggested that restoration of HRV indices to a near-normal range occurs at long-term follow-up [7, 30–32]. In our study, although the mean post-transplant duration was 22 months, the pre-exercise cardiac ANS parameters remained depressed in the sedentary RT controls. Both time- and frequency-domain HRV measures assessed from 24-h recordings showed that our RT patients at baseline had evidence of cardiac autonomic dysfunction. Specifically, they showed moderately depressed SDNN and increased LF/HF ratio that suggest either increased sympathetic or decreased parasympathetic drive to the heart [14, 33]. These findings in combination with the reduced rMSSD, pNN50 and HF power that reflect vagal activity indicate a shift of sympathovagal balance towards a reduced vagal tone. Apart from the time-dependent restoration of HRV after RT, the presence of the diseased native kidneys in all our RT patients may have also affected our results. It is suggested that afferent impulses by circulating uraemia-related toxins from the failing native kidneys may cause an increase in sympathetic nerve activity, independent of correction of uraemia [11]. However, there is an inability to study the sympathetic overactivity related to native kidneys, the effects of calcineurin inhibitors on sympathetic nerve trafficking and the evolution of denervation and functional reinnervation on the transplanted kidneys in patients.

Similarly, our RT recipients showed reduced BRS and BEI compared with healthy individuals, indicating impaired baroreceptor reflex of changes in HR and BP. Several studies have shown an improvement in baroreflex function following RT [1, 4, 6, 31]. Significant improvement in baroreflex function was found in the RT patients with a well-functioning kidney for at least 1 year [6]. Moreover, normalization of baroreflex indices was observed in their RT recipients only after partial correction of HRV alterations [6], which is in agreement with our results. Apart from sympathetic and vagal activity, several other factors have been suggested as determinants of baroreflex function in CKD patients, such as age, hypertension [34], vascular calcification, endothelial dysfunction, arterial stiffness [35] and especially carotid artery compliance [31], the presence of the native kidneys and functioning arteriovenous fistula [36] and the use of cyclosporine A [4]. It has also been suggested that certain regions of the cerebral cortex, as the medial prefrontal cortex and the insular cortex participate in the modulation of the arterial baroreflex [16]. The importance of physical fitness for the modulation of cardiac ANS and arterial baroreflex function has also been previously reported [16]. Our results showed that there is a significant correlation between BRS and aerobic capacity and ExTime.

RT recipients in our study had lower VO_2peak and ExTime values compared with that of the healthy control subjects. The

reduced exercise tolerance in RT recipients was found to be related to the skeletal abnormalities caused by several factors, as inactivity, the use of corticosteroids, metabolic risk factors and the reduced renal and cardiac function [37–40].

After a 6-month exercise training programme, all the HRV time- and frequency-domain indices were normalized and even reached better levels than those of the sedentary healthy controls. Our results are indicative of a shift towards greater vagal modulation, which mainly led to normalization of sympathovagal balance. A similar improvement in HRV time- and frequency-domain indices following exercise training has been reported in healthy elderly individuals and in cardiac, diabetic and HD patients [19, 23, 24, 26, 41–44]. The exact mechanisms by which exercise training modifies the HRV indices are still unclear. It is suggested that exercise training suppresses angiotensin II expression, which inhibits cardiac vagal activity [44]. Another possible mechanism is the nitric oxide bioavailability leading to improved endothelial function [44]. It is also supported that exercise training affects directly the sinus pacemaker cells independent of neural input [45]. Additionally, our previous work in HD patients suggests that there is a link between depression and HRV indices and that exercise training acts effectively on both mental and cardiac autonomic disturbances, reducing emotional distress and concomitantly improving HRV indices [46].

Moreover, the 6-month exercise training programme led to a significant improvement in baroreflex activity in our RT recipients. Most studies suggest that a sufficient long-term exercise stimulus enhances BRS and BEI in elderly individuals [43] and patients with chronic diseases [18, 21, 22, 25, 47, 48]. Several mechanisms have been proposed to explain the beneficial effects of exercise training on baroreflex function. Deley *et al.* [43] found that the increase in baroreflex gain was directly related to the amount of exercise performed and was derived mainly from an increase in the neural component of the arterial baroreflex in older individuals. This gain may be, in part, attributed to the aortic depressor nerve sensitivity, which may be mediated by an enhancement in arterial compliance [48]. Arterial vascular stiffness or distensibility may also relate to baroreflex gain [43]. It is suggested that the change in muscarinic receptor sensitivity after exercise training is responsible for the increased high-pressure baroreceptor stimulation [47]. Moreover, exercise training may change central neural regulation of BP through the plasticity of gamma-aminobutyric acidergic neurotransmitter function in the hypothalamus [43, 49]. Restoration of autonomic function is known to enhance BRS [47, 50]. We found a significant correlation between BRS and BEI and VO_2peak in our trained RT recipients, which indicates that the most fit RT patients have greater baroreflex function. This relationship is also noted in previous studies with exercise in patients with other chronic diseases [21, 22, 25, 51].

The improvement in VO_2peak after exercise training was in line with expectations and indicated the effectiveness of our exercise regimen. The improvement in cardiorespiratory fitness after training is attributed to both central and peripheral adaptations such as enhanced cardiac performance, improved muscle morphology and function and restored cardiovascular autonomic function [45, 52, 53].

A limitation of our study was the relatively small sample size, which was mainly due to the strict inclusion criteria and the fact that the RT patients had to be highly motivated to complete the 6-month study. Since the cardiac ANS indices studied are found to be independently affected by several factors including immunosuppressive, antihypertensive and other cardiovascular drugs, several referred patients, including hypertensives with poor control and patients with cardiovascular diseases and diabetes, could not be included in the study, which may have limited its external validity. Secondly, there was no follow-up period after the 6-month exercise training programme, and thus, it was not possible to evaluate the clinical meaning and the prognostic value of the improvements in cardiac ANS noted. Finally, there are no data available for a group of exercise trained healthy controls that may discern a gradient of effect size.

In conclusion, exercise training improves cardiorespiratory fitness and restores HRV and baroreflex function which are depressed in RT recipients. These alterations may have clinical implications, since they are all found to be predictors of cardiovascular outcomes.

CONFLICT OF INTEREST STATEMENT

None declared.

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Received for publication: 5.7.2012; Accepted in revised form: 28.8.2012

Nephrol Dial Transplant (2013) 28: 1305–1314
doi: 10.1093/ndt/gfs472
Advance Access publication 9 December 2012

ORIGINAL ARTICLE

The long-term outcome of renal transplantation of IgA nephropathy and the impact of recurrence on graft survival*

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*This paper has been inspired by our gratitude to the illuminating teaching of Professor Claudio Ponticelli.

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Keywords: IgA nephropathy, renal transplantation, recurrent glomerulonephritis

ABSTRACT

Background. Few data are available on allograft survival at 15 years, the impact and the predictors of recurrence of the original disease in renal transplanted patients with IgA nephropathy (IgAN).

Methods. In this retrospective study, we compared the long-term outcome of renal transplant in 190 patients with IgAN