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J.R. Poortmans
L. Hermans
A. Vandervliet
G. Niset
C. Godefroid

Renal Responses to exercise in heart and kidney transplant patients

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J.R. Poortmans (✉) · L. Hermans
A. Vandervliet · G. Niset
Chimie Physiologique,
I.S.E.P.K. C.P. 168,
Université Libre de Bruxelles,
28 Avenue Paul Héger,
B-1000 Bruxelles, Belgium
Fax: + 32 2 650 4209
e-mail:jrpoortm@ulb.ac.be

G. Niset
Service de Cardiologie,
Hôpital Universitaire Erasme,
808 route de Lennik,
B-1070 Bruxelles, Belgium

C. Godefroid
Service de Néphrologie,
Hôpital Universitaire Erasme,
808 route de Lennik,
B-1070 Bruxelles, Belgium

Abstract There is a lack of information about renal responses in heart and kidney transplant patients after intense physical exercise. Eleven heart and ten kidney transplant recipients, as well as two control groups of healthy subjects, were given a maximum exercise test on a bicycle ergometer. One control group was also given a moderate load corresponding to the peak load of the kidney transplant group. Blood and urine samples were collected before and after exercise and assayed for lactate, creatinine, total protein, and albumin. The glomerular filtration rate remained stable at the end of exercise in the transplant patients, while there was a slight (17 %) decrease in the control group. Albumin excretion rates after maximum exercise attained a mean of 237 $\mu g \cdot min^{-1}$ in the control group and a mean of 45 and 16 $\mu g \cdot min^{-1}$, respectively, in the heart and kidney groups. Postexercise proteinuria seemed to be related to the absolute intensity of the event, but kidney transplant patients showed a reduced effect as compared to heart transplant patients. We conclude that short-term, maximum exercise in heart and kidney transplant recipients is not detrimental to kidney function.

Key words Exercise, kidney transplantation, heart transplantation · renal function

Introduction

Exercise induces profound changes in renal hemodynamics [20] and protein excretion in healthy human subjects [15]. The latter phenomenon induces a transient state in the kidney that involves both glomerular membrane permeability and the tubular reabsorption process of filtered proteins [19]. The severity of protein excretion in urine depends on the intensity of exercise and this phenomenon occurs from childhood to adults [18]. The increased clearance of plasma proteins suggests an increased glomerular permeability and a partial inhibition of the tubular reabsorption process [16].

Cardiac transplant patients are encouraged to exercise regularly since endurance training appears to restore lean tissue and increase cardiac function and peak oxygen transport [11, 21]. However, there are only a few publications on renal responses to exercise after heart [7] and kidney transplantation [2, 12].

A few reviews have focused attention on the benefits of exercise for end-stage renal [2, 12, 14] and uremic patients [1]. Recent publications have pointed out the benefits of exercising to one's maximum capacity after renal transplantation in patients under 60 years of age [2] and noted a lack of improvement in patients over 60 [12]. In brief, patients with adequate renal function after transplantation improve their maximal oxygen uptake and their isokinetic muscle function, and they are better able to control their blood pressure. Nevertheless, strenuous exercise is known to dramatically divert renal

Table 1 Characteristics of the subjects

a Heart transplant recipients

Subject	Age (years)	Weight (kg)	Height (cm)	Sex	Time after transplantation (months)	Etiology
1	43	71	179	Male	25	Ischemia
2	40	79	172	Male	25	Ischemia
3	62	77	175	Male	18	Ischemia
4	46	94	180	Male	24	Ischemia
5	57	77	170	Male	12	Unknown
6	49	76	170	Male	13	Unknown
7	30	71	178	Male	34	Unknown
8	58	73	174	Male	19	Ischemia
9	40	79	170	Male	30	Ischemia
10	35	65	165	Male	13	Ischemia
11	43	60	169	Male	12	Ischemia

b Kidney transplant recipients

1	21	62	169	Male	8	Renal athrophy
2	24	59	167	Female	8	Glomerulonephritis
3	38	60	165	Female	9	Glomerulonephritis
4	24	65	167	Female	15	Unknown
5	42	76	173	Male	24	Glomerulonephritis
6	46	65	168	Male	1	Glomerulonephritis
7	44	68	165	Female	2	Pyelonephritis
8	27	54	169	Male	8	Chronic nephritis
9	28	70	162	Female	2	Glomerulonephritis
10	25	60	170	Male	9	Nephritis

c Healthy controls

Group 2

Subject	Age (years)	Weight (kg)	Height (cm)	Sex
1	22	59	175	Male
2	25	52	165	Female
3	38	65	164	Female
4	24	61	169	Female
5	45	68	172	Male
6	41	82	195	Male
7	45	60	170	Female
8	26	90	185	Male
9	27	52	165	Female
10	24	84	178	Male

Group 1

Subject	Age (years)	Weight (kg)	Height (cm)	Sex
1	36	78	183	Male
2	38	55	166	Male
3	39	84	181	Male
4	38	73	177	Male
5	44	74	174	Male
6	37	78	196	Male
7	36	65	175	Male
8	43	70	179	Male
9	36	60	178	Male

blood flow towards the active muscle. Transient proteinuria may be a predictor of renal impairment that may be induced by the exercise.

Yet, there is a lack of information regarding renal responses to intense exercise in both heart and kidney transplant patients. Thus, we investigated whether strenuous short-term exercise could impair the kidney's ability to protein reabsorption in kidney and heart transplant recipients.

Materials and methods

Subjects

Eleven male subjects (mean age 47 ± 3 years) received a heart transplant 20 months (mean) before being tested on a bicycle ergometer. They had been doing some light exercise before discharge from the hospital [10], but they did not follow any further supervised outpatient rehabilitation program. Ten subjects (five male and five female, mean age 32 ± 3 years) who had received a kidney transplant were given the same test 9 months (mean) after transplantation.

All subjects were receiving immunosuppression therapy consisting of cyclosporin A, azathioprine, and prednisolone. The heart transplant patients were placed on a sodium-free diet and three were administered diuretics, calcium antagonists, or angiotensin-converting enzyme inhibitors to reduce their tendency to hypertension. Their mean (± SEM) systolic and diastolic blood pressures at rest were 146 ± 4 and 96 ± 3 mm Hg, respectively. The kidney transplant recipients were selected from subjects without hypertension (systolic pressure < 150 mm Hg). Under resting conditions, all subjects were within the normal range of proteinuria (< 100 μg/min) and albuminuria (< 20 μg/min).

Healthy control groups were chosen for each group of patients. The control group for the heart recipients (group 1) included nine males (mean age 39 ± 3 years), while the control group for the kidney recipients (group 2) included five males and five fe-

Table 2 Responses to exercise in transplant patients

	Control 1	Heart	Control 2	Kidney
VO_2 peak (l/min)	3064 ± 179	1603 ± 88	2261 ± 205	1535 ± 131
Peak intensity (watts)	242 ± 15	115 ± 7	211 ± 19	111 ± 7
Heart rate peak (bpm)	180 ± 2	152 ± 8	174 ± 6	166 ± 5
Plasma lactate (mmol/l)				
Rest	1.20 ± 0.08	1.78 ± 0.18	1.30 ± 0.15	1.90 ± 0.18
Exercise 242 W	11.04 ± 0.81*, **			
Exercise 115 W		8.33 ± 0.42*	3.43 ± 0.37*, **	8.49 ± 0.11*

* $P \leq 0.05$ between rest and exercise; ** $P \leq 0.05$ for exercise between controls and transplant patients

Table 3 Excretion rates and clearances in transplant patients

	Control 1	Heart	Control 2	Kidney
Creatinine clearance (ml/min)				
Rest	116 ± 11	76 ± 10	90 ± 7	60 ± 9
Exercise 242 W	94 ± 7*			
Exercise 115 W		64 ± 9	97 ± 7	52 ± 7
Protein excretion rate (μg/min)				
Rest	58 ± 14	78 ± 28	75 ± 15	59 ± 10
Exercise 242-211 W	271 ± 106		480 ± 141*	
Exercise 115 W		195 ± 65*, **	103 ± 16	74 ± 18
Albumin excretion rate (μg/min)				
Rest	10.9 ± 2.9	17.0 ± 0.3	10.7 ± 3.0	8.2 ± 1.8
Exercise 242-211 W	105 ± 23*		237 ± 90*	
Exercise 115 W		45 ± 12*, **	19.7 ± 6.8	15.8 ± 3.6*
Albumin clearance (μl/min)				
Rest	0.23 ± 0.06	0.38 ± 0.08	0.22 ± 0.06	0.19 ± 0.04
Exercise 242 W	2.08 ± 0.08*			
Exercise 115 W		0.98 ± 0.25*, **	0.38 ± 0.14*	0.34 ± 0.08*

* $P \leq 0.05$ between rest and exercise in each group; ** $P \leq 0.05$ for exercise between heart and kidney transplant recipients

males (32 ± 3 years). Their mean (± SEM) systolic and diastolic blood pressures at rest were 130 ± 4 and 80 ± 3 mm Hg, respectively.

All subjects gave their free and informed consent to participate in the present study. Their main characteristics are included in Table 1.

Experimental protocol

Approval for the exercise protocol was obtained from the medical committee of the Hôpital Erasme (Université Libre de Bruxelles, Belgium). Each patient was asked to do a stepwise exercise, with increases of 10 W/min, on a cycle ergometer up to exhaustion. The control groups were given the same protocol, but the load was increased by 30 W/min. Heart and oxygen consumption rates were determined according to an Ergopneumotest Jaeger (Germany). One week later, one of the control groups (group 2) was tested again; this time the work load represented the maximal load sustained by the kidney recipients (mean 115 W), using the same protocol as for the patients. Immediately before the test and 5 min after stopping the exercise, blood samples were drawn from a cubital vein while the subjects were in a sitting position. Urine samples, collected over a 2-h period while the subjects were at rest, were voluntarily obtained before the test. In order to ensure a reliable urine output, the subjects drank 100 ml of plain water every 20 min prior to the exercise, as well as immediately after stopping the exercise. Urine was again collected 30 min after the test. All urine samples were preserved by adding 0.01 % sodium merthiolate and were stored at 4 °C.

Analytical methods

Albumin and lactate concentrations in plasma were determined by the bromocresol green method [4] and an enzymatic technique [6], respectively. Urine protein and albumin levels were assayed by the colorimetric technique [22] and by an immunological method (Turbiquant albumin/urine Behring), respectively [9]. Plasma and creatinine concentrations were determined by the alkaline picrate method [8]. The interassays coefficients of variation for the measurements of all components were under 10 %.

Clearances at rest were calculated from pre-exercise samples while clearances after exercise were obtained from 5-min postexercise blood and 30-min postexercise urine collection.

Statistical methods

Data are reported as means and standard error of the mean ($x \pm$ SEM). Significance between the values was established using the Wilcoxon matched-pairs signed-rank test for results within the

same group. The Mann-Whitney test for independent samples was applied to test the difference in results between the different groups. A P value of 0.05 (two-tailed) was considered significant.

Results

The physiological parameters of the subjects are shown in Table 2. As expected, the transplant recipients had a peak VO_2, heart rate, and sustained work load that were inferior to those of the sedentary subjects. The maximum plasma lactate level recorded after the exercise was higher for the control group than for the transplant recipients. When the peak load recorded for the patients (mean 115 W) was applied to the control group, a much lower plasma lactate level was observed.

After exercise, plasma creatinine levels increased by 8 %–10 % ($P < 0.05$) in all groups. The creatinine excretion rate did not change significantly after exercise as compared to in the rest condition. As expressed by the creatinine clearance (Table 3), the estimated glomerular filtration rate at rest was higher in the control group than in the transplant groups. The maximum exercise protocol reduced only slightly (17 %) the plasma filtration in the control group; no modification was noted for the patient groups.

The protein excretion rates at rest were below the upper limit of healthy subjects ($< 100\ \mu g \cdot min$) in both groups transplant patients (Table 3). The maximum exercise test induced a proteinuria that appeared to be dependent on the absolute intensity of the exercise for both healthy controls and heart recipients. In contrast, kidney recipients showed a lesser response to maximum exercise. The albumin excretion rates rose 21-fold, 3-fold and 2-fold after exercise in the control group, the heart group, and the kidney transplant group, respectively. As a consequence, the albumin clearance increased nearly 9-fold in the control group, 2.6-fold in the heart transplant patients, and 2-fold in the kidney tranplant patients. The work load of 115 W did not influence the protein and albumin excretion rates in the healthy control group (versus the kidney recipients).

Discussion

A previous study by Haywood et al. [7] showed that short-term, maximum supine bicycle exercise induced a 44 % decrease in renal blood flow in heart transplant recipients, as compared to a 4 % decrease in a healthy control group. These authors suggested that the surgical division of the cardiac ventricular afferent fibers resulted in an increased vasoconstrictor drive to the kidneys and nonexercising muscle during exercise. They added that this mechanism might contribute to persistent exercise limitations and renal impairment after heart transplantation.

The present investigation showed that despite the greater reduction in renal blood flow suggested by the previous authors under similar conditions, there was no major stress imposed on the kidney in the transplant recipients as far as protein handling was concerned. Nor was the estimated glomerular filtration rate modified by the maximum exercise test given to the transplant patients. Moreover, given the same work load, it appeared that the kidney recipients had a lesser response than the heart recipients, despite a similar increase in venous lactate induced by the exercise. Nevertheless, the heart transplant patients had a greater increase (two-fold) in protein and albumin excretion rates and albumin clearance than healthy subjects when the same absolute work load was taken into consideration.

In a recent publication on postexercise proteinuria in childhood and adolescence, we emphasized the importance of the intensity of exercise, expressed in absolute terms, on the magnitude of protein excretion [18]. The same observation was made in the present study when comparing the control group and the heart recipients. However, this situation did not apply to the kidney recipients. Indeed, despite the same plasma lactate level at peak exercise in transplant patients, there was no relationship between venous plasma lactate and protein excretion rate as observed in healthy subjects [19].

The excess protein excretion found after exercise may be the consequence of two mechanisms, namely, an increased membrane permeability of the glomeruli and a saturation of the tubular reabsorption process of filtered protein. Previously, we provided evidence of an enhanced glomerular permeability induced by short-term exercise [17]. A recent study by O'Hagan et al. [13] demonstrated that the renal sympathetic nerve activity response to exercise in conscious rabbits is related to the intensity of the exercise. We were also able to relate the excretion of urine albumin to the increase in plasma noradrenaline during strenuous exercise in healthy subjects [16]. It may be argued that the kidney denervation could reduce the hypothetical induction of the catecholamines in the genesis of glomerular membrane permeability. This assumption has yet to be confirmed. Indeed, Gazdar and Dammin [5] have noted that the regeneration of renal nerves begins as early as 28 days after transplantation in humans. As pointed out by DiBona [3], renal denervation is not permanent, and time-dependent regeneration of renal nerves clearly occurs. However, our results showed that the heart recipients, with intact renal nerve distribution, had a higher postexercise proteinuria and albumin clearance than kidney transplant patients. Therefore, more relevant techniques must be used to examine the physiological effects of alteration in renal sympathetic nerve activity on renal function.

To conclude, the moderate exercise load imposed on heart and kidney recipients in this study, although maximal for these subjects, did not interfere with certain aspects of renal function, i.e., glomerular filtration rate and postexercise proteinuria. Thus, there is no reason to believe that this type of exercise is detrimental to kidney function. In other words, common occupational (general housework, stair climbing, gardening) and recreational (walking, jogging, swimming, bicycling) activities should be encouraged in transplant patients with normal cardiac function in order to improve their physical functioning.

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