Combined Infusion of Epinephrine and Norepinephrine During Moderate Exercise Reproduces the Glucoregulatory Response of Intense Exercise

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Intense exercise (IE) (>80% $\dot{V}O_{2max}$) causes a seven- to eightfold increase in glucose production (R_a) and a fourfold increase in glucose uptake (R_d), resulting in hyperglycemia, whereas moderate exercise (ME) causes both to double. If norepinephrine (NE) plus epinephrine (Epi) infusion during ME produces the plasma levels and R_a of IE, this would prove them capable of mediating these responses. Male subjects underwent 40 min of 53% $\dot{V}O_{2max}$ exercise, eight each with saline (control [CON]), or with combined NE + Epi (combined catecholamine infusion [CCI]) infusion from min 26–40. In CON and CCI, NE levels reached 7.3 ± 0.7 and 33.1 ± 2.9 nmol/l, Epi 0.94 ± 0.08 and 7.06 ± 0.44 nmol/l, and R_a 3.8 ± 0.4 and 12.9 ± 0.8 mg · kg^{-1} · min^{-1} ($P < 0.001$), respectively, at 40 min. R_d increased to 3.5 ± 0.4 vs. 11.2 ± 0.8 mg · kg^{-1} · min^{-1} and glycemia 5.2 ± 0.2 mmol/l in CON vs. 6.5 ± 0.2 mmol/l in CCI ($P < 0.001$). The glucagon-to-insulin ratio did not differ. Comparing CCI data to those from 14-min IE ($n = 16$), peak NE (33.6 ± 5.1 nmol/l), Epi (5.32 ± 0.93 nmol/l), and R_a (13.0 ± 1.0 mg · kg^{-1} · min^{-1}) were comparable. The induced increments in NE, Epi, and R_a, all of the same magnitude as in IE, strongly support that circulating catecholamines can be the prime regulators of R_a in IE.
***Diabetes* 52:1347–1354, 2003**

Glucoregulation during low- and moderate-intensity exercise is primarily mediated by an increase in the portal venous glucagon-to-insulin ratio (1), which stimulates hepatic glucose output, maintaining euglycemia largely through a feedback mechanism (2–4) that matches the increment to the increased requirements. However, in intense exercise (IE) 80% $\dot{V}O_{2max}$, an up to eightfold increase in glucose production (R_a) and a rise in glycemia occur, but plasma insulin (immunoreactive insulin [IRI]) changes little and glucagon (immunoreactive glucagon [IRG]) increases less than twofold (5). It seems unlikely that such changes, even insofar as they reflect portal vein concentrations, would mediate the R_a response in IE. Furthermore, the R_a response was unaffected in islet cell clamp studies using somatostatin and exogenous hormone infusions, in which peripheral IRG-to-IRI ratios (representative of portal levels) were kept unchanged or even decreased (6).

A "feedforward" control of R_a during IE has been proposed (4,7). We (5) and others (7,8) have proposed that the rapid and marked catecholamine response of IE could be such a mechanism. Plasma norepinephrine (NE) and epinephrine (Epi) concentrations both increase 15-fold, and we have demonstrated highly significant correlations of both with R_a during IE (5). We recently found that the patterns of responses of plasma catecholamines and R_a persist in glucose-infused subjects (9) and in the postprandial state (10). These are situations in which endogenous R_a suppression from hyperinsulinemia must be overcome, the latter being the situation under which most IE is performed. In contrast, at lower-intensity exercise, attenuation or prevention of the R_a increment occurs with exogenous glucose infusion (2–4,11,12).

Catecholamine infusions stimulate R_a in both dogs (13–15) and humans (16–21). Most of these studies involved only Epi and were done at rest. Although some (16,19) produced Epi levels comparable to those of IE, the 1.5- to 2.5-fold increments in R_a were considerably smaller. One study of Epi infusion during exercise was performed on celiac-ganglion–blocked and islet cell–clamped human subjects exercising at 74% $\dot{V}O_{2max}$. Epi was doubled, to concentrations typical of IE, causing a further increment in R_a over that of the exercise alone (18). Another study (17) with Epi infusion during 40% $\dot{V}O_{2max}$ exercise suggested that Epi contributes to, but does not fully account for, the R_a increment of IE. Our recent studies of Epi (22) or NE (23) infusions during 50% $\dot{V}O_{2max}$ exercise suggest that plasma levels of each could provide a sizable contribution toward the R_a increment of IE. Therefore, to test the hypothesis that catecholamines are the primary mediators of the markedly greater R_a response to IE than to moderate exercise (ME), we studied the metabolic effects of an incremental combined catecholamine infusion (CCI) designed to approximate the pattern of changes of IE. Subjects undergoing 40 min of 50% $\dot{V}O_{2max}$ exercise were studied with and without CCI from 26–40 min.

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Received for publication 30 October 2002 and accepted in revised form 27 February 2003.

CCI, combined catecholamine infusion; Epi, epinephrine; FFA, free fatty acid; IE, intense exercise; IRG, immunoreactive glucagon; IRI, immunoreactive insulin; MCR, metabolic clearance rate; NE, norepinephrine; R_a, glucose production; R_d, glucose uptake; RER, respiratory exchange ratio; SA, specific activity.

TABLE 1
Subject data

	CON	CCI*
n	8	8
Height (cm)	176 ± 2.4	183 ± 2.1
Weight (kg)	72.6 ± 2.4	77.8 ± 3.0
BMI (kg/m^2)	23.4 ± 0.6	23.1 ± 0.7
Age (years)	25.5 ± 0.6	22.4 ± 1.7
$\dot{V}O_{2max}$ (l/min)	4.1 ± 0.4	4.5 ± 0.1
$\dot{V}O_{max}$ (ml · kg^{-1} · min^{-1})	57.1 ± 2.7	57.2 ± 2.4
Maximum workload (W)	272 ± 10.0	282 ± 8.0
Study % $\dot{V}O_{2max}$	52.8 ± 0.7	53.3 ± 0.8
Study workload (W)	113 ± 6	108 ± 4

Data are means ± SE. *Combined infusion of norepinephrine and epinephrine.

RESEARCH DESIGN AND METHODS

Subject data are given in Table 1. Screening included medical history, physical examination, hemogram, blood biochemistry, urinalysis, hepatitis B and human immunodeficiency virus serology, electrocardiogram, and chest roentgenogram. Subjects were fully informed and gave signed consent as prescribed by the human ethics committee. $\dot{V}O_{2max}$ was determined during an incremental workload on a cycle ergometer (Collins Metabolic Cart; Collins, Braintree, MA). Oxygen uptake ($\dot{V}O_2$, standard temperature and pressure, dry gas [STPD]), carbon dioxide output ($\dot{V}CO_2$, STPD), ventilation (l/min, body temperature and pressure, saturated with water vapor [BTPS]), respiratory exchange ratio (RER), and heart rate were measured. The studies with glucose turnover measurements began at 0800 in the 12-h overnight fasting state. Intravenous cannulas were placed in both arms. A bolus of 22 μCi high-performance liquid chromatography–purified [3-^{3}H]glucose tracer (Perkin-Elmer-NEN, Billerica, MA) was followed by a constant infusion of 0.24 μCi/min in 0.9% saline, except where otherwise specified. Blood was sampled at intervals indicated by the data points of the figures. In the CCI experiment, NE (Sanofi Canada, Markham, ON, Canada) and Epi HCl (Abbott Laboratories, Saint-Laurent, QC, Canada) in isotonic saline and 1 mg/ml ascorbic acid (Sabex, Boucherville, QC, Canada) were infused from 26 to 40 min of exercise. In the CON experiment, only ascorbic acid in saline was infused. Subjects were unaware of which infusate was received. Glucose specific activity (SA) was maintained by increasing the tracer infusion incrementally to a maximum of sixfold the rates at rest during the infusion period in CCI and then returning it to the pre-exercise rate in early recovery. The goal was to introduce labeled glucose into the circulation at a rate proportional to endogenous R_a, thereby attenuating changes in [^{3}H]glucose SA to <25% during the rapid changes in glucose kinetics, as in previous experiments (5,6,9,10,22,23). This step would ensure the validity of glucose turnover calculations, even if there were changes in pool fraction during this time.

Samples for glucose turnover, insulin and glucagon, catecholamines, and lactate and pyruvate measurements were collected and processed as previously described (9) and analyzed as previously detailed (6). R_a and glucose uptake (R_d) were calculated from the variable isotope infusions with the one-compartment model using a glucose distribution space of 25% of body weight and a pool fraction of 0.65. Data were systematically smoothed using the OOPSEG (optimized optimal segments) program. References for glucose kinetic analyses are given in studies by Sigal et al. (6), Manzon et al. (9), and Kreisman et al. (10). The glucose metabolic clearance rate (MCR) was calculated by dividing R_d by the plasma glucose concentration.

Baseline characteristics were compared between groups with the independent samples t test. Other variables were analyzed by repeated-measures ANOVA. Significant within-study differences ($P < 0.05$) by ANOVA were analyzed by the Student-Newman-Keuls t test. Between-study differences significant by ANOVA had individual time points compared with the independent samples t test. Linear correlations were calculated using the Pearson correlation coefficient as previously detailed (6). The SPSS-Windows Release 10.0 software package (SPSS, Chicago, IL), Microsoft Excel 7.0 Analysis ToolPak (GreyMatter International, Cambridge, MA), and Primer Biostats (McGraw-Hill, New York) were used. Data are presented as means ± SE.

RESULTS

No untoward effects were experienced, and subjects were not able to distinguish between protocols. The subject groups were comparable (Table 1). RER increased in both

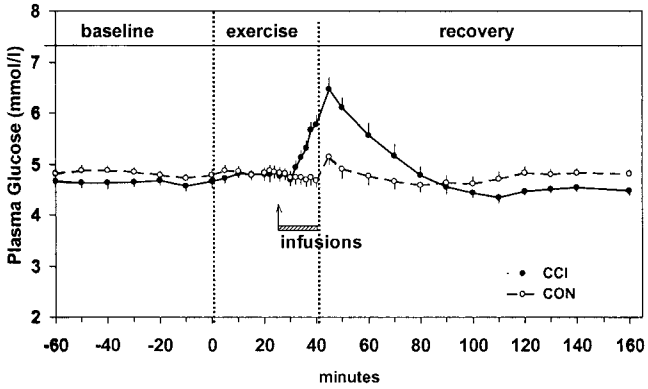

FIG. 1. Plasma glucose concentration during baseline, 40 min of 50% $\dot{V}O_{2max}$ exercise with and without combined Epi and NE infusion (CCI) from minutes 26 to 40 (indicated by the horizontal bar labeled "infusions"), and 120 min of postexercise recovery. Time 0 indicates the beginning of exercise. Data for CCI studies (n = 8) and CON studies (n = 8) are indicated. Data are presented as means ± SE. Where SE bars are not present, they are smaller than the symbol or would overlap with the SE from the other group. Significant differences are specified in the text.

to 0.93 ± 0.01 by 6 min, then declined to 0.90 ± 0.01 at 30 min, remaining at ~0.86 ± 0.01 until 40 min in CON, but rising in CCI to 0.93 ± 02 at 31 min and 0.91 ± 0.01 at 40 min ($P < 0.03$ during infusion). Heart rate did not change with infusion in CCI. Blood pressure did not differ between studies at any time.

Plasma glucose concentrations (Fig. 1) were not different at baseline and did not change with ME. They rose abruptly (21.1%) from 26 to 40 min in CCI to 5.78 ± 0.18 mmol/l, becoming higher than CON (4.68 ± 0.14 mmol/l) from 26 to 40 min ($P = 0.030$). Peak glycemia was reached at 5 min of recovery (6.47 ± 0.22 in CCI, 5.15 ± 0.16 mmol/l in CON), and it remained higher in CCI ($P = 0.018$) for 50 min. In CON, no significant change occurred during recovery. The approach to altering labeled glucose infusion rates in CCI was successful in limiting blood glucose SA changes: it was stable at 1.63 ± 0.04 μCi/g for the 30 min before exercise, and its average during infusion was 1.54 ± 0.06 to 1.60 ± 0.06 μCi/g. R_a (Fig. 2*A*) did not differ between studies at baseline nor during the progressive 75% rise during the first 26 min of exercise. Whereas R_a remained at this level in CON (4.53 ± 0.43 mg · kg^{-1} · min^{-1} at 32 min), it increased progressively in CCI to 12.94 ± 0.76 mg · kg^{-1} · min^{-1} at 40 min ($P < 0.001$ vs. CON, during infusion). It then returned to comparable levels the first 10 min of recovery but was lower than in CON from 20 to 60 min of recovery ($P = 0.026$). It was not different between groups after 80 min of recovery. Neither glucose R_d (Fig. 2*B*) nor MCR (Fig. 2*C*) differed at baseline or during the first 26 min of exercise, both increasing twofold. In CCI, both increased to a maximum R_d of 11.18 ± 0.82 mg · kg^{-1} · min^{-1} at 40 min (vs. 4.72 ± 0.51 mg · kg^{-1} · min^{-1} at 28 min in CON) and a MCR of 10.93 ± 0.96 ml · kg^{-1} · min^{-1} at 40 min (vs. 5.57 ± 0.67 ml · kg^{-1} · min^{-1} at 28 min in CON). Both R_d ($P = 0.031$ from 32 min) and MCR ($P = 0.010$ from 36 min) increased in CCI with increasing infusion rates. Both fell abruptly early in recovery and then remained at slightly higher than baseline for the first 60 min of recovery in CCI and 70–80 min in CON. Neither R_d nor MCR differed significantly during recovery.

IRI (Fig. 3*A*) did not differ at baseline and declined from

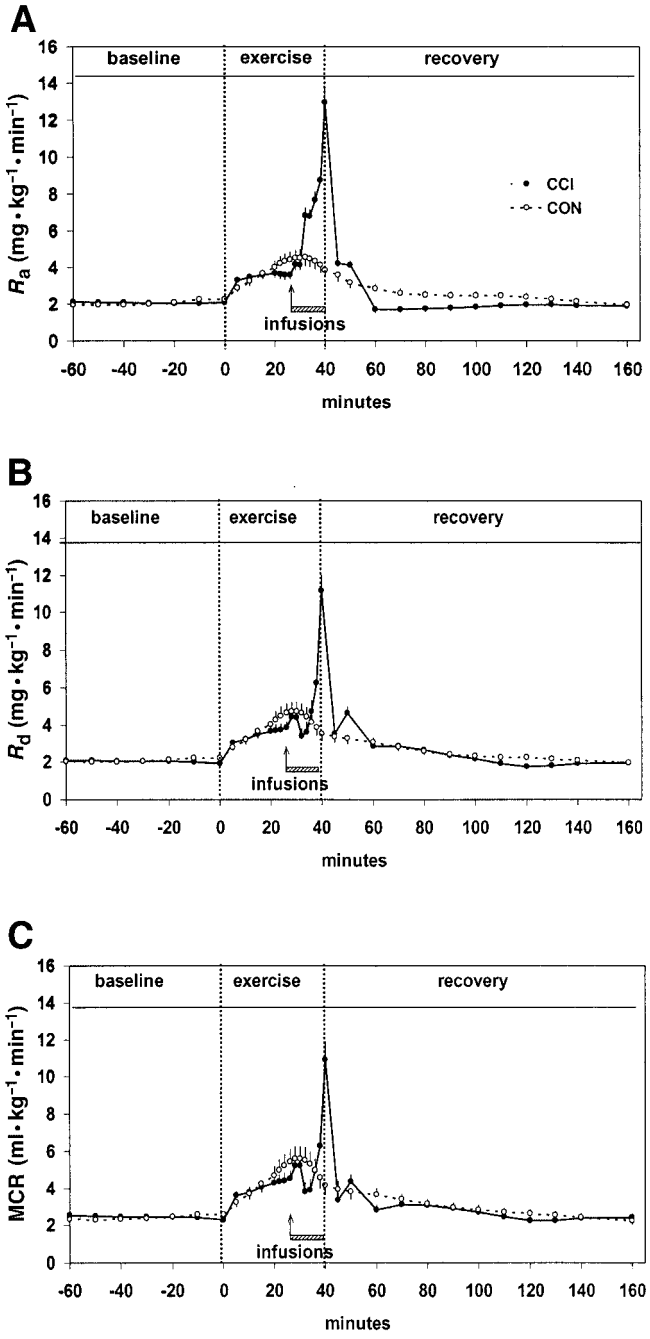

FIG. 2. R_a (*A*), R_d (*B*), and glucose MCR (*C*) during baseline, 40 min of 50% $\dot{V}o_{2max}$ exercise with and without CCI from minute 26 to 40, and recovery periods. Data are presented as in Fig. 1.

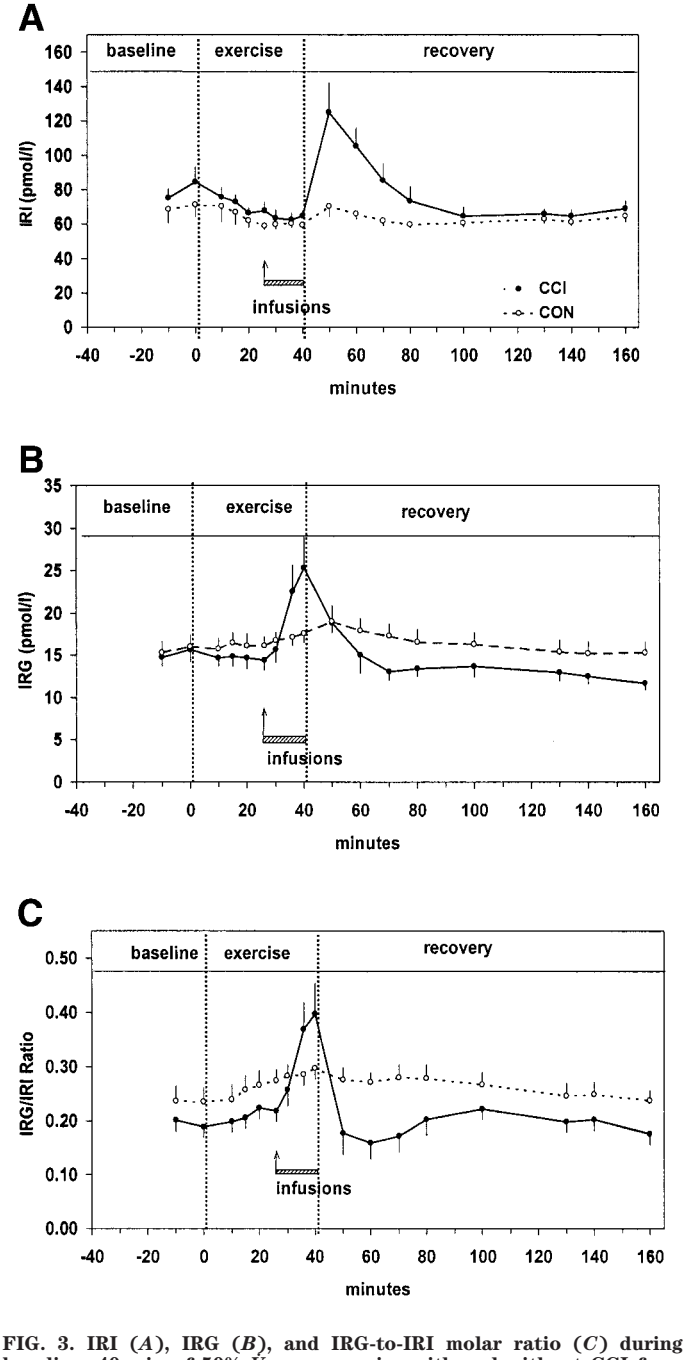

FIG. 3. IRI (*A*), IRG (*B*), and IRG-to-IRI molar ratio (*C*) during baseline, 40 min of 50% $\dot{V}o_{2max}$ exercise with and without CCI from minute 26 to 40, and recovery periods. Data are presented as in Fig. 1.

0 to 26 min in CCI ($P = 0.003$), but only with borderline significance in CON ($P = 0.052$). It declined further from 26 to 40 min ($P < 0.05$) in CCI, although levels were not different between CON and CCI. The early-recovery rise in IRI was much greater in CCI (93 vs. 19%, $P = 0.016$) and remained higher for the first 40 min ($P = 0.011$). IRG (Fig. 3*B*) remained constant during the first 26 min of exercise in both studies and then increased from 26 to 40 min in CON ($P < 0.001$). During the infusions in CCI, it rose 1.75-fold ($P < 0.001$) but reached values that were not significantly different from CON and did not differ during recovery. The IRG-to-IRI molar ratio (Fig. 3*C*) also did not differ at baseline and tended to increase during the first 26 min of exercise ($P = 0.023$ in CON, but NS in CCI). It increased 1.82-fold during the combined infusion, and although mean levels were higher, the response did not differ from CON. The ratio then fell in early recovery in CCI and remained lower thereafter ($P = 0.002$).

Plasma Epi (Fig. 4*A*) did not differ at baseline (0.41 ± 0.05 in CCI, 0.35 ± 0.06 nmol/l in CON) or during the first 26 min of exercise, rising ~2.5-fold. Whereas in CON it did not change from 26 to 40 min of exercise (0.94 ± 0.08 nmol/l at 40 min), in CCI, it rose progressively to 7.06 ± 0.44 nmol/l at 40 min ($P < 0.001$ vs. CON from 30 to 40 min). Levels fell abruptly after the termination of exercise and infusions, such that baseline values were approached at 5 min and reached at 20 min of recovery (as in CON).

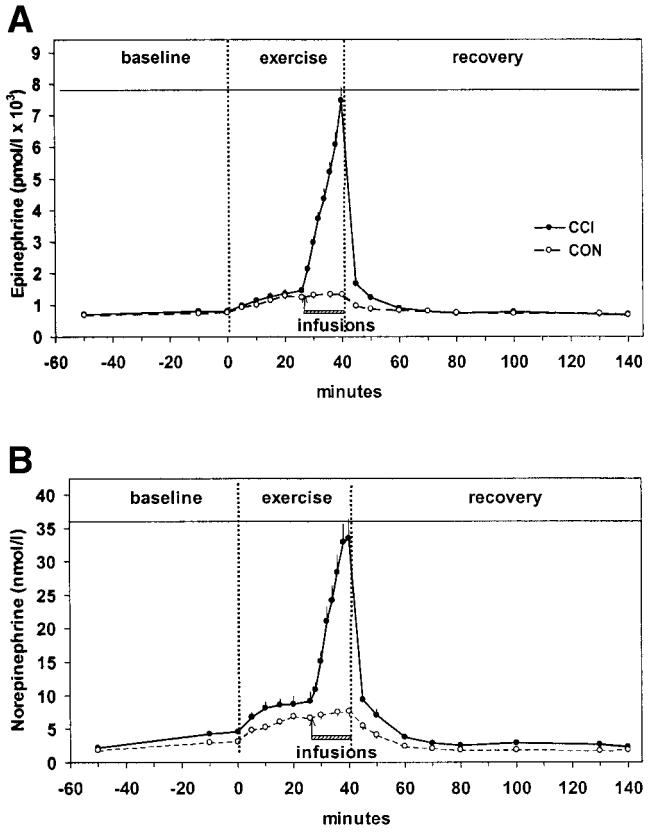

FIG. 4. Plasma Epi (*A*) and NE (*B*) during baseline, 40 min of 50% $\dot{V}o_{2max}$ exercise with and without CCI from minute 26 to 40, and recovery periods. Data are presented as in Fig. 1.

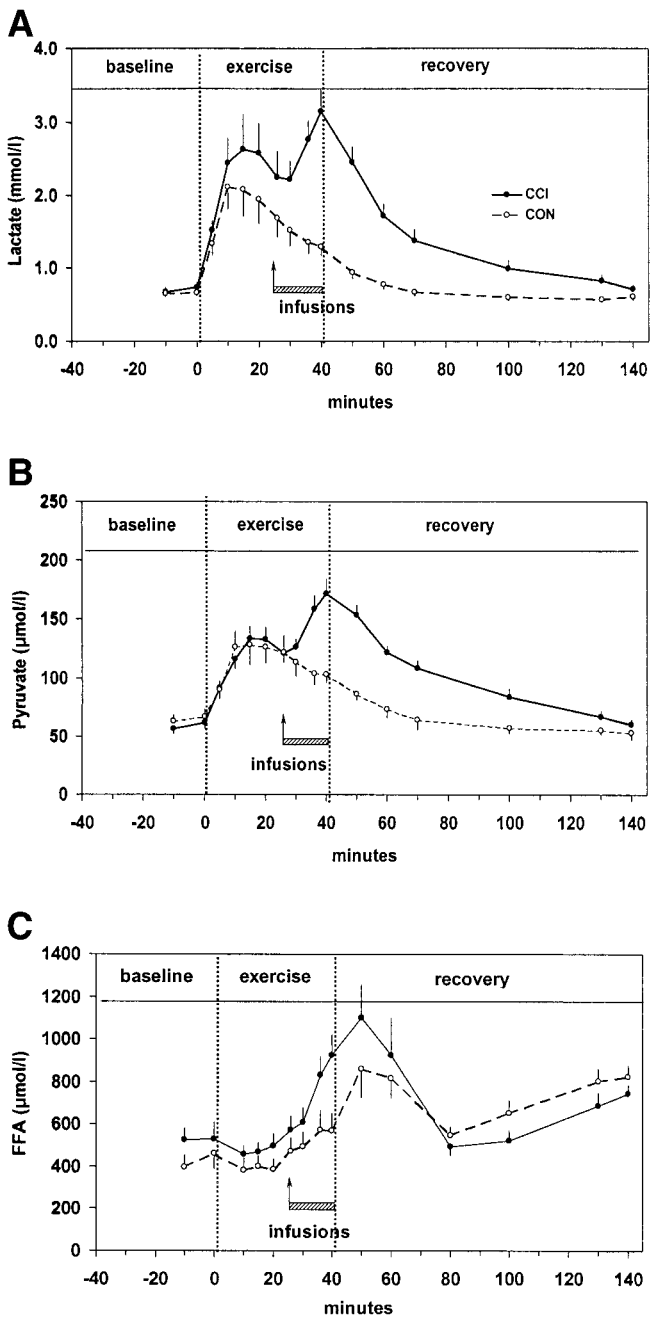

FIG. 5. Blood lactate (*A*), pyruvate (*B*), and FFAs (*C*) during baseline, 40 min of 50% $\dot{V}o_{2max}$ exercise with and without CCI from minutes 26 to 40, and recovery periods. Data are presented as in Fig. 1.

Epi correlated significantly with R_a in all eight subjects when taken individually from 26 min of exercise to 5 min of recovery (mean $r = 0.938$, $P < 0.003$).

Plasma NE (Fig. 4*B*) differed slightly between groups at baseline (4.13 ± 0.36 vs. 2.74 ± 0.24 nmol/l, $P = 0.006$) and for the first 26 min of exercise, during which it gradually doubled ($P = 0.035$) in both groups. The increment to 26 min exercise showed no between-group difference. Whereas in CON, it increased from 26 to 40 min (peak 7.28 ± 0.74 nmol/l, $P = 0.014$), in CCI it rose to 33.07 ± 2.91 nmol/l at 40 min ($P < 0.001$ vs. CON from 30 to 40 min as absolute levels or as change from baseline). Levels fell abruptly after the termination of exercise and infusions, such that baseline values were approached at 5 min and reached at 20 min of recovery. They were higher in CCI during early recovery as absolute levels ($P = 0.011$) or change from baseline ($P = 0.041$). NE correlated significantly with R_a in all eight subjects from 26 min of exercise to 5 min of recovery (mean $r = 0.877$, $P < 0.02$).

Neither blood lactate (Fig. 5*A*) nor pyruvate (Fig. 5*B*) differed at baseline. Both rose comparably between studies during the first 26 min. However, both lactate ($P = 0.001$ vs. CON from 30 min) and pyruvate ($P = 0.004$ vs. CON from 30 min) then underwent another rise in CCI, peaking at 40 min and remaining higher ($P = 0.001$) throughout recovery. Free fatty acids (Fig. 5*C*) did not differ between groups at baseline or during the first 26 min of exercise. They rose to a greater extent in CCI from 30 to 40 min of exercise ($P = 0.044$). They did not differ during recovery, reaching a nadir at 40 min and rising thereafter.

Interpretation of the R_a and R_d responses that might be attributable to the catecholamines requires reference to those of exercise at >80% $\dot{V}o_{2max}$. Figures 6 and 7 present results of the present CCI experiment, compared with those observed during 14 min of IE in 16 comparable subjects from previous studies (5). The pattern of glucose response is similar, and although the means of CCI were all lower, this difference was not significant by ANOVA during exercise, during recovery, or in peak levels reached (Fig. 6*A*). There was no difference in R_a response (Fig. 6*B*), comparing the 14 min of CCI versus IE, and the peak reached was not significantly different. The corresponding R_d (Fig. 6*C*) was very similar in response, with only the

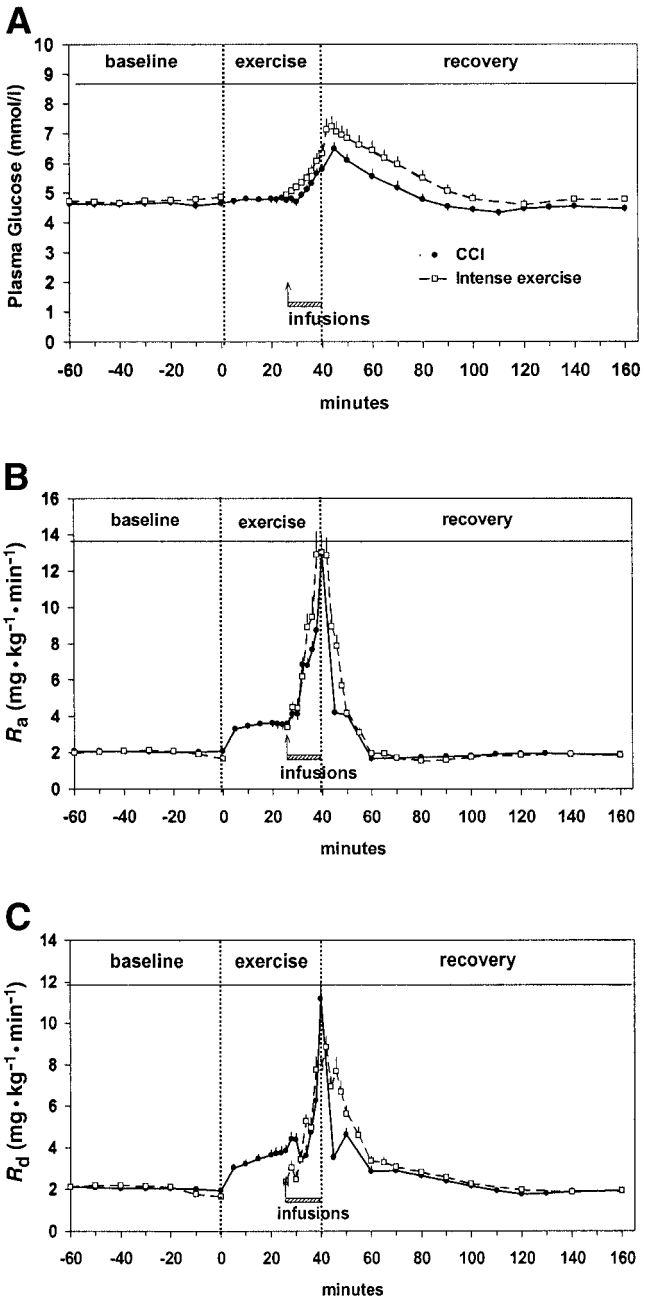

FIG. 6. Plasma glucose (*A*), R_a (*B*), and R_d (*C*) during ME with CCI from minutes 26 to 40 (●) compared with IE in 16 comparable subjects exercised at >80% $\dot{V}O_{2max}$ (□) (data from previously published studies [5]). For IE, the graph is interrupted because the first result of 14 min of exercise is plotted after 26 min, for comparison with the CCI experiment. Data are otherwise presented as in Fig. 1.

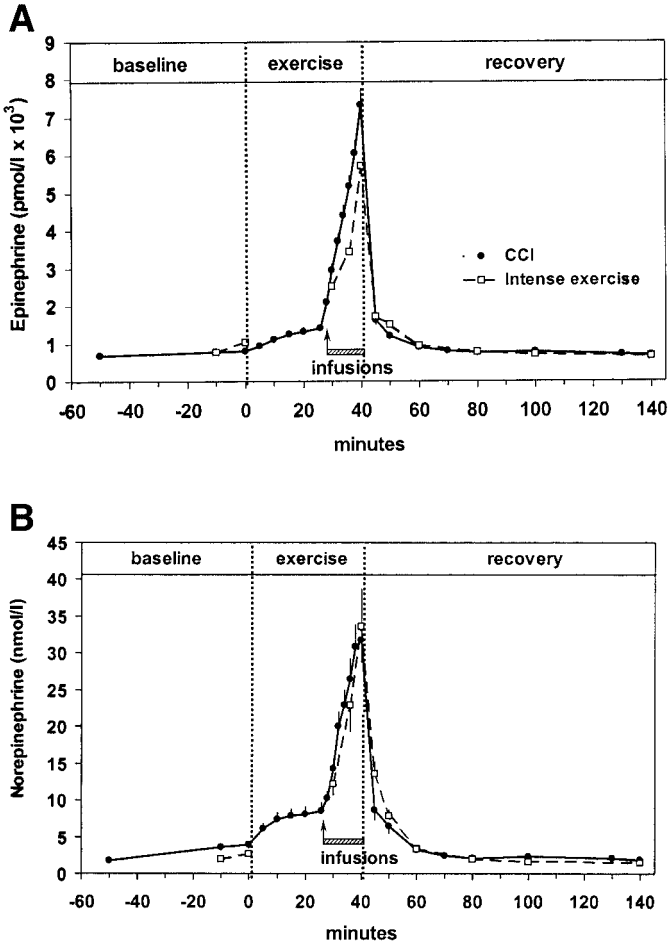

FIG. 7. Plasma Epi (*A*) and NE (*B*) during ME with CCI from minutes 26 to 40 (●) compared with 16 comparable subjects exercised at >80% $\dot{V}O_{2max}$ (□) (5). Data are presented as in Fig. 6.

peak value higher in CCI ($P = 0.002$). The corresponding catecholamines were likewise remarkably similar between the CCI studies and IE (Fig. 7*A* and *B*).

DISCUSSION

A feedforward mechanism for the regulation of hepatic glucose output during IE has been proposed (4,7,24). Our previous results have been consistent with plasma catecholamines being the primary mediators of this response (5,6,9,10,22,23), although a clear cause-effect relationship had not been established. Thus, this hypothesis has remained controversial (18,25–29). Our recent work suggests that alone, Epi (22) and NE (23) are each capable of producing a portion of the IE R_a response. Therefore, the goal of the present study was to define the potential role of the circulating catecholamines in stimulating R_a during IE, by attempting to "convert" the modest R_a response of moderate-intensity exercise to mimic the much larger R_a response to IE. The results confirm that exogenous CCI is sufficient to reproduce the large increment of R_a observed during IE compared with ME. Following the typical modest glucoregulatory and catecholamine responses to 50% $\dot{V}O_{2max}$ exercise, the infused subjects showed a marked and progressive R_a increment equivalent to that in IE, in association with the corresponding equivalent increment in plasma catecholamines. Furthermore, other responses typical of IE were generated, including rising glycemia due to a lesser increment of R_d than R_a, elevated RER, and rises in lactate and pyruvate levels. The early-recovery hyperglycemia and hyperinsulinemia typical of IE also occurred. These findings support the hypothesis that the much greater metabolic responses during IE compared with ME could result primarily from the systemic effects of released catecholamines.

Whereas catecholamines can stimulate glucagon release, their effects on glucose turnover are independent of this effect (14). The rise in IRG-to-IRI molar ratio during

CCI (Fig. 3*C*) may be an underestimate of its portal venous changes (30). Nonetheless, the magnitude of this change is likely to be too small to account for such a large R_a response (31,32). The most compelling argument for this in IE is that during our islet cell clamp study, their portal levels were likely equal to peripheral levels and either did not change or their ratio decreased, yet the rapid and large R_a response was unaffected (6).

Some data have been interpreted as inconsistent with the hypothesis of circulating catecholamine mediation of R_a in IE (18,25–29). Many of these may be explained by the absolute intensity of the exercise studied being lower than that which we hypothesize as the threshold above which the catecholamines become key regulators. In a study of celiac ganglion blockade (18), there was no attenuation of R_a despite lowering of plasma Epi and NE levels in subjects not infused with Epi. However, the subjects were exercising at <75% $\dot{V}O_{2max}$, and R_a increased only threefold. Another study (29) showed no significant attenuation of R_a in subjects who had undergone liver transplantation, exercising at 82% $\dot{V}O_{2max}$. However, the absolute intensity was quite low (only 68 vs. 108 W in our CCI subjects and ~260 W in our subjects exercising at 87% $\dot{V}O_{2max}$ [10]). Their R_a and R_d increments were only 2.1-fold, resulting in constant plasma glucose, typical of only low- to moderate-intensity exercise. Several animal studies (cited in 23) have also been used to argue against a role for liver sympathetic nerve activity in stimulating R_a. Apart from the low intensity, their designs would not be anticipated to affect R_a if NE were functioning as a hormone (especially on the denervated liver). Untrained subjects cycling 30 min at 80% $\dot{V}O_{2max}$ (25) showed no attenuation of the R_a response during islet cell clamp. However, the duration of exercise, constant glycemia, matched R_a and R_d increments of only 3- to 3.5-fold, and the only fourfold Epi responses again point to a lower absolute intensity of exercise. It does however suggest that our results may not be applicable to untrained individuals, except possibly at the highest exercise intensities. Lack of attenuation of R_a in dogs during "heavy" exercise was reported with portal vein infusion of phentolamine and propranolol (26). Beyond potential species-related differences, R_a increased only ~2.5-fold, plasma catecholamines increased only 2.5- to 3-fold, and lactate increased <2.5-fold. Two studies support our findings. In one (28), R_a rose significantly early during Epi infusion, when it would be expected to have its greatest effect (33), despite the very low exercise capacity of the subjects. In the other (27), Epi accounted for a significant proportion of the response despite a somewhat lower exercise intensity and much lower Epi levels than in our IE subjects (5). The lower peak of lactate and pyruvate in CCI than in IE is undoubtedly related to the difference in exercise intensity: much greater muscle glycogenolysis would be expected in IE.

Although in this study systemic NE and Epi were able to reproduce the entire R_a increment of IE, suggesting that they are the principal mediators of this effect, we agree that the glucoregulatory control mechanisms during exercise have some redundancy (5,24). The portal venous IRG-to-IRI ratio provides some contribution, and this may have been responsible for the slightly lower IE R_a in glucose-infused (9) postprandial (10) and islet cell–clamped (6) subjects. Additionally, given the rich sympathetic innervation of the human liver, direct stimulation of which leads to incremental glycemia (34), NE probably plays some role as a neurotransmitter, although this cannot be quantified in our experiments.

Our finding of increased glucose disposal during the CCI is in keeping with our recent work (22,23) suggesting that each catecholamine stimulates glucose disposal during exercise—a novel finding because it is generally accepted that glucose uptake should be inhibited. Although in studies of Epi infusion at rest (16,19,20,35), R_d changed little and MCR declined 20–40%, results during exercise have varied. One study (28) with Epi infusion showed declines in both R_d and MCR in adrenalectomized subjects exercising at high relative intensities but very low absolute exercise intensities. Another study (17) showed no significant change (though an upward trend) in R_d and MCR during infusion of Epi to plasma levels of ~2 nmol/l in subjects exercising at 40% $\dot{V}O_{2max}$. In our Epi infusion study (22), R_d rose an additional 57% and MCR an additional 44% from their values at 50% $\dot{V}O_{2max}$. Whereas the differences between our results and those of Howlett et al. (17) could be due to the Epi dose, those from another study by Howlett et al. (28) could potentially relate to the very low absolute exercise intensity or a training dependence of the Epi-R_d effect during exercise. These studies (17,28) and a recent study (36) did not alter glucose tracer infusions to maintain their SA constant and presented no SA data. Our work predicts there would have been a substantial SA decrease (5,22,23), leading to underestimation of R_a and therefore of R_d. This result could account for the divergent effects reported during a very similar experiment to ours with Epi infusion (22) and with the present study. Furthermore, the data presented for their deuterated glucose infusion rates (36) suggest a substantial total glucose infusion that was not taken into account in the calculations.

Although NE is usually considered to have an inhibitory effect on glucose disposal (13,37,38), we are unaware of studies before ours that assessed this during exercise. It could be viewed as advantageous for catecholamines to have different effects on glucose disposal between IE and severe nonexercise-related metabolic stresses. In a dog model of central carbachol-induced stress, glucose disposal rose, suggesting that the integrated stress response may have effects that differ from isolated catecholamine infusions, even at rest (39–41). This is pertinent to the "stress" of IE that was mimicked in the present experiment. Central sympathetic activation in other animal models also increases skeletal muscle glucose uptake (42). Clearly, differences between observations in vitro and effects in vivo can also be explained in part by the net in vivo effects resulting from multiple different effects in different cells and tissues, including those on blood flow and other hormones and mediators (42). Part of the NE inhibitory effect on R_d at rest is possibly due to α-adrenergic vasoconstriction, whereas vasodilation in muscular beds occurs during exercise. If muscle blood flow did increase in CCI, this could have contributed part of the increased R_d.

In vitro data could explain our observation, at least in part. Epi has been considered to inhibit insulin-mediated

muscle glucose uptake, but high concentrations do translocate GLUT4 to the plasma membrane (42). Further, Epi has been shown to translocate GLUT4 while increasing glucose transport in the absence of insulin, but to inhibit glucose transport in its presence (43). Specific β-adrenergic agonists have been shown in vivo to increase glucose transport in myocytes without an effect on GLUT4 content in the plasma membrane (42). It has also been shown that Epi inhibits glucose phosphorylation, which may become the rate-limiting step in glucose utilization under certain circumstances, but much less during muscle contraction than during insulin stimulation (44). Elevated free fatty acid (FFA) levels suppress glucose utilization, and lowered FFA levels increase it (45–47). However, plasma FFA levels fall during IE (5,9), whereas they rise in nonexercise forms of stress and increase more during CCI than in CON. Despite this greater FFA increment, RER increased, reflecting greater carbohydrate oxidation. The increased R_d with catecholamine infusions is surprising in light of augmented R_d with β-blockade (48) and unaltered R_d with α-blockade (49) in IE. This could, however, be explained by redundant α and β effects on R_d during exercise given the higher catecholamine levels in the adrenergically blocked groups in both these studies. One other possibility for the increased total-body R_d is that the glucose could be taken up elsewhere, such as in adipose tissue, where catecholamines may increase glucose uptake (42).

In summary, this study has shown that the R_a, R_d, glycemic, lactate, and RER responses to combined peripheral catecholamine infusion during moderate-intensity exercise can reproduce the pattern of those of IE. This gives strong support to the view that the pronounced rise of plasma catecholamines during IE is the primary drive behind the markedly greater stimulation of glucose output than during ME. Additionally, we have shown that the effect of catecholamines on glucose uptake and clearance during exercise appears to differ from their effects at rest, becoming stimulatory rather than inhibitory. This would enhance the body's ability to shift to higher levels of muscular carbohydrate use during IE, but does not preclude catecholamine-induced hyperglycemia during nonexercise-related stresses.

ACKNOWLEDGMENTS

This work was supported by grants MT9581 (to E.B.M.) and MT2197 (to M.V.) from the Canadian Institutes of Health Research. The laboratory of J.B.H. is supported by the Medical Research Service of the U.S. Department of Veterans Affairs.

The authors gratefully acknowledge the contributions of the following, whose roles were essential to this research: Mary Shingler, RN, of the Royal Victoria Hospital Clinical Investigation Unit; Madeleine Giroux, RT, Marie Lamarche, BSc, and Ginette Sabourin, BSc, for technical assistance in Montreal; Marla Smith, BS, for technical assistance in Ann Arbor, Michigan; and Josie Plescia for secretarial assistance. We acknowledge the role of Sharon Nessim, MD, who suggested this line of investigation while working with us as a medical student.

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