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Metabolic response to exercise in dialysis patients

PIETRO CASTELLINO, MARGARET BIA, and RALPH A. DEFRONZO

Divisions of Nephrology and Endocrinology/Diabetes, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, USA, and Istituto di Medicina Interna e Nefrologia, University of Napoli, Naples, Italy

Metabolic response to exercise in dialysis patients. The metabolic and hormonal response to acute moderate intensity (40% of VO_2 max) bicycle exercise was examined in eight uremic subjects maintained on chronic dialysis and in 12 age- and weight-matched controls before and after the administration of low dose, selective (metoprolol) and non-selective (propranolol), beta adrenergic antagonists. The fasting plasma glucose concentration and basal rates of hepatic glucose production (HGP) and tissue glucose disappearance (Rd) were similar in control and uremic subjects. In both groups HGP and Rd increased in parallel during exercise, and the plasma glucose concentration remained constant at the fasting level. However, the increments in Rd (2.27 ± 0.27 vs. 0.87 ± 0.31 mg/kg · min, $P < 0.01$) and HGP (2.47 ± 0.22 vs. 0.92 ± 0.19 mg/kg · min, $P < 0.01$) were 2.5-3 fold greater in the control compared to uremic subjects. Although the VO_2 max was decreased by 50% (39 ± 2 vs. 20 ± 2 ml/min · kg; $P < 0.01$), the correlation between Rd and VO_2 max was weak ($r = 0.33$, $P < 0.10$), suggesting that factors other than diminished physical fitness contribute to diminished tissue uptake of glucose in the dialyzed uremic patients. Following the cessation of exercise, HGP and Rd promptly returned toward basal levels in both uremic and control subjects. The glucose homeostatic response to exercise was not significantly altered by either propranolol or metoprolol. In the postabsorptive state fasting levels of insulin, glucagon, epinephrine, and norepinephrine all were significantly increased in the uremic group ($P < 0.01$ to 0.05). During exercise in the healthy young controls the plasma insulin concentration declined and plasma epinephrine and norepinephrine levels rose three- to fourfold. In contrast, in uremics plasma insulin failed to fall ($P < 0.05$) and the increase in circulating epinephrine and norepinephrine levels was markedly impaired ($P < 0.01$). The plasma glucagon concentration did not change significantly from baseline in either the control or uremic groups during exercise. Neither low dose propranolol nor metoprolol altered the hormonal response to exercise in either group.

Patients maintained on chronic hemodialysis are characterized by a sedentary lifestyle, a lower degree of physical fitness, and reduced maximum aerobic capacity [1]. These changes may, in part, contribute to the accelerated rate of atherosclerosis [2], impaired glucose tolerance [3], and insulin resistance [4, 5] in uremic patients. In a recent study, Goldberg and colleagues demonstrated that a chronic physical training program is capable of ameliorating many of the endocrine-metabolic abnormalities observed in non-diabetic patients with end-stage renal failure [6]. However, little is known about the acute effects of exercise on glucose metabolism in uremic patients who are maintained on chronic dialysis.

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During acute exercise in healthy subjects there is an increase in glucose utilization by the exercising muscle which is precisely balanced by an equivalent increase in hepatic glucose production, such that the plasma glucose concentration is maintained close to the fasting level [7, 8]. This balance between peripheral glucose uptake and hepatic glucose output is, in large part, regulated by changes in circulating hormone levels [7, 8]. Thus, increases in glucagon and epinephrine secretion, in combination with a decline in plasma insulin concentration, facilitate the increase in hepatic glucose production. At present it is unknown whether the metabolic/hormonal response to exercise is normal in end-stage renal failure patients who are maintained on dialysis.

Many dialysis patients receive beta adrenergic antagonists for the treatment of hypertension. Recently, we have demonstrated that type I diabetic patients demonstrate an altered sensitivity to the adrenergic regulation of glucose metabolism during acute exercise [9]. At present, little is known about the adrenergic regulation of glucose homeostasis during exercise in patients with end-stage renal failure. This is of interest for several reasons. First, exercise has been advocated as a means to improve some of the metabolic disturbances observed in uremic individuals [6]. And second, uremic patients are commonly treated with beta adrenergic blocking agents, which may alter the glucose homeostatic responses to exercise [9].

The present study was undertaken to examine the effect of acute exercise on glucose metabolism in uremic patients maintained on dialysis and to define whether the metabolic/hormonal responses to exercise are altered by low dose, beta adrenergic blocking-agents.

Methods

Subject population

Twelve, healthy normal subjects and eight uremic patients who were maintained on chronic dialysis treatment were studied. The control group consisted of nine males and three females (mean age = 27 ± 2 yrs) who were within 15% of their ideal body weight (mean = 108 ± 3%) based upon medium frame individuals of the 1959 Metropolitan Life Insurance Tables. The uremic group consisted of five males and three females with a mean age of 36 ± 2 yrs who were within 15% of ideal body weight (mean = 109 ± 4%). The individual clinical data for the uremic group are summarized in Table 1. No subject had any evidence of hepatic, cardiovascular, endocrine, or other major organ system disease other than kidney failure.

Table 1. Summary of the clinical characteristics of the 8 uremic patients who participated in the study

Patient	Sex	Diagnosis	Years on dialysis	Dialysis treatment	Serum urea nitrogen *mg/dl*	Creatinine *mg/dl*	Plasma potassium *mEq/liter*	Plasma bicarbonate *mEq/liter*	Plasma phosphate *mg/dl*
TL	M	Malignant hypertension	8	Hemodialysis	74	20.5	5.0	18	5.0
PL	M	Glomerulonephritis	10	CAPD	99	18.5	4.9	19	4.9
GD	F	Glomerulonephritis	1	Hemodialysis	52	18.5	5.1	20	6.4
EL	M	Unknown	5	CAPD	62	14.5	4.2	25	5.0
ZL	F	Interstitial nephritis	3	CAPD	55	20.0	4.1	26	4.8
GB	F	Glomerulonephritis	2	CAPD	47	9.5	3.9	27	4.3
GM	M	Unknown	3	Hemodialysis	116	18.5	5.0	15	5.0
MJ	M	Interstitial nephritis	4	Hemodialysis	71	14.5	4.3	16	4.2
Mean ± SEM			4.5 ± 1.0		72 ± 8	16.8 ± 1.2	4.6 ± 0.2	21 ± 2	4.9 ± 0.2

Except for vitamin supplementation and phosphate binders, uremic subjects consumed no medications for at least seven days prior to their participation in the study. There was no family history of diabetes mellitus in any subject. For at least three days prior to study all subjects consumed a weight maintaining diet containing at least 200 grams of carbohydrate per day. None of the uremic subjects were on a protein restricted diet. The purpose, nature and potential risks of the study were explained to each subject before obtaining his/her voluntary written consent. The experimental protocol was reviewed and approved by the Human Investigation Committee of the Yale University School of Medicine.

Experimental protocol

All subjects initially underwent a measurement of their maximum aerobic work capacity (VO_2 max) using a bicycle ergometer. Mean maximal oxygen consumption for the normal subjects was 39 ± 2 ml/min · kg and for uremics was 20 ± 2 ml/min · kg ($P < 0.01$). Following determination of the VO_2 max, each subject participated in three exercise protocols that were performed in randomized order at seven to ten day intervals. The exercise was performed on a bicycle ergometer and the intensity was adjusted to 40% of each subject's VO_2 max. All studies were begun at 0800 hours following a 10 to 12 hour overnight fast. In the peritoneal dialysis patients all fluid was drained from the abdomen on the evening prior to study and the exercise study was carried out on the following morning. In the hemodialysis patients all studies were carried out 36 to 48 hours after the last dialysis. After the exercise study was completed, dialysis was begun in both the peritoneal and hemodialysis groups.

The exercise protocols are described below:

Protocol I. Subjects exercised at 40% of their VO_2 max for 40 minutes and this was followed by a 30 minute postexercise recovery period.

Protocol II. For three days prior to exercise subjects ingested propranolol (Ayerst Laboratories, New York, USA), 40 mg orally every 12 hours. The last dose of propranolol was taken at 0800 hours on the day of study. Exercise was performed as described under Protocol I.

Protocol III. For three days prior to exercise subjects ingested metoprolol (Ciba Geigy, Summit, New Jersey, USA), 50 mg orally every 12 hours. The last dose of metoprolol was taken at 0800 hours on the day of study. Exercise was performed as described under Protocol I.

Neither the subjects nor the investigators knew which drug (that is, propranolol or metoprolol) had been consumed until after the study was completed and the data analyzed.

Two hours prior to the start of exercise a catheter was inserted into an antecubital vein and subjects received 25 μCi of ^{3}H-3-glucose (New England Nuclear, Boston, Massachusetts, USA) as an intravenous bolus. This was immediately followed by a continuous intravenous infusion of tritiated glucose at the rate of 0.25 μCi/min. The continuous infusion was maintained for a two hour period prior to starting exercise, during the 40 minute exercise period, and throughout the 30 minute postexercise recovery period. Plasma samples for the determination of tritiated glucose specific activity were obtained from a catheter inserted into the contralateral antecubital vein at five minute intervals starting 30 minutes prior to exercise and at five minute intervals throughout the exercise and postexercise recovery period. Plasma hormone (insulin, glucagon, epinephrine, and norepinephrine) and free fatty acid (FFA) concentrations were determined at five to ten minute intervals before, during, and after exercise.

Calculations

In the basal state the rates of glucose appearance (Ra) and disappearance (Rd) are equal and were calculated by dividing the tritiated glucose infusion rate (CPM/min) by the steady plateau of tritiated glucose specific activity (CPM/mg) which was achieved during the last 30 minutes of the control period in all subjects. Following the start of exercise a non-steady state condition existed for tritiated glucose specific activity and Ra and Rd were calculated using Steele's equations in their derivative form [10] with a pool fraction of 0.65 [11]. This technique has previously been validated for non-steady state conditions [12, 13]. Data from the peritoneal and hemodialysis patients were initially analyzed separately. Since no differences between the two groups were observed, these data were combined for presentation.

All values in the text and figures represent the mean ± SEM. Comparisons between groups were made by analysis of variance. Changes from baseline within a group were made with the paired *t*-test.

Analytical determinations

Plasma glucose concentration was measured using the glucose oxidase method (Glucose Oxidase Analyzer, Beckman Instruments, Fullerton, California, USA). Plasma insulin con-

Table 2. Effect of beta adrenergic blockade on glucose turnover during exercise in normal subjects

Protocol	Basal	Study period	
		Exercise	Recovery
Control			
HGP *mg/kg · min*	2.01 ± 0.10	4.48 ± 0.31[a]	2.70 ± 0.29
Rd *mg/kg · min*	2.01 ± 0.10	4.28 ± 0.31[a]	2.75 ± 0.38
Plasma glucose *mg/dl*	81 ± 2	81 ± 2	79 ± 3
Propranolol			
HGP	1.84 ± 0.12	4.39 ± 0.15[a]	1.79 ± 0.12
Rd	1.84 ± 0.12	3.98 ± 0.23[a]	1.76 ± 0.21
Plasma glucose	84 ± 2	79 ± 1	81 ± 3
Metoprolol			
HGP	1.76 ± 0.17	3.74 ± 0.36[a]	1.51 ± 0.22
Rd	1.76 ± 0.17	3.60 ± 0.10[a]	1.88 ± 0.21
Plasma glucose	83 ± 2	83 ± 2	81 ± 2

Plasma glucose concentration, HGP, and Rd are shown during the basal state, at the end of the 40 min exercise period, and at the end of the 30 min postexercise recovery period. All results are expressed as the mean ± SEM.

[a] $P < 0.01$ vs. baseline

centration was determined with a double antibody technique [14]. Plasma glucagon concentration was measured by radioimmunoassay using the 30K antibody of Unger [15]. Samples for catecholamines were collected in glutathione and analyzed using a radioenzymatic assay (Cat-a-Kit, Upjohn Co., Kalamazoo, Michigan, USA). Plasma free fatty acid concentrations (FFA) were determined according to the method of Dole [16] as modified by Novak [17]. Methods for the determination of tritiated glucose specific activity have been published previously [18].

Results

Normal controls

Plasma glucose concentration and glucose turnover. The fasting plasma glucose concentration, the basal rate of hepatic glucose production (HGP) and the basal rate of glucose disappearance (Rd) were similar in all three study protocols (Table 2).

During the control study there was a prompt increase in hepatic glucose production with the onset of exercise, and this reached a maximum of 4.48 mg/kg · min at 40 minutes. The increase in HGP was closely matched by an increase in Rd such that the plasma glucose concentration remained at the fasting level (Table 2, Fig. 1). Following the cessation of exercise both HGP and Rd declined in parallel, reaching values of 2.70 ± 0.29 and 2.75 ± 0.38 mg/kg · min at 70 minutes, respectively. During the postexercise recovery period the plasma glucose concentration did not change significantly from baseline (Table 2, Fig. 1).

When exercise was performed following beta adrenergic blockade with propranolol, the rises in HGP and Rd were similar to those observed during the control study. During the postexercise recovery period both glucose disappearance and production declined more promptly to baseline compared to the control study (Table 2, Fig. 1). Changes in HGP and Rd following metoprolol were quite similar to those observed with propranolol (Table 2, Fig. 1).

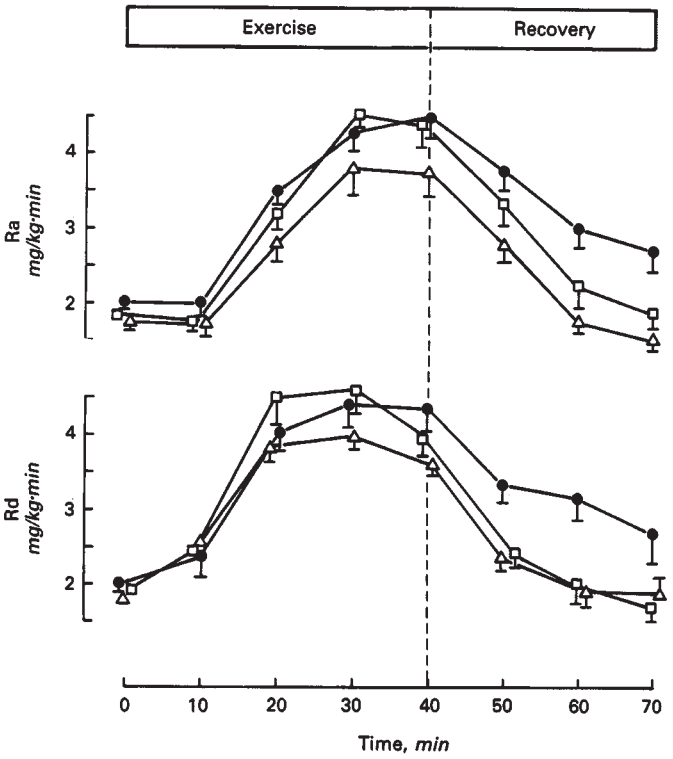

Fig. 1. *Time related change in the rate of glucose appearance (Ra), and the rate of glucose disappearance (Rd) in healthy young subjects during exercise (0 to 40 min) and during the postexercise recovery period (40 to 70 min) in the control (solid circles), propranolol (open squares), and metoprolol (open triangles) studies.* Ra is equivalent to the rate of hepatic glucose production (HPG). All values represent the mean ± SEM.

Plasma hormone and FFA concentrations. In the control study the fasting plasma insulin concentration declined from 14 to 11 μU/ml ($P < 0.05$) during exercise and then increased to levels slightly above basal during the postexercise recovery period. The decrease in plasma insulin concentration when exercise was performed with both propranolol and metoprolol was more pronounced than during the control study (Table 3). Plasma glucagon tended to rise during both the exercise and postexercise recovery periods during all three study protocols, but in none did the increase reach statistical significance (Table 3).

Both epinephrine and norepinephrine rose five- to sixfold during exercise in the control study and returned toward baseline during the postexercise recovery period. A similar pattern was observed during both the propranolol and metoprolol studies.

Basal plasma FFA concentrations, 731 ± 68 μmol/liter, increased during exercise in the control study and remained elevated during the postexercise recovery period (Table 3). Following both propranolol (495 ± 46 μmol/liter) and metoprolol (530 ± 57 μmol/liter) the fasting plasma FFA concentrations were significantly reduced ($P < 0.01$). In contrast to the increase in plasma FFA observed in the control study, following both propranolol and metoprolol exercise was associated with a decline in the plasma FFA concentration (Table 3). During the postexercise recovery period the plasma FFA

Table 3. Effect of beta adrenergic blockade on the hormonal response to exercise in normal subjects

Protocol	Basal	Study period	
		Exercise	Recovery
Control			
Insulin *μU/ml*	14 ± 2	11 ± 2[a]	16 ± 2
Glucagon *pg/ml*	86 ± 11	95 ± 12	100 ± 12
Epi *pg/ml*	26 ± 3	166 ± 36[b]	40 ± 6
NE *pg/ml*	215 ± 15	1269 ± 115	300 ± 32[a]
FFA *μmol/liter*	731 ± 68	988 ± 142[a]	1019 ± 118[a]
Propranolol			
Insulin	16 ± 2	10 ± 1[a]	16 ± 1
Glucagon	111 ± 18	133 ± 23	147 ± 27
Epi	27 ± 4	188 ± 19[b]	53 ± 5[a]
NE	219 ± 25	1058 ± 124[b]	273 ± 29[a]
FFA	495 ± 46[c]	381 ± 45[c]	536 ± 64[c]
Metoprolol			
Insulin	18 ± 2	11 ± 2[a]	17 ± 2
Glucagon	125 ± 30	118 ± 27	127 ± 20
Epi	30 ± 4	157 ± 16[b]	48 ± 6
NE	223 ± 14	1224 ± 142[b]	289 ± 26[a]
FFA	530 ± 57[c]	436 ± 62[c]	594 ± 87[c]

Plasma insulin, glucagon, epinephrine (Epi), norepinephrine (NE), and free fatty acid (FFA) concentrations are shown during the basal state, at the end of the 40 min period of exercise and at the end of the 30 min postexercise recovery period. All results are expressed as the mean ± SEM.

[a] $P < 0.05$ vs. basal

[b] $P < 0.01$ vs. basal

[c] $P < 0.01$ vs. the control study

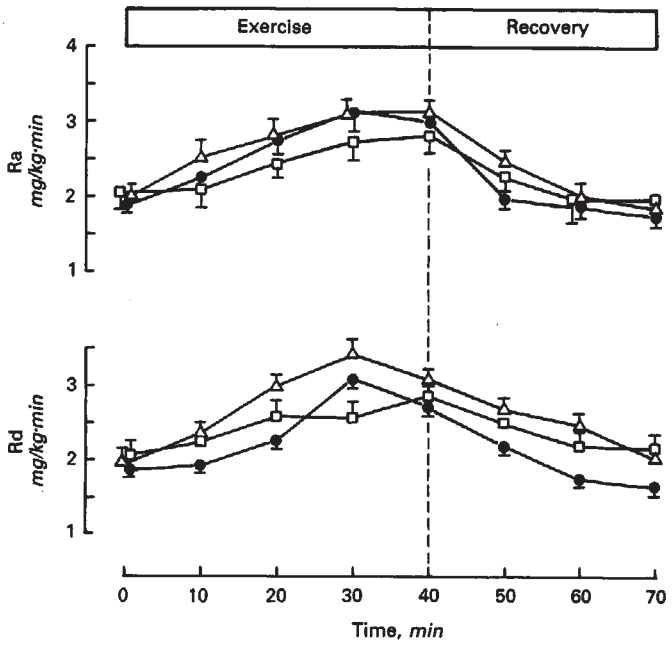

Fig. 2. *Time related change in the rate of glucose appearance (Ra), and the rate of glucose disappearance (Rd) in uremic subjects during exercise (0 to 40 min) and during the postexercise recovery period (40 to 70 min) in the control (solid circles), propranolol (open squares), and metoprolol (open triangles) studies.* Ra is equivalent to the rate of hepatic glucose production. All values represent the mean ± SEM.

Table 4. Effect of beta adrenergic blockade on glucose turnover during exercise in uremic subjects

Protocol	Basal	Study period	
		Exercise	Recovery
Control			
HGP *mg/kg · min*	1.88 ± 0.10	2.80 ± 0.35[b,c]	1.94 ± 0.26
Rd *mg/kg · min*	1.88 ± 0.10	2.75 ± 0.18[b,c]	1.72 ± 0.10
Plasma glucose *mg/dl*	77 ± 2	81 ± 2	75 ± 2
Propranolol			
HGP	2.06 ± 0.20	2.79 ± 0.23[a,c]	2.33 ± 0.20
Rd	2.06 ± 0.20	2.88 ± 0.15[a,c]	2.20 ± 0.31
Plasma glucose	82 ± 2	80 ± 4	74 ± 3
Metoprolol			
HGP	1.98 ± 0.10	3.23 ± 21[b,c]	1.85 ± 0.15
Rd	1.98 ± 0.10	3.12 ± 0.23[b,c]	2.11 ± 0.23
Plasma glucose	82 ± 2	82 ± 3	79 ± 3

Plasma glucose concentration, HGP, and Rd are shown during the basal state, at the end of the 40 min exercise period, and at the end of the 30 min postexercise recovery period. All results are expressed as the mean ± SEM.

[a] $P < 0.05$ and [b] $P < 0.01$ vs. baseline; [c] $P < 0.05$ vs. healthy control subjects

increased to or above the basal level in the propranolol and metoprolol studies.

Uremic patients

Plasma glucose concentration and glucose turnover. In the basal state the fasting plasma glucose concentration, hepatic glucose production (HGP), and the rate of glucose disappearance (Rd) were similar in all three study protocols (Table 4, Fig. 2).

During the control study the fasting plasma glucose concentration in the uremic subjects increased slightly during exercise and then returned to the basal level during the postexercise recovery period. The plasma glucose concentration did not change significantly from baseline during exercise in either the propranolol or metoprolol studies (Table 4, Fig. 2). The basal rates of hepatic glucose production and tissue glucose disappearance in uremic subjects (Table 4) were similar to those observed in the healthy controls (Table 2) during all three study protocols. During exercise the increase in Rd was closely paralleled by the increase in HGP in the control, propranolol, and metoprolol protocols (Table 4, Fig. 2). However, the increment in both Rd and HGP were reduced by 50 to 60% in the uremic compared to healthy control subjects ($P < 0.01$). Even if the increment in Rd (Rd max–Rd basal) is factored by the increment in oxygen consumption (VO_2max–VO_2basal), a significant reduction is observed in the uremic group (0.048 ± 0.009 vs. 0.067 ± 0.008 mg/kg · min, $P < 0.05$).

Within the uremic group no differences in Rd or HGP were observed between patients maintained on hemo- versus peritoneal dialysis.

Plasma hormone and FFA concentrations. The fasting plasma insulin concentration in the uremic patients was slightly, although not significantly greater than in the controls in all three study protocols. In contrast to the controls, the plasma insulin concentration failed to decrease from basal levels during exercise in either of the three studies. The fasting plasma glucagon concentration was elevated approximately fivefold in the ure-

Table 5. Effect of beta adrenergic blockade on the hormonal response to exercise in uremic subjects

Protocol	Basal	Study period	
		Exercise	Recovery
Control			
Insulin *μU/ml*	16 ± 2	16 ± 2	16 ± 2
Glucagon *pg/ml*	550 ± 80[d]	486 ± 40	561 ± 80
Epi *pg/ml*	94 ± 19[d]	147 ± 31[a]	93 ± 23
NE *pg/ml*	823 ± 200[d]	1498 ± 210[b]	775 ± 157
FFA *μmol/l*	554 ± 110	713 ± 102[b]	811 ± 190[a]
Propranolol			
Insulin	20 ± 4	20 ± 4	20 ± 4
Glucagon	477 ± 35[d]	460 ± 15	472 ± 33
Epi	80 ± 26[d]	195 ± 54[a]	109 ± 26[a]
NE	868 ± 153[d]	1423 ± 224[b]	947 ± 170
FFA	449 ± 110	356 ± 60[c]	606 ± 136
Metoprolol			
Insulin	20 ± 4	19 ± 4	20 ± 4
Glucagon	489 ± 73[d]	459 ± 42	476 ± 57
Epi	93 ± 33[d]	220 ± 40[a]	103 ± 38
NE	907 ± 239[d]	1791 ± 319[b]	972 ± 161
FFA	404 ± 60	359 ± 52[c]	443 ± 126[c]

Plasma insulin, glucagon, epinephrine (Epi), norepinephrine (NE), and free fatty acid (FFA) concentrations are shown during the basal state, at the end of the 40 min exercise period, and at the end of the 30 min postexercise recovery period. All results are expressed as the mean ± SEM. [a] $P < 0.05$ and [b] $P < 0.01$ vs. basal; [c] $P < 0.05$ vs. the control study; [d] $P < 0.05$ vs. healthy young subjects

Table 6. Effect of beta adrenergic blockade on mean arterial blood pressure and heart rate during exercise in control and uremic subjects

Protocol	Basal	Study period	
		Exercise	Recovery
Normals			
Control			
Heart rate	62 ± 4	142 ± 3[d]	73 ± 5[c]
Mean BP	91 ± 3	95 ± 2	89 ± 3
Metoprolol			
Heart rate	50 ± 2[a]	108 ± 5[b,d]	64 ± 3[b,c]
Mean BP	86 ± 3[a]	91 ± 5	87 ± 3
Propanolol			
Heart rate	54 ± 3[a]	111 ± 4[b,d]	61 ± 4[b,c]
Mean BP	84 ± 4[a]	90 ± 4	88 ± 4
Uremics			
Control			
Heart rate	73 ± 3	125 ± 4[d]	86 ± 3[c]
Mean BP	96 ± 3	102 ± 3	98 ± 3
Metoprolol			
Heart rate	62 ± 3[a]	91 ± 5[b,d]	68 ± 3[b,c]
Mean BP	83 ± 6[a]	87 ± 3[b]	82 ± 4[b]
Propranolol			
Heart rate	65 ± 3[a]	98 ± 3[b,d]	74 ± 3[b,c]
Mean BP	88 ± 5[a]	94 ± 4[a]	85 ± 5[a]

Mean arterial blood pressure (mm Hg) and heart rate (beats/minute) are shown during the basal state, at the end of the 40 min exercise period, and at the end of the 30 min post exercise recovery period in control and uremic subjects. All results are expressed as the mean ± SEM. [a] $P < 0.05$ vs. control, [b] $P < 0.01$ vs. control, [c] $P < 0.05$ vs. basal, [d] $P < 0.01$ vs. basal

mic compared to healthy control subjects and, as was observed in the controls, failed to increase following exercise (Table 5). Baseline epinephrine and norepinephrine concentrations were increased three- to four-fold in the uremic group ($P < 0.01$). During exercise both the incremental response, as well as the percent increment above baseline, were significantly diminished in the uremic compared to control subjects ($P < 0.01$), even though the absolute plasma catecholamine concentrations achieved were similar in two groups (Tables 2, 5). During the postexercise recovery period plasma epinephrine and norepinephrine concentrations returned to basal levels in all three study protocols.

The fasting plasma FFA concentration was moderately, although not significantly reduced in the uremic group (Table 5). Following exercise and during the postexercise recovery period the incremental plasma FFA response was similar to that observed in the healthy control group. Following both propranolol and metoprolol the fasting plasma FFA concentration decreased slightly and the normal increase in circulating FFA levels in response to exercise was not observed; in contrast, a significant decline in plasma FFA occurred in response to exercise. During the postexercise recovery period the plasma FFA concentration increased to or above basal levels in the propranolol and metoprolol studies.

Discussion

Decreased physical fitness has been associated with an accelerated rate of atherosclerosis [19], impaired glucose tolerance [20, 21], insulin resistance [22, 23], hyperinsulinemia [19, 20], and hyperlipidemia [24]. Similar metabolic disturbances and cardiovascular risk factors have been reported in uremic individuals [1–5]. Recently, Goldberg and colleagues demonstrated that a chronic exercise program can reverse many of the metabolic disturbances that have been demonstrated in uremic patients [6] and they have suggested that exercise be employed to improve the cardiovascular risk profile in such individuals [25]. However, little information is presently available concerning the metabolic compensations to a bout of acute physical exercise in patients with end-stage renal failure. In the present study we have examined the glucose and hormonal responses to moderate intensity exercise in uremic patients maintained on chronic dialysis. The intensity of exercise was set at 40% of VO_2 max because this is within the capacity of an average untrained individual without causing profound exhaustion. Because many uremic patients are treated with beta adrenergic blocking agents and these agents have been shown to alter the metabolic response to exercise in patients with impaired glucose tolerance such as diabetes mellitus [9], we also examined the effect of low dose, non-specific (propranolol) and specific (metoprolol), beta blocking agents on the glucose/hormonal responses to exercise.

In healthy young subjects exercise was associated with a five to sixfold rise in circulating epinephrine and norepinephrine levels and a decline in the plasma insulin concentration. Similar changes have been reported by others [7, 8, 26, 27]. The decline in plasma insulin has been shown to be mediated via alpha adrenergic stimulation which inhibits insulin secretion by the pancreas [28, 29]. The increase in plasma catecholamine concentration, in combination with the decrease in plasma insulin, are believed to facilitate the rise in hepatic glucose production to meet the demands of the exercising muscle [7, 8, 26, 27, 30]. No change in circulating plasma glucagon levels was observed.

This is consistent with previously published reports in which moderate intensity exercise has been employed [9, 31]. When exercise was performed with the chronic administration of beta adrenergic antagonists (both propranolol and metoprolol), the increases in Rd and HGP were similar to the control study, indicating that beta stimulation is not an absolute requirement in order to observe a normal glucose homeostatic response to exercise. We [9], as well as others [32], have reported similar results when exercise was performed after acute adrenergic blockade with propranolol. In contrast, in insulin-dependent diabetic subjects propranolol markedly inhibited the exercise induced rise in HGP and augmented peripheral glucose disposal, leading to significant hypoglycemia [9].

In uremic subjects maintained on chronic dialysis the maximum aerobic capacity was decreased by 50%, documenting a markedly reduced level of physical fitness. Similar observations have been made by others [1]. Nonetheless, when exercise was performed at the same relative intensity (40% of VO_2 max) as in healthy young control subjects, tissue glucose disposal (Rd) increased and this was precisely matched by a rise in HGP, such that the plasma glucose concentration did not change significantly from baseline. It is noteworthy, however, that the absolute, as well as the incremental rises in both Rd and HGP were reduced by approximately 60 – 65% ($P < 0.01$) in the uremic compared to control group.

It is particularly noteworthy that the VO_2 max in the uremic subjects was reduced by 40 to 50% compared to controls ($P < 0.01$). Since all subjects exercised at a constant percentage (40%) of their VO_2 max, the absolute work intensity must have been reduced by 40 to 50% in the uremic group. Since the absolute work intensity is an important determinant of amount of glucose utilized by the exercising muscle [7], it is not surprising that tissue glucose uptake (Rd) was significantly lower in the uremic patients. However, the increment in Rd in the uremic compared to control group (0.87 vs. 2.27 mg/kg · min) was lower than what could be expected on the basis of the reduction in VO_2 max. Thus, if one calculates the increment in Rd per increment in oxygen consumption, a significant reduction (0.048 vs. 0.067; $P < 0.05$) is observed. Furthermore, the VO_2 max was poorly correlated with the Rd ($r = 0.32$, $P < 0.10$). These results suggest that factors other than the degree of physical fitness may be responsible for the diminished increase in tissue glucose disposal during exercise in the uremic group. Since plasma FFA levels tended to be lower in uremic compared to control subjects, this substrate can not account for the diminished increase in Rd. It is well documented that peripheral tissues, primarily muscle, of uremic patients are markedly resistant to the action of insulin [3–5]. It is possible that this resistance also extends to the ability of exercise to promote muscle glucose uptake.

The possibility should also be considered that the decrease in peripheral glucose uptake is, in part, related to decreased substrate availability due to an impairment in hepatic glucose output. With regard to this possibility, basal plasma insulin levels tended to be increased in uremic patients and failed to decline during exercise. This would tend to inhibit hepatic glucose output. Similarly, although fasting plasma catecholamine levels were increased in uremic individuals, the increases in both plasma epinephrine and norepinephrine (Table 5) during exercise were markedly diminished compared to control subjects (Table 3). It is possible that the diminished incremental plasma catecholamine response in uremic subjects, in combination with the lack of decline in plasma insulin concentration, may in part be responsible for the failure of HGP to increase to the same level as observed in the controls.

It is important to emphasize that neither propranolol, a non-specific beta 1-beta 2 antagonist, nor metoprolol, a specific beta 1 antagonist, altered the exercise-related increase in Rd or HGP in uremic subjects. This has important clinical implications, since it indicates that exercise can safely be performed in uremic subjects who are being treated with beta blocking agents without the risk of developing hypoglycemia. This is in contrast to diabetic subjects who manifest an altered adrenergic sensitivity to beta adrenergic antagonists and are predisposed to the development of clinically significant hypoglycemia [9].

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Reprint requests to Ralph A. DeFronzo, M.D., 2071 LMP Building, Yale-New Haven Hospital, 333 Cedar Street, New Haven, Connecticut 06510, USA.

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