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The effect of exercise during haemodialysis on solute removal

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Abstract

Background. Urea rebound results as urea re-equilibrates between intracellular and intravascular compartments post haemodialysis. The mechanism of the rebound is thought to be due to either a reduced diffusion rate or blood flow. It is hypothesized that low blood flow in the skeletal muscles might be responsible. We tested this by studying the effect of exercise during dialysis on the removal of urea, creatinine and potassium.

Methods. Eleven patients (aged 32–78 years) on haemodialysis (4–58 months) were studied on paired dialysis sessions; one with exercise and the other as a control. Patients pedalled on a cycle for 5–20 min at submaximal workload followed by 10 min rest to achieve a total of 60 min exercise. Plasma concentrations of urea, creatinine and potassium were measured pre-, post- and 30-min post dialysis. The post-dialysis rebound (% rebound) and reduction ratios (RR) of the solutes and equilibrated (two-pool) urea Kt/V were calculated for comparison.

Results. The rebound of all three solutes was reduced significantly following exercise. The rebound of urea decreased from 12.4 to 10.9% (median, $P<0.01$ Wilcoxon signed rank test), creatinine from 21.2 to 17.2% ($P<0.001$) and potassium from 62 to 44% ($P<0.05$). Kt/V and RR increased significantly as a result: Kt/V urea from 1.00 to 1.15 ($P=0.001$), RR urea from 0.63 to 0.68 ($P<0.001$); Kt/V creatinine from 0.71 to 0.84 ($P<0.01$); and RR creatinine from 0.51 to 0.57 ($P<0.05$).

Conclusion. Exercise increased the efficiency of dialysis by reducing the rebound of solutes due to increased perfusion of the skeletal muscles.

Key words: blood flow; diffusion rate; exercise; haemodialysis; solute removal; urea rebound

Introduction

The phenomenon of post-dialysis urea rebound is well documented, immediately after haemodialysis is terminated the plasma concentration of urea rises rapidly [1,2]. During dialysis, urea is removed quickly from the blood but is retained disproportionately in the peripheral body compartments. Rebound results as urea re-equilibrates after dialysis. This limits the efficacy of dialysis. To achieve the target Kt/V extra time has to be added to the dialysis. Although other solutes are likely to be retained in the same way, their behaviour has been poorly studied. Since most urea is intracellular, it has been assumed that the retention is due to either slow diffusion of urea across cell membranes or low blood flow in some body compartments.

Dialysis is usually carried out in the resting semi-recumbent position in which the circulation is relatively stagnant, particularly in the leg muscles. This could contribute to the delay in the equilibration of urea during dialysis. If significant quantities of urea are retained in the leg muscle during dialysis, then exercising the legs during dialysis should increase the efficiency of dialysis and reduce the post-dialysis urea rebound. This study was undertaken to test this hypothesis and to quantify any effect of exercise on the mass of urea, creatinine and potassium removed during a typical dialysis.

Subjects and methods

Patients

Eleven patients were studied. All consented to the study, which was approved by the North Herts Ethical Review Committee. They were 10 males and one female aged between 32 and 78 years. The clinical details of the patients are given in Table 1. Eight patients had no residual renal function. In the remaining three the urea clearance (KRU) ranged from 3.87 to 8.84 ml/min. All were dialysed thrice weekly through an arterio-venous fistula, except for one whose access was a internal jugular Permcath. No patient had appreciable access recirculation. All took multivitamins, phosphate binders and human recombinant erythropoeitin. Four patients were receiving an antihypertensive drug (two on a beta-adrenoreceptor blocker and two on an angiotensin-converting enzyme inhibitor). Their haemoglobin values ranged from 9.5 to 13.9 g/dl. Dialysis treatments consisted of haemodiafiltration with on-line production of replacement fluid (10 patients) and high-flux haemodialysis (one patient). Median blood flow rate was 450 ml/min (range

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Table 1. Clinical characteristics of the dialysis patients

Patient	Sex	Age (years)	Residual renal clearance (KRU) (ml/min)	Duration of dialysis (months)	Cause of renal failure
JW	m	42	0	33	diabetic glomerulosclerosis
MU	m	35	0	47	chronic glomerulonephritis
CD	f	54	0	58	polycystic kidney disease
RP	m	67	8.84	8	nephrosclerosis
OH	m	78	0	30	renal cell carcinoma
RK	m	37	0.15	12	hydronephrosis
KB	m	43	3.87	45	membranous nephritis
AY	m	32	5.77	4	sponge kidney
LD	m	46	0	28	renal cell carcinoma
GD	m	52	0	31	polycystic kidney disease
AJ	m	74	0	36	unknown

350–550 ml/min). All dialysate flows were 800 ml/min. Dialysers were Gambro Polyflux 21 (10 patients) and Fresenius HF80 (one patient). Median treatment time was 206 min (range 117–240 min).

Protocol

All patients were studied on two dialysis sessions with identical prescriptions on the same day of consecutive weeks. They were randomly allocated to start with an exercise session or the control dialysis session. The dialyses were prescribed using the patients' usual prescription parameters (blood flow, dialysate flow, dialyser type, dialysis time), which had been planned previously to deliver a two-pool Kt/V of 1.1 including residual renal function. The prescription parameters were not varied between the experimental and control dialyses. During the experimental session patients pedalled on a purpose-built cycle for 5–20 min at a time at submaximal workload followed by 10 min rest. The aim was to achieve a total of 60 min of exercise during the dialysis session. To maintain constant body temperature, the dialysate temperature was maintained between 35.5 and 36°C and the patients blood temperature was monitored using a sensor on the arterial blood line (BTM, Fresenius).

Patients were asked to keep their fluid intake and diet as constant as possible for 2 weeks prior to and during the study. Blood samples were taken from the arterial needle just before the start of each dialysis, from the arterial line after 20 s of slow blood flow (100 ml/min) immediately before the end of dialysis and from venepuncture 30 min after the end of dialysis. Plasma was separated promptly from the samples by centrifugation and concentrations of urea, creatinine and potassium were measured in the plasma.

The heart rate and blood pressure were monitored using an automatic monitor (*Dynamap*) before and during exercise. Oxygen saturation (pulse oximeter) was also monitored throughout dialysis.

Calculations

The post-dialysis rebound was quantified as follows:

$$rebound\ \% = \frac{(Ct_{30} - Ct)}{(C_0 - Ct)} \times 100,$$

where C_0, is the pre-dialysis concentration (mmol/l) and Ct and Ct_{30} are the concentrations immediately after and 30 min after dialysis.

The reduction ratios (RR) were calculated as follows:

$$RR = 1 - \frac{Ct_{30}}{C_0}.$$

Equilibrated (2-pool) Kt/V was calculated from the following:

$$Kt/V = \ln\left(\frac{C_0}{Ct_{30}}\right).$$

The patient clearance time, tp, was calculated as follows:

$$tp = t \times \ln\left(\frac{Ct_{30}}{Ct}\right) / \ln\left(\frac{C_0}{Ct_{30}}\right).$$

No attempt was made to correct for the effects of urea generation and ultrafiltration, which were held to be constant between the two treatments.

Plasma concentrations were measured using a Hitachi 717 autoanalyser. Coefficients of variation for urea, creatinine and potassium measurements were 3.2%, 1.78% and 2.3% respectively.

Wilcoxon's signed rank and Spearman's rank correlation tests were used to test for significance.

Results

All of the patients were able to cycle during the experimental session without any discomfort or adverse symptoms except for one who complained of a slight leg cramp. Four of them agreed to repeat the study.

Altogether 16 paired dialyses were obtained for comparison of the effect of exercise during dialysis (Table 2). The workload achieved varied between 25 and 75 W depending on the age and fitness of the patients. The mean increase in heart rate during exercise was 25% (range: 11–41%). The heart rate remained relatively constant in the control session. The mean blood pressure at the start of the exercise session was 137/76 mmHg (range: 100–174/58–92 mmHg), while that of the control session was 130/79 mmHg (range: 94–171/59–95 mmHg). With exercise systolic pressure increased by a mean of 14 mmHg (range:

Table 2. Characteristics of the dialysis treatments

	Exercise	Control
Pre-dialysis weight (kg)	79.2 (113.2–60.5)	78.8 (113.9–61.2)
UF volume (l)	2.2 (0.1–2.9)	2.2 (0.6–3.5)
Pre-dialysis temperature (°C)	36.3 (35.6–36.9)	36.1 (35.2–36.8)
Temperature change (°C)	0.05 (−0.3–1.3)	−0.05 (−0.6–0.5)
Workload (Watts)	35 (25–75)	0
Exercise duration (min)	61 (45–80)	0

The median ranges are shown. Apart from the exercise, there was no significant difference between control and exercise treatments.

Table 4. Parameters calculated from pre-, post-and 30-min post-dialysis concentrations

		Exercise	Control	*P*
Urea	Kt/V	1.15	1.00	0.001
	RR	0.68	0.63	<0.001
	% rebound	10.9	12.4	<0.01
	tp	40	51	<0.05
Creatinine	RR	0.57	0.51	<0.05
	% rebound	17.2	21.2	<0.001
	tp	67	95	<0.01
Potassium	% rebound	44.0	62.0	<0.05

Kt/V, refers to normalized urea clearance delivered by dialyser (this excludes residual renal function); RR, reduction ratio; *tp*, patient clearance time. Median values are shown. The *P*-values relate to the difference between control and exercise values (Wilcoxon signed rank).

11–18 mmHg) and diastolic pressure by 4–17 mmHg. The mean duration of exercise was 61 min. Oxygen saturation remained fairly constant at 98 ± 2% throughout both control and experimental conditions.

Exercise significantly reduced the rebound of all three solutes studied (Tables 3 and 4). The RR for these solutes and urea Kt/V (Figure 1) were significantly greater in the dialyses with exercise as a result of the lower rebound. Patient clearance time (a measure of the time taken for solutes to transfer between body compartments) decreased from a median of 51 min without exercise to 40 min with exercise ($P<0.05$) for urea and from 95 to 67 min ($P<0.01$) for creatinine. Both values were within the range determined by a previous study [3].

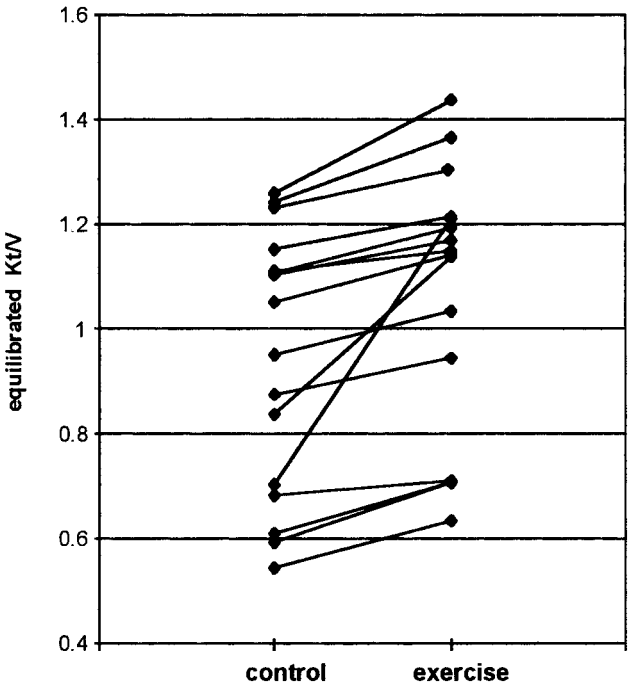

Fig. 1. Comparison of urea Kt/V with and without exercise.

Discussion

We have shown that dialyses performed during exercise removed more urea and creatinine as measured by pre- and 30-min post-dialysis urea and creatinine concentrations compared with dialyses performed at rest. Exercise increased the urea Kt/V by 14%, equivalent to increasing the dialysis time by 20 min. We were not able to quantify the effect of exercise on creatinine removal as precisely since it is known that the creatinine rebound is only 70–80% complete at 30 min post dialysis [3]. However, our results do show that the creatinine reduction ratio calculated from pre- and 30-min post-dialysis plasma concentrations was 6% higher when dialysis was performed with exercise compared with controls. Using a validated two-pool creatinine kinetic model [3] we calculated that this difference is equivalent to extending the dialysis time by 30 min.

Table 3. Plasma urea and creatinine concentrations – mean (25th and 75th centiles); the effect of dialysis with and without exercise

	Urea (mmol/l)		Creatinine (μmol/l)	
	Exercise	Control	Exercise	Control
Pre-dialysis	22.7 (20.1–29.1)	22.8 (19.2–29.1)	988 (808–1155)	1004 (843–1118)
Post-dialysis	5.8* (4.25–8.0)	6.6 (4.8–9.5)	341 (292–387)	331 (280–398)
30-min post-dialysis	7.4*** (6.1–10.2)	9.4 (6.5–12.5)	465** (398–510)	499 (401–598)

*$P<0.05$, **$P<0.01$, ***$P<0.005$ (compared with control, Wilcoxon signed rank).

In fact, by taking the post-dialysis sample before the creatinine rebound is complete we very likely underestimated the effect of exercise on the rebound.

Since the rebound is due to solute generation and transfer between compartments, the exercise must either be reducing the rate of solute generation or increasing the rate of transfer between compartments. On the one hand, urea is generated mainly by hepatic metabolism and it is possible, although unlikely, that it could be slowed by exercise. On the other hand, creatinine is generated from muscle turnover and it seems very unlikely that this could be reduced by exercise. For these reasons, it is most likely that exercise is increasing the rate of transfer of solute between body compartments.

Skeletal muscle mass constitutes ~40–45% of the total body weight, although it may be less in patients with end-stage renal failure [4]. Since the water content of muscles is relatively high, most of the body water is within the muscles. For solutes such as urea and creatinine, which are distributed in the body water, more than half of the total mass of these solutes will be held within the muscles. In order to be removed by dialysis, these solutes must transfer from the intracellular water, across the cell membranes, and into the fistula via the venous system and systemic circulation. At rest, most of the capillaries in the muscles are collapsed resulting in some of the regions of the skeletal mass being by-passed by dialysis. However, during exercise blood flow can rise from 3–4 ml/min per 100 g to 80 ml/min per 100 g, depending on the intensity, by opening up the capillary bed in the muscles. This increase in perfusion increases the area of exchange between the intravascular and intracellular compartments. This is the most likely explanation for our observations. It may be relevant that the two patients with the largest increase in Kt/V (Figure 1) and reduction in rebound with exercise were both relatively muscular males.

Creatinine rebound was higher than urea rebound. If the mechanism of intercompartment transfer is mediated entirely by blood flow, then the rebound should be similar for both solutes. Our results indicate that creatinine transfer within the body cannot be mediated by blood flow alone. The molecular mass of creatinine is almost twice that of urea which would account for its significantly lower rate of diffusion in *in vitro* studies [5,6], and it seems likely that, while at rest, the rate of creatinine transfer from cells to the circulation is limited mainly by its rate of diffusion. We also found that exercise reduced the difference between the urea rebound and the creatinine rebound. This could be explained by an exercise-induced increase in capillary blood flow, resulting in increased capillary filtration and re-absorption and mixing of the interstitial space. This mixing will increase the rate of creatinine transfer through the interstitial fluid. Alternatively, exercise may increase the permeability of the cell membrane to creatinine. The diffusion rate of creatinine has been shown to increase dramatically with an increase in temperature in *in vitro* studies [6,7], and it is possible that *in vivo* the transmembrane-diffusion component may be increased by exercise as a result of a rise in body temperature. However, since the temperature change in our patients was minimal, this was unlikely to be the mechanism responsible for the increase in rate of transfer.

The mechanisms governing potassium removal during dialysis are less clear. Potassium is predominantly intracellular and the most significant barrier to intercompartment transfer is the cell membrane. Transmembrane potassium efflux is controlled by Na-K-ATPase activity, which may be defective in uraemia [8]. During exercise the plasma concentration of potassium increases due to efflux from the contracting muscles [9]. This rise is also observed when exercising during dialysis [10]. This exercise-induced potassium flux out of cells will increase the efficiency of potassium removal during dialysis. Plasma potassium levels do not reflect whole-body concentrations even in equilibrium, so it is impossible to quantify potassium removal using blood side measurements. However, exercise did reduce the potassium rebound, indicating a possible role for exercise in increasing potassium removal by dialysis.

There are two inherent difficulties in a study such as this. First, it is not possible to double-blind the study, therefore there is a possibility that biased application of the protocol (higher blood pump flows, fewer stoppages, etc.) could have resulted in more dialysis being delivered during the treatments with exercise than the controls. Secondly, it is impossible to control all aspects of a dialysis (number of alarms, blood-pump calibration, etc.) and more dialysis could have been delivered during the treatments with exercise by chance. We were careful to ensure that the same dialysis machine with the same blood-pump calibration and dialyser type were used for the two dialysis sessions. An independent observer, i.e. the dialysis nurse, would key in the identical prescription parameters (blood flow, dialysis time) each time. However, if more dialysis was delivered during the exercise treatments the rebound would have been higher; we found the opposite. We also calculated the patient clearance time (*tp*) for each treatment. This parameter is the time needed to clear all body compartments to a Kt/V of 1 with infinite dialyser clearance. It is a measure of the compartmentalization of the patient's solute space and is independent of the actual dose of dialysis delivered. The *tp* values measured indicated less compartmentalization during exercise to a degree which entirely explained the difference in dialysis dose delivered.

In conclusion, our data demonstrate that exercise may significantly increase the efficiency of dialysis. The increase is equivalent to extending the dialysis time by 15–20 min. Since exercise has other beneficial effects [11,12], exercising during dialysis is likely to prove an economic, safe and highly efficacious method for increasing the health of dialysis patients. While we cannot prove the mechanism of this increase, our data support the hypothesis that it is mediated by an increase in muscle and systemic blood flow.

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