Glucoregulation During and After Intense Exercise: Effects of α-Adrenergic Blockade

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In intense exercise (>80% maximal oxygen consumption [Vo_2 max]), the 7- to 8-fold increase in glucose production (Ra) is tightly correlated with the greater than 14-fold increase in plasma norepinephrine (NE) and epinephrine (EPI). To distinguish the relative roles of α- and β-adrenergic receptors, the responses of 12 control (C) lean, healthy, fit young male subjects to 87% Vo_2 max cycle ergometer exercise were compared with those of 7 subjects (at 83% Vo_2max) receiving intravenous phentolamine (Ph). The Ph group received a 70-μg/kg bolus and then 7 μg/kg/min from −30 minutes, during exercise and for 60 minutes of recovery. The data were analyzed by comparing exercise responses to exhaustion in Ph subjects (11.4 ± 0.6 min) with those at both 12 minutes and at exhaustion in C subjects (14.6 ± 0.3 min) and during recovery. There were no significant differences between groups in the plasma glucose response during exercise, but values were higher in C versus Ph subjects during the first 40 minutes of postexercise "recovery." The Ra response during the first 12 minutes of exercise was not different by repeated-measures ANOVA, reaching 10.6 ± 1.3 mg/kg/min in C and 9.6 ± 1.5 in Ph subjects at 12 minutes. However, in C subjects, Ra increased significantly to 14.1 ± 1.2 mg/kg/min by exhaustion, and remained higher versus Ph subjects until 15 minutes of recovery. The Rd during recovery was not different between groups; thus, the higher Ra in C subjects in early recovery was responsible for the greater hyperglycemia observed in C subjects. Ph subjects showed a more rapid, marked increment ($P = .002$) in both plasma NE (to 64 *v* 38 nmol/L) and EPI at exhaustion, and catecholamine concentrations remained higher in Ph versus C subjects during recovery. Whereas plasma insulin (IRI) declined in the C group, it increased 3-fold ($P = .001$) in the Ph group during exercise and until 15 minutes of recovery. Ph had no effect on glucagon (IRG). Thus, the glucagon to insulin ratio decreased in Ph subjects from baseline levels during exercise and early recovery, but increased in C subjects. The increase in Ra among Ph subjects despite the decrease in the glucagon to insulin ratio supports our earlier evidence that these hormones are not principal regulators of the Ra in intense exercise. The shorter time to exhaustion and markedly higher catecholamine levels in Ph subjects limited our ability to isolate the effects of α-adrenergic receptors on the Ra. α-Adrenergic receptors appear to have little influence on the Rd.

GLUCOSE TURNOVER appears to be regulated differently in low- to moderate-intensity compared with high-intensity exercise. The plasma glucose concentration is tightly regulated in exercise at 60% or less of maximum oxygen uptake ($\dot{V}o_2$max), with the increment of uptake (Rd) precisely matched by that of production (Ra). It is generally held that this Ra response is due to the increase in the portal vein glucagon to insulin ratio and that the afferent signals for the increase in glucagon and decrease in insulin arise from the exercising muscle itself,[1-3] constituting a "feedback" mechanism. In contrast, we have demonstrated that the glucagon to insulin ratio is relatively unimportant in glucoregulation during intense exercise (≥80% $\dot{V}o_2$max).[4-10] In islet-cell clamp experiments, the catecholamine response to exercise was intact, and even a substantial increase in immunoreactive insulin (IRI) did not attenuate the Ra response.[10] In another islet-cell clamp experiment with exogenous glucose infusion and exercise at 80% $\dot{V}o_2$ max, constant glucagon and an increase in IRI did not affect the 4-fold increase in Ra.[11]

Therefore, a signal for rapid and marked hepatic glycogenolysis (apart from immunoreactive glucagon [IRG]/IRI responses) is required that anticipates the need for the increase in Ra in intense exercise. This has been suggested to be "feedforward" and centrally originated.[12,13] Our group[5,6,8-10,14] and others[12,15] have proposed that the catecholamine response is the primary regulator of Ra. Circulating plasma norepinephrine (NE) and epinephrine (EPI) increase at least 14-fold during exercise,[4-6,8,9,12] and these concentrations are tightly correlated with the corresponding values for Ra during intense exercise and early recovery.

One standard approach to assess the role of catecholamines in glucoregulation is adrenergic receptor blockade. We have evaluated the role of β-adrenergic receptors in intense exercise during propranolol infusion.[16] Compared with control subjects exercised at the same percentage $\dot{V}o_2$max, there was a greater Ra response in β-blocked subjects. This Ra response and the NE and EPI responses were comparable to those of unblocked subjects exercised at an even higher workload. There was a concomitant increase in Rd with propranolol, such that the hyperglycemia was of shorter duration in recovery. These findings demonstrated the key role of β-receptors in Rd, and suggested an important potential role for α-adrenergic receptors in Ra. The present study was undertaken to test the effects of the α-adrenergic–blocking agent phentolamine (Ph) in a similar

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Table 1. Anthropometric and Exercise Data in the Subjects

Parameter	C Group	Ph Group
No. of subjects	12	7
Age (yr)	22.0 ± 1.5	25.6 ± 2.6
Height (cm)	175 ± 3	176 ± 3
Weight (kg)	71 ± 2	67 ± 4
BMI (kg/m²)	23.2 ± 0.5	21.7 ± 0.6
$\dot{V}o_2max$		
L/min	4.42 ± 0.21	3.83 ± 0.34
mL/kg/min	62.9 ± 3.2	56.7 ± 3.4
Study $\dot{V}o_2$ (L/min)	3.88 ± 0.21	3.21 ± 0.34
Study$\dot{V}o_2$/$\dot{V}o_2$max (%)	87 ± 2	83 ± 3
Workload (W)		
Maximal	331 ± 18	306 ± 29
Study	263 ± 13	211 ± 23*
Heart rate at exhaustion (bpm)	179 ± 5	180 ± 6
Exercise duration (min)	14.3 ± 0.3	11.4 ± 0.6*

NOTE. Data are presented as the mean ± SE.
Abbreviation: BMI, body mass index.
*$P < .05$ *v* C subjects.

manner. We predicted that blockade would attenuate the Ra response and have little effect on Rd. The results of these studies have been presented in abstract form.[17]

SUBJECTS AND METHODS

The study participants were 19 fit, lean, weight-stable young men, aged 18 to 36 years. All engaged in regular activity such as aerobic training, running, cycling, soccer, and/or rowing, combined with resistance training in some. Anthropometric and exercise data are presented in Table 1. None of the subjects had evidence of cardiovascular, pulmonary, hepatic, hematologic, renal, or other systemic disease. All were nonsmokers who were on no medications. Subjects were informed of the purpose of the study and the possible risks of the exercise, Ph, cannulations, blood sampling, and tritiated glucose administration. They provided consent as prescribed by the institutional human ethics committee. Screening prior to the study included a medical history, physical examination, hemogram, blood biochemistry, hepatitis B serology, urinalysis, electrocardiogram, and chest roentgenogram. All studies were performed in the exercise physiology laboratory of the McGill Nutrition and Food Science Centre at Royal Victoria Hospital.

Each subject underwent 3 exercise tests. In the first test, $\dot{V}o_2max$ was determined with continuous breath-by-breath analysis during an incremental workload test in the sitting upright position on an electrically braked cycle ergometer (Collins Metabolic Cart; Warren E. Collins, Braintree, MA). Resistance was increased by 20 W each minute until exhaustion. In this and the subsequent tests, exhaustion was defined by the subject as the time at which he was unable to continue cycling, uniformly reported as being due to leg muscle fatigue. The same investigators used the same approach with verbal encouragement to the subjects to exercise to their individual limits. $\dot{V}o_2$ (STPD, liters per minute), carbon dioxide output ([$\dot{V}co_2$] STPD), ventilation (BTPS, liters per minute), and the respiratory exchange ratio were recorded at 30-second intervals. The heart rate was displayed electrocardiographically.

On a separate occasion at least 2 days after the $\dot{V}o_2max$ test, each subject underwent a second test without blood sampling at 50% for 30 seconds followed by 80% of the previously established maximum workload. This test was used to familiarize the subjects with the workload protocol and to determine that the time to exhaustion would be 12 to 15 minutes, to ensure intersubject uniformity in endurance. When it was apparent that the workload selected would not lead to exhaustion in the desired time, the workload was adjusted upward or downward by 10-W steps during exercise.

The third exercise study was performed after an interval of at least 2 days from the second test, and in most cases, after an interval of more than 1 week. Seven subjects underwent alpha blockade with Ph while 12 others served as control subjects (C). This study began at 8 to 9 AM, with subjects in the 12-hour overnight-fasted (postabsorptive) state without any significant exercise in the preceding 24 hours. A 20-gauge Cathlon IV cannula (Critikon Canada, Markham, Ontario, Canada) was inserted into one antecubital vein for blood sampling, and another into a forearm vein of the other arm for infusion. The subjects remained sitting, with the catheters kept patent by a slow infusion of physiologic saline. After 20 to 30 minutes, a preinfusion blood sample was drawn, and the infusion of high-performance liquid chromatography–purified [3-^{3}H]-glucose tracer (DuPont-NEN, Billerica, MA) began. A priming bolus of 11 mL at time 0 minutes was followed by a constant infusion at 0.109 mL/min (of a solution containing 2 μCi/mL in 0.9% saline) for 150 minutes. Blood was sampled at 90, 100, 110, 120, 130, 140, and 150 minutes to ensure a near–steady-state enrichment of plasma [^{3}H]-glucose. In Ph subjects at 30 minutes prior to exercise, intravenous Ph was started: a bolus of 70 μg/kg was followed by a continuous infusion of 7 μg/kg/min that was continued throughout exercise and stopped at 60 minutes of recovery. This infusion rate was chosen because it was previously used in human exercise studies[18] and had significant physiological effects without compromising safety. Blood pressure and pulse were monitored every minute for 10 minutes and then every 5 minutes. The rate of tracer infusion was increased stepwise during exercise and returned stepwise to the original rate during recovery (Table 2), a method that attenuates changes in [^{3}H]-glucose specific activity during the rapid changes in glucose kinetics and thereby ensures the validity of glucose turnover calculations.[19] Different patterns of change in infusion rates were selected for C and Ph subjects based on the different peak Ra responses found in the pilot studies. The peak infusion rate was greater in C versus Ph subjects because pilot studies suggested that peak Ra would be lower in the latter. The [^{3}H]-glucose

Table 2. Study Protocol

	Period (min)																				
	Baseline		Exercise							Recovery											
Treatment	−150	−30	0	3	5	6	9	10	12	0	3	4	6	8	9	10	12	15	60	120
Ph group																					
Ph (μg/kg/min)	0	7*	0.7	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	0	0
3-^{3}H-glucose (μCi/min)	0.22†	→	0.44	→	0.60	→	→	0.88	→	→	→	0.60	→	0.44	→	→	0.22	→	→	0
C group																					
3-^{3}H-glucose (μCi/min)	0.22†	→	0.44	0.60	→	0.88	1.21	→	1.70	→	1.21	→	0.88	→	0.60	→	0.44	0.22	→	0

NOTE. Entries indicate time at which infusions began, stopped, or changed rates.
*This followed a bolus of Ph 70 μg/kg.
†This followed a bolus of 3-^{3}H-glucose 22 μCi.

infusion was continued for the 2 hours of recovery. During exercise, blood was sampled at 2-minute intervals. A sample was drawn at exhaustion, and this time was defined as time 0 of recovery, such that samples were drawn at 2, 4, 6, 8, 10, 15, 20, 30, 40, 50, 60, 80, 100, and 120 minutes thereafter for glucose and radioactivity measurements. Samples for all other measurements were drawn at 0 and 10 minutes prior to exercise, at 4 and 10 minutes of exercise, exhaustion, and recovery 4, 8, 10, 15, 20, 30, 40, 60, and 100 minutes.

Samples for glucose turnover measurements were placed into tubes that contained heparin and sodium fluoride and were processed as described previously.[5] Heparinized plasma was collected with aprotinin (Trasylol 10,000 kallikrein inhibitor U/mL; FBA Pharmaceuticals, New York, NY) in a volume one tenth that of the added blood for subsequent insulin (IRI), glucagon (IRG), and free fatty acid (FFA) assays. For catecholamine measurements, blood was added to EGTA- and reduced-glutathione–containing tubes and the plasma was frozen at −70°C until assay. One aliquot of whole blood was immediately deproteinized in an equal volume of cold 10% (wt/vol) perchloric acid and kept on ice until centrifugation at 4°C, and then frozen at −20°C for later lactate and pyruvate assays.

Glucose was measured by the glucose oxidase method using a Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Blood lactate and pyruvate levels were measured by 2-channel automated enzymatic microfluorometric methods, enabling assay of replicate 5- or 10-μL aliquots of the perchloric acid supernatants using two Turner model 430 spectrofluorometers (Sequoia-Turner, Mountain View, CA) by methods previously detailed.[10] Plasma insulin was determined by radioimmunoassay using an anti–beef insulin antiserum, purified human insulin standard (27.3 μU/ng), and [^{125}I]-labeled human insulin (Linco Research, St Louis, MO). IRG was measured in plasma by double-antibody radioimmunoassay using purified porcine glucagon for the standard and as [^{125}I] label and a pancreatic glucagon–specific antibody (Linco). FFA levels were estimated by a radiochemical method. All assays performed on aprotinin-containing plasma were corrected for the plasma dilution introduced by the concurrently obtained hematocrit. Plasma NE and EPI concentrations were measured using a radioenzymatic technique.[20] The sensitivity of this method is less than 50 pmol/L. The intraassay and interassay coefficients of variation for all assays were less than 10%; for enzymatic assays, they were less than 5%. Glucose production (Ra) and utilization (Rd) were calculated from the variable isotope infusion protocols according to the 1-compartment model with a pool fraction of 0.65,[21] with data systematically smoothed using the Optimized Optimal Segments (OOPSEG) program.[22,23] The glucose metabolic clearance rate (MCR) was calculated by dividing Rd by the plasma glucose concentration at each time point.

Baseline characteristics were analyzed using *t* tests. The study workload was calculated as the mean workload for all but the first 30 seconds of exercise. Study $\dot{V}O_2$ was calculated as the mean $\dot{V}O_2$ during the last half of exercise, by which time further increases in $\dot{V}O_2$ were generally small. Glucose, glucose turnover, and other metabolite and hormone results were analyzed by ANOVA for repeated measures. Because Ph affected the duration and intensity of exercise, intergroup differences were also compared using the product of each individual's duration and intensity of exercise as a covariate in the repeated-measures ANOVA. For this secondary analysis, intensity was calculated as the mean workload (watts) during the final study divided by the maximum workload from the $\dot{V}O_2$max test. Linear regression was used to compute a slope for each subject of Ra versus catecholamine concentrations for all time points. Linear correlations were calculated using the Pearson correlation coefficient. Individual correlation coefficients and regressions of Ra on catecholamines were calculated using all 12 data points for each subject at which they were measured. These correlation coefficients and slopes were then treated as continuous variables on which the mean ± SE was calculated, and intergroup differences were assessed using *t* tests. In addition, for each subject group, the values for Ra at 10 minutes of exercise were regressed on catecholamine concentrations from the same time point. The SAS-STAT software package (SAS Institute, Cary, NC), SPSS-Windows Release 6.0 software package (SPSS, Chicago, IL), Microsoft Excel 5.0 Analysis ToolPak (GreyMatter International, Cambridge, MA), and Primer Biostats (McGraw-Hill, New York, NY) were used. Data are presented as the mean ± SE.

RESULTS

No untoward effects were experienced during any of the exercise tests. Ph infusion was associated with symptoms of mild nasal stuffiness in most subjects, but this had no influence on exercise performance, since the breath-by-breath measurements required the use of a nose clip and mouthpiece. No Ph subjects experienced a Ph-induced decline in systolic or diastolic blood pressure of more than 5 mm Hg. Ph subjects exercised at a similar intensity versus the C group but reached exhaustion more quickly (Table 1). However, the study $\dot{V}O_2$ values were not significantly different, nor were the $\dot{V}O_2/\dot{V}O_2$max or heart rate at exhaustion. Plasma glucose specific activity did not vary by more than 25% within each subject despite the rapid changes in glucose turnover during and following exercise (data not shown).

During the first 12 minutes of exercise, responses in the two groups were not different with respect to (1) the plasma glucose increase, (2) the marked increase in Ra, (3) the lesser increase in Rd versus Ra, and (4) the MCR. This occurred despite the following findings in Ph subjects: (1) a marked increase in IRI, (2) no change in IRG (resulting in a decline in IRG/IRI), and (3) markedly greater plasma NE and EPI responses in Ph subjects. The slightly higher peak plasma glucose at exhaustion in C subjects was attributable to the additional 2 minutes of exercise in C subjects at a time of continuing rapid Ra increase. Plasma glucose increased further in early recovery, and remained higher in C versus Ph subjects.

Ph infusion prior to exercise had no effect on plasma glucose concentrations (Fig 1A). By repeated-measures ANOVA, the response to exercise was not significantly different between Ph and C subjects up to 12 minutes. At exhaustion in C subjects, a further increment occurred, but it was followed by a much higher peak value at 4 minutes of recovery (8.05 ± 0.48 *v* 6.00 ± 0.56 mmol/L in Ph, $P = .016$) that was sustained until 40 minutes ($P = .026$ for the whole recovery period). However, these differences were not significant after adjusting for the duration and intensity of exercise.

The Ra was higher after 20 and 30 minutes of Ph infusion prior to exercise (2.35 ± 0.15 *v* 1.97 ± 0.09 mg/kg/min in C, $P = .028$). Although it was still significantly greater at 2 and 6 minutes, the ANOVA of responses to 12 minutes of exercise was not different between groups. In C subjects, Ra increased 5.3-fold to 10.49 ± 1.31 mg/kg/min, and in Ph subjects by 4.6-fold to 10.75 ± 1.08 mg/kg/min. It was higher in C subjects at exhaustion ($P = .022$ *v* Ph at exhaustion). Since time 0 of recovery was taken as the point of exhaustion, Ra in C subjects remained higher than in Ph subjects until 15 minutes of recovery ($P = .032$). However, these differences were no longer significant after adjusting for the duration and intensity of exercise (Fig 1B).

Although the mean Rd before exercise was slightly higher in

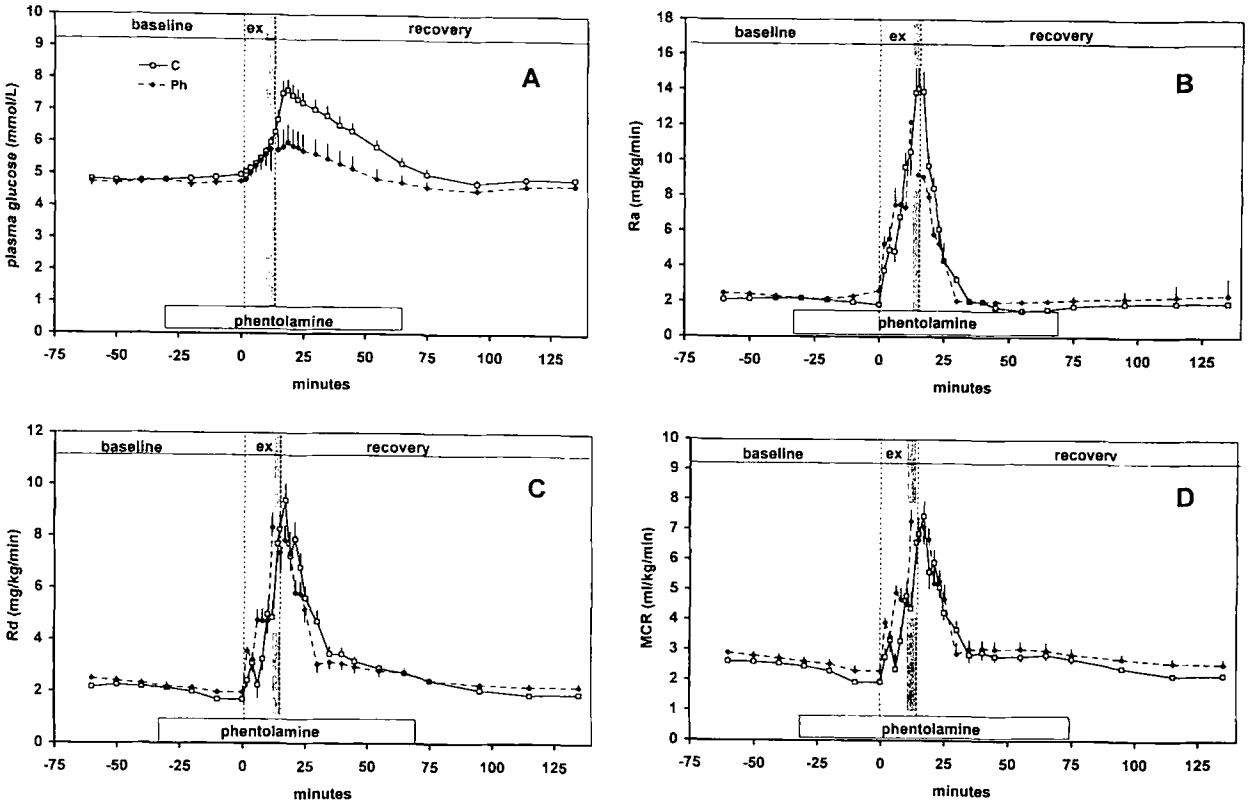

Fig 1. Plasma glucose concentration (A), Ra (B), Rd (C), and MCR (D) at rest (baseline), during intense exercise (Ex), and recovery. Time 0 indicates the beginning of exercise. Data from C subjects (□, n = 12) are compared with those from Ph subjects (◆, n = 7). The primed-continuous Ph infusion, indicated by the horizontal bar, began 30 minutes prior to exercise and ended at 60 minutes of recovery. The shaded area in the exercise period indicates the difference in duration of exercise; the result at exhaustion is plotted for both groups at the end of the exercise interval. Data are presented as the mean ± SE. Where SE bars are not present, they are smaller than the symbol. Significant differences are specified in the text.

Ph than in C subjects, this was not significantly different (Fig 1C). The overall Rd response to 12 minutes did not differ by ANOVA (or at 12 minutes by *t* test), but values in Ph subjects at 2 and 6 minutes of exercise were higher ($P < .02$). The Rd increased further in C subjects at exhaustion (NS *v* Ph at exhaustion). In recovery, although Rd was higher at 5 and 15 minutes in C subjects, ANOVA showed no overall difference. The much higher early-recovery plasma glucose levels in C subjects are thus explained by the longer duration of exercise causing a higher Ra rather than a difference in Rd. The MCR results (Fig 1D) are consistent with this, with no intergroup differences throughout recovery. The ANOVA did not show differences overall during exercise to 12 minutes, despite differences at some individual time points.

IRI was 36% to 40% higher at −10 minutes and time 0 in Ph versus C subjects ($P = .004$); it increased by the same extent in Ph subjects as a consequence of Ph infusion ($P = .007$; Fig 2A). Whereas IRI declined significantly during exercise in C subjects, it increased 3-fold in Ph subjects to 12 minutes ($P = .004$). This resulted in a much higher IRI in Ph versus C subjects throughout exercise. In early recovery, it increased markedly in C subjects and remained above pre-exercise values up to 40 minutes of recovery. Nonetheless, the levels were higher in Ph subjects up to 30 minutes of recovery even after adjusting for the duration and intensity of exercise. Thereafter, they declined in both groups to reach baseline values by 60 minutes of recovery. The overall IRI response from 4 to 100 minutes of recovery was different between groups ($P = .007$).

Prior to exercise, IRG was unaffected by Ph infusion (Fig 2B). It showed neither a significant increase in either group nor intergroup differences during exercise, nor changes during recovery. Thus, the insulin responses were largely responsible for the divergent changes in the glucagon to insulin ratio ($P = .001$) during exercise (Fig 2C). Interestingly, at 10 minutes prior to exercise, the ratio was higher in C subjects ($P = .025$), then showed no change to 12 minutes of exercise, and then declined below baseline values in recovery to 40 minutes. In Ph subjects, the ratio declined by greater than 50% to exhaustion ($P < .001$) and then returned by 20 minutes of recovery to values that were superimposable on those for C subjects thereafter.

NE was higher during Ph infusion at rest (time 0, 6.79 ± 1.18 *v* 2.78 ± 0.24 nmol/L, $P = .0005$; Fig 3A). The marked 14-fold increase in C subjects to exhaustion was dwarfed by the more rapid and greater increase in Ph subjects ($P = .002$), despite the shorter exercise duration. In both groups, NE declined promptly in recovery, although remaining higher at several time points in Ph subjects. Values reached pre-exercise levels by 20 minutes.

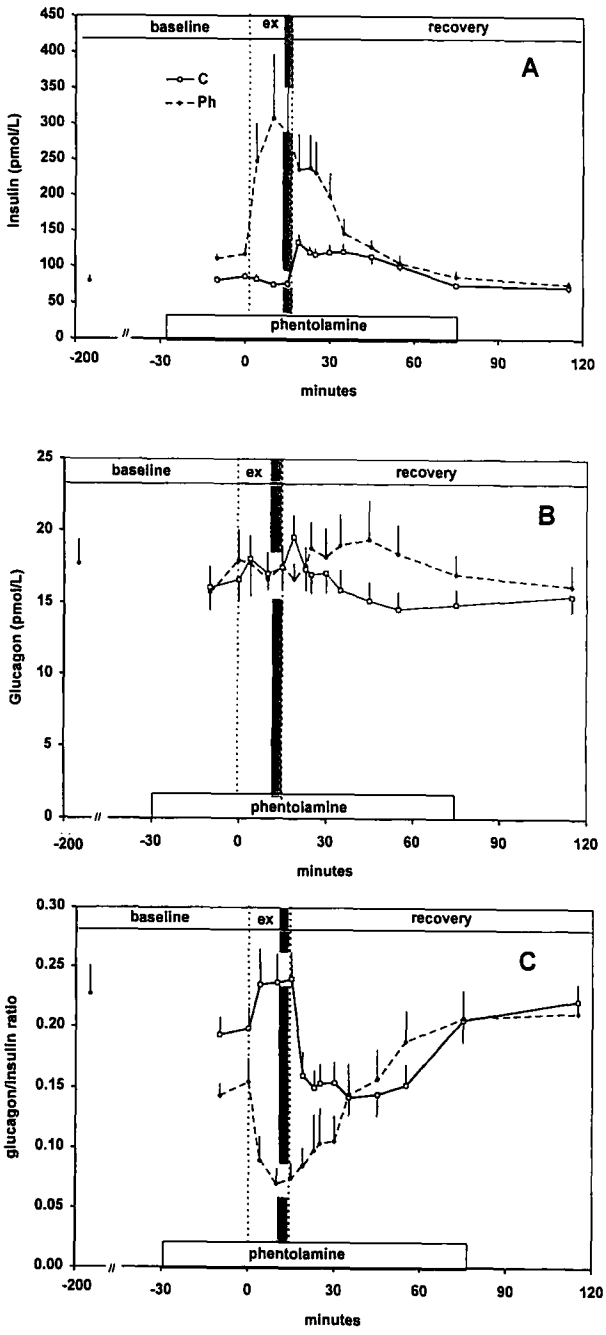

Fig 2. Plasma IRI (A), IRG (B), and glucagon to insulin molar ratio (IRG/IRI)(C) during baseline, intense exercise, and recovery periods. Data are presented as in Fig 1.

EPI levels (Fig 3B) were not different at −10 minutes, but were higher at time 0 in Ph subjects (762 ± 87 *v* 445 ± 52 pmol/L, $P = .004$). They increased 15-fold in C subjects and, as was the case for NE, increased much more in Ph subjects ($P = .001$). The pattern of return to baseline concentrations was similar to that of NE. Correlations of the catecholamines with the corresponding Ra values are shown in Table 3. The correlation coefficients were highly significant. It is noteworthy that the slopes of the regression equations of Ra on catecholamine

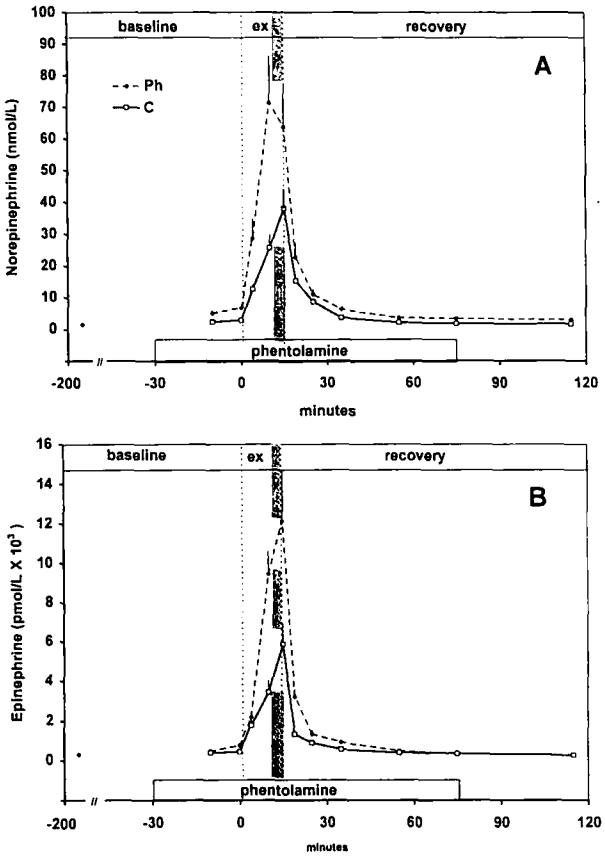

Fig 3. Plasma NE (A) and EPI (B) concentrations during baseline, intense exercise, and recovery periods. Data are presented as in Fig 1.

concentrations were considerably lower in Ph versus C subjects (70% less for NE and 75% less for EPI). For the data from 10 minutes of exercise, the slope was 58% less for NE and 36% less for EPI. This is consistent with greater NE and EPI responses being required in Ph subjects to generate a given Ra response.

Responses for lactate, pyruvate, and FFA are shown in Fig 4. Ph infusion did not affect lactate or pyruvate before exercise. As is typical for this exercise intensity, blood lactate and pyruvate

Table 3. Correlations Between Plasma Catecholamines and Ra

	NE			EPI		
Group	*r*	*P*	m	*r*	*P*	m
C						
All measurements	.94	.004	.3984	.89	.01	.0028
10 min exercise	.85	.001	.1605	.77	.005	.0011
Ph						
All measurements	.89	.002	.1220	.85	.002	.0007
10 min exercise	.83	.020	.0667	.76	.047	.0007

NOTE. Correlation coefficients were calculated for each subject, and the mean value is presented. The *P* value is for the individual who had the value with the lowest level of statistical significance for that group.

Abbreviation: m, mean slope of the regression equation for the correlation for all measurements and at 10 min exercise for the number of subjects in each group. Ra = m [NE or EPI] + b, where b is the intercept (m is in mg/kg/min per nmol/L).

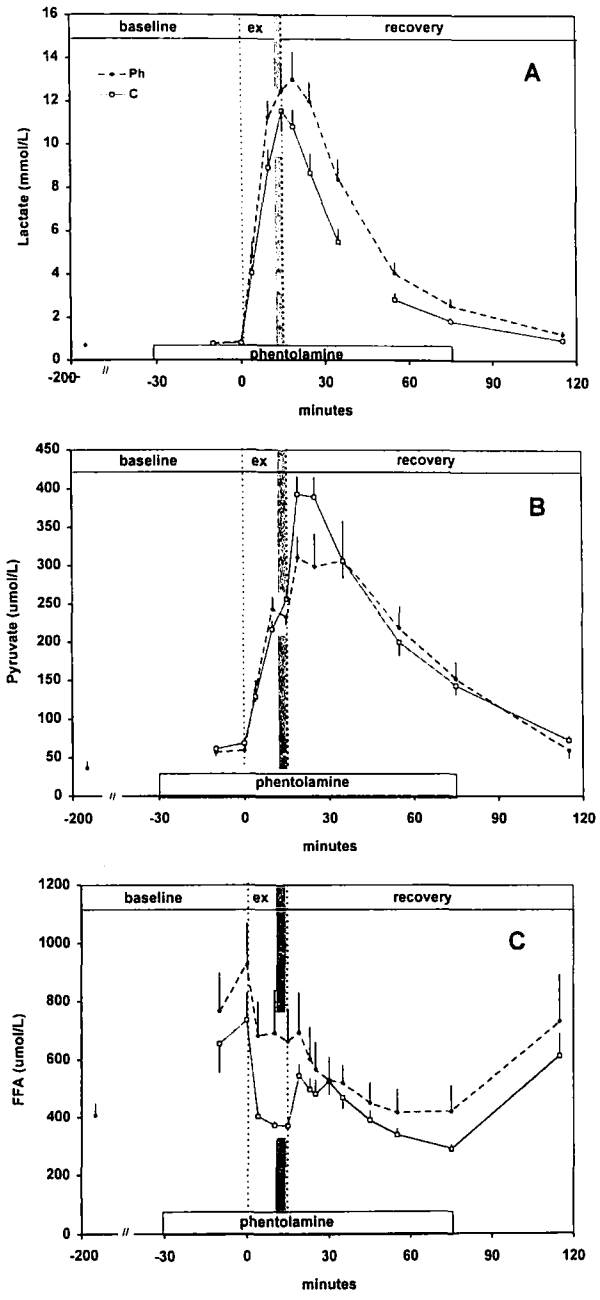

Fig 4. Blood lactate (A), pyruvate (B), and plasma FFA (C) during baseline, intense exercise, and recovery periods. Data are presented as in Fig 1.

concentrations increased markedly during exercise. Lactate (Fig 4A) increased at a comparable rate and reached equivalent levels at exhaustion despite both the longer duration of exercise and the higher Rd in C subjects. It remained more elevated in Ph subjects during its gradual decline toward resting values in recovery ($P = .036$) even after adjusting for the duration and intensity of exercise, and then reached similar values only at 100 minutes. In contrast, for pyruvate (Fig 4B), there were no intergroup differences in the increase, the peak value in early recovery, or the rate of decrease in later recovery.

Plasma FFA (Fig 4C) increased from the −180-minutes value by almost 2-fold prior to exercise in Ph subjects ($P < .001$). The responses during exercise diverged markedly: a marked greater than 50% decrease occurred in C subjects, followed by a transient partial return to resting values in early recovery and a second decrease until 60 minutes of recovery, with a return to resting values at 120 minutes. In Ph subjects, the small decrease during exercise did not reach significance, with values thus remaining higher than in C subjects ($P = .046$) even after adjusting for the duration and intensity. Thereafter, during recovery, there was a pattern of response similar to that of the C subjects, with a decline followed by a return to baseline only at 120 minutes.

DISCUSSION

The C subjects demonstrated the metabolic and humoral-mediator responses that are well documented to occur during and after intense exercise.[4-7,10,12,15-17,24] The small increase in plasma glucose (along with decreasing IRI) during exercise was followed by a marked increment at exhaustion that lasted until 60 minutes of recovery and was associated with a sustained hyperinsulinemic response. The rapidity and magnitude of both the increase and decrease in Ra are perhaps the greatest observed in physiologic glucoregulation, and correlated highly with marked catecholamine responses.

When an adrenergic-blocking agent is used in vivo to dissect the relative importance of α-versus β receptor activation, one must take into account the concurrent changes in other regulators of the endpoint response. Normally, during intense exercise, there is vasodilation in arteries supplying the exercising muscle and vasoconstriction in vessels supplying the viscera. By interfering with the normal exercise-induced vasoconstriction in vessels supplying the viscera, Ph in the present study may have impeded the body's ability to maximize blood flow and oxygen delivery to muscle during strenuous exercise. This may have been responsible for the earlier exhaustion. Ph also influences insulin secretion by blocking the normal α-adrenergic inhibition of insulin secretion,[25,26] leading to unopposed β-adrenergic stimulation.

Because Ph subjects were not able to exercise as long as the C group, we compared the responses over the time points from time 0 until exhaustion in Ph subjects at 11.4 minutes and until 12 minutes in C subjects. Despite the extraordinarily large increments in NE and EPI in Ph subjects, which far exceeded the already marked 14-fold increments in C subjects, there were only transient differences in Ra (higher in Ph group early in exercise) that were not significantly different by repeated-measures ANOVA over the 12-minute exercise period. It is probable that this very large catecholamine increment was related to increased release via blockade of the presynaptic α-receptors that inhibit NE and EPI release. To the extent that adrenergic stimulation of Ra occurs via β-receptors, the Ra response would have been enhanced by the greater NE and EPI response. If stimulation occurs by α-receptors, there are several possible explanations for the lack of a decreased Ra response. The Ra response may have been incompletely blocked by the dose of Ph used, or the inhibition may have been partially overcome by the extremely high NE and EPI levels reached. It is possible that the rate of increase in Ra was already at its

maximum, such that further catecholamine increases would have no greater effect. A further possibility is that α-receptors play no role in stimulating Ra in intense exercise, but this is unlikely, for reasons given later. Our data do not permit us to differentiate among these alternatives.

Previous studies of the roles of α- and β-adrenergic receptor activation in stimulation of Ra yielded inconsistent results and species differences.[27-31] These were performed at rest with differing experimental paradigms. In rats, α-receptors have been found to be most important in stimulating hepatic glucose production.[32] In dog hepatocytes, β-receptors have been reported to be dominant, and both play a role in cats.[28] Propranolol and Ph infused together into the portal vein were unable to prevent the Ra increment in dogs exercised to 85% of their maximum heart rate, an intensity that caused a 4-fold Ra increment.[33] However, these blockers were able to block the Ra response to portal infusion of NE and EPI. A recent study of intraportal catecholamine and adrenergic-blocker infusions in resting dogs suggested that stimulation of Ra by NE occurs mainly via α_1- and by EPI via β_2-adrenergic receptors.[34]

Similar ambiguity remains as to receptor mechanisms during moderate-intensity exercise in humans,[29,30] also in part because of differences among studies in experimental paradigms and subject characteristics. Most human studies have suggested a predominance of β-receptors.[27,28] One would therefore expect that beta blockade should decrease Ra. However, the opposite was found in the only study reported in human subjects with at least 87% $\dot{V}O_2$max exercise.[16] In that study, which used the same paradigm as the present one but with the nonspecific β-blocker propranolol, we found that the higher plasma NE and EPI attained were associated with a 2-fold higher peak Ra versus C subjects exercised at the same intensity and an equal Ra versus subjects exercised at about 94% $\dot{V}O_2$max for the last half of a 14-minute exercise bout (reaching 100% of their $\dot{V}O_2$max at exhaustion). The interpretation of these findings was not straightforward, because during exercise in the propranolol subjects, there was also a greater increase in EPI and NE levels versus C subjects, along with a decrease in plasma insulin and an increase in plasma glucagon, resulting in an increase in the glucagon to insulin ratio. Furthermore, while beta blockade was evidenced by an attenuated increase of the heart rate and lipolysis, it cannot be argued that the blockade was complete, and some β-adrenergic contribution to the increase in Ra remains a possibility. In studies with beta blockade in subjects with type 1 diabetes mellitus kept euglycemic before exercise by insulin infusion, a similar enhanced increase in Ra was found, despite an increase in free IRI during exercise, compared with nondiabetic control subjects.[35] Thus, we consider that the decrease in IRI was probably not the main mediator of the greater Ra response observed in propranolol subjects.

Our present results prior to exercise, in which Ra was increased during Ph infusion associated with a modest increase in NE (despite the increase in IRI), would be consistent with an unmasked β-receptor–mediated effect. Some studies using catecholamine infusions with or without adrenergic blockade support a role for α stimulation of Ra,[31,36,37] whereas others do not.[27,30,38] Interestingly, NE infusion increased Ra only at or above plasma levels of about 10.6 nmol/L.[36] As NE acts mainly via α-receptors, one possibility is that α-adrenergic stimulation of Ra occurs only when the level exceeds such a threshold. This could well explain the small or absent effects attributed to catecholamines in studies where this threshold was not reached.

If one were to consider the results of the present study in isolation, an equally plausible explanation for our findings is that greater hyperinsulinemia in Ph subjects caused the increase in Ra during exercise to be less than it would otherwise have been. While this is not impossible, two lines of evidence from other studies suggest that the insulin effect during intense exercise is likely to be small. First, in the islet-cell clamp studies, if replacement hormone infusion rates were not decreased during exercise, their plasma levels increased.[10,11] It was presumed that this was due to decreased disposal of the infused peptide related to altered splanchnic and/or renal blood flow. In Sigal et al,[10] the greatest increase was for insulin and it resulted in a decrease in the glucagon to insulin ratio, but Ra response was unaffected compared with C subjects and subjects in whom the infusion rates were decreased during exercise. Catecholamine responses were likewise identical. Second, very similar results were observed in euglycemic type 1 diabetic subjects in whom insulin was infused at a constant rate before, during, and after exercise.[6] IRI was 2- to 3-fold higher during exercise than in C nondiabetic subjects, but both groups had identical Ra (and catecholamine) responses. Thus, in other studies, an increase in IRI (and decrease in glucagon to insulin ratio) during intense exercise was unable to suppress the stimulation of Ra. We are unaware of any study in which exogenous insulin was given only during intense exercise. The situation appears different if a sustained increase in IRI sufficient to suppress Ra precedes the exercise. In our study in which glucose was infused at 4 mg/kg/min starting 210 minutes prior to exercise and continued until 60 minutes of recovery, there was partial attenuation of the Ra response, despite similar catecholamine responses.[39] The small IRI increase before exercise in the present study had no effect on Ra.

The substantial differences in the plasma glucose elevation in early recovery in C and Ph subjects is attributable both to the greater duration and intensity of the exercise period in C subjects and also possibly to the greater postexercise hyperinsulinemia in Ph subjects. We have previously demonstrated that hyperinsulinemia is important in restoring plasma glucose levels to normal during early recovery.[7] In the present study, the Ra increased a further 4 mg/kg/min to 14 mg/kg/min from 12 minutes to exhaustion in C subjects, and the Rd increased, but by a smaller amount. This higher Ra persisted for the first 15 to 20 minutes of recovery. The lesser hyperglycemia with alpha blockade is thus primarily due to the peak and early-recovery Ra values being lower. This is in contrast to the greater peak but shorter-duration hyperglycemic response with beta blockade, in which the Ra was higher than in C subjects and the Rd was also markedly enhanced.[16] There was no sustained overall effect of alpha blockade on Rd during or following intense exercise.

The site(s) and mechanism(s) responsible for the sustained blood lactate increase in Ph subjects are not clear from this study. Despite the fact that $\dot{V}O_2$ increased at comparable rates and to similar levels by 12 minutes of exercise (data not shown) and that exercise duration was longer in C subjects, and

especially that differences in Rd were minimal, this greater hyperlactatemia developed at the end of the exercise and persisted well into recovery. It is possible that Ph-induced systemic vasodilation attenuated the usual exercise-induced vasoconstriction of vessels supplying the viscera, resulting in reduced oxygen delivery to exercising muscles. The result would have been greater reliance on anaerobic metabolism in Ph subjects' exercising muscles. That the same pyruvate response occurred in both groups meant that the lactate to pyruvate ratio was considerably higher in Ph subjects (eg, at 4 minutes recovery, 44.4 ± 6.5 *v* 28.0 ± 2.0, $P = .009$). If the effect were primarily at the level of lactate production by muscle glycolysis, it implies a more reduced cytoplasmic redox state with Ph infusion, which in the presence of comparable $\dot{V}O_2$ is difficult to explain mechanistically. Since intracellular lactate is likely even higher than the blood levels, this could have contributed to the earlier development of fatigue in these subjects. Another factor possibly contributing to the recovery hyperlactatemia may have been the high portal vein insulin concentrations, restraining hepatic uptake for gluconeogenesis. Measurements of lactate kinetics would be desirable to clarify the mechanisms.

The differences in FFA response during exercise are likewise difficult to explain in the absence of kinetic data. Although the responses of lipolytic and antilipolytic mediators in C subjects would all tend to favor lipolysis (decreased IRI and increased catecholamines), FFA declined, as we observed previously. We have postulated this to be due to the even greater rates of uptake in less intensely exercised muscles than the increment in release from lipolysis. Alternatively, blood flow to adipose tissue might decrease in response to the catecholamines, although there are likely both species differences and differences between the effects of NE and EPI.[40,41] Unmasked, enhanced β effects on lipolysis in the presence of alpha blockade and the higher catecholamine levels are a possible explanation for this decline not occurring in Ph subjects. On the other hand, the marked hyperinsulinemia should have suppressed lipolysis, consistent with its regulation by the balance between β-adrenergic and insulin effects. Following exercise, the significant decline in both groups is probably explained by the hyperinsulinemia, and the later increase at 120 minutes by the return of IRI to baseline values.

In summary, the present study supports the results of prior experiments that implicate the catecholamine response to intense exercise as a mediator of the Ra response, although the shorter exercise duration and markedly higher catecholamine concentrations in Ph subjects limited our ability to isolate the α-adrenergic contribution to Ra. The presence of similar Ra responses until exhaustion in Ph subjects, notwithstanding their markedly higher catecholamine levels versus C subjects, is consistent with a contribution of α-adrenergic receptor activation to the Ra increase in response to the intense exercise. A β-receptor–mediated component of the Ra stimulation cannot be excluded, and could have offset that portion blocked by phentolamine. α-Adrenergic receptors appear to be less important than β-receptors in modulating Rd. Further studies of more specific receptor subtype blocking agents, especially if selectively taken up by the liver (with minimal peripheral effects), are required to define the mechanisms of adrenergic effects on the human liver.

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