Epinephrine infusion during moderate intensity exercise increases glucose production and uptake

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H3A 1A1; Department of Internal Medicine and Institute of Gerontology, University of Michigan and Veterans Affairs Medical Center, Ann Arbor, Michigan 48109; and Departments of Physiology and Medicine, University of Toronto, Toronto, Ontario, Canada M5S 1A8

Kreisman, Stuart H., Nicholas Ah Mew, Mylène Arsenault, Sharon J. Nessim, Jeffrey B. Halter, Mladen Vranic, and Errol B. Marliess. Epinephrine infusion during moderate intensity exercise increases glucose production and uptake. Am J Physiol Endocrinol Metab 278: E949–E957, 2000.—The glucoregulatory response to intense exercise [IE, >80% maximum O\textsubscript{2} uptake (V\textsubscript{O\textsubscript{2max}})] comprises a marked increment in glucose production (Ra) and a lesser increment in glucose uptake (Rd), resulting in hyperglycemia. The Ra correlates with plasma catecholamines but not with the glucagon-to-insulin (IRG/IRI) ratio. If epinephrine (Epi) infusion during moderate exercise were able to markedly stimulate Ra, this would support an important role for the catecholamines’ response in IE. Seven fit male subjects (26 ± 2 yr, body mass index 23 ± 0.5 kg/m\textsuperscript{2}, V\textsubscript{O\textsubscript{2max}} 65 ± 5 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}) underwent 40 min of postabsorptive cycle ergometer exercise (145 ± 14 W) once without [control (CON)] and once with Epi infusion [EPI (0.1 µg·kg\textsuperscript{-1}·min\textsuperscript{-1}) from 30 to 40 min. Epi levels reached 9.4 ± 0.8 nM (20× rest, 10× CON). Ra increased ~70% to 3.75 ± 0.53 in CON but to 8.57 ± 0.58 mg·kg\textsuperscript{-1}·min\textsuperscript{-1} in EPI (P < 0.001). Increments in Ra and Epi correlated (r\textsuperscript{2} = 0.923, P ≤ 0.01). In EPI, peak Ra (5.55 ± 0.54 vs. 3.38 ± 0.46 mg·kg\textsuperscript{-1}·min\textsuperscript{-1}, P = 0.006) and glucose metabolic clearance rate (MCR, P = 0.018) were higher. The Ra-to-Rd imbalance in EPI caused hyperglycemia (7.12 ± 0.22 vs. 5.59 ± 0.22 mM, P = 0.001) until minute 60 of recovery. A small and late IRG/IRI increase (P = 0.015 vs. CON) could not account for the Ra increase. Norepinephrine (5× increase at peak) did not differ between EPI and CON. Thus Epi infusion during moderate exercise led to increases in Ra and Rd and caused rises of plasma glucose, lactate, and respiratory exchange ratio in fit individuals, supporting a regulatory role for Epi in IE. Epi’s effects on Rd and MCR during exercise may differ from its effects at rest.

glucose turnover; catecholamines; insulin; glucagon

METABOLIC RESPONSES TO EXERCISE differ according to its intensity and duration. Glucose regulation at low and moderate intensity is primarily mediated by an increase in the portal venous glucagon-to-insulin ratio [IRG/IRI (36)], which stimulates hepatic glucose output (endogenous Ra), thereby maintaining euglycemia largely through a feedback mechanism (2, 17, 18, 45) that matches the increment in Ra to the increased requirements. However, in intense exercise [IE, >80% of maximum O\textsubscript{2} uptake (V\textsubscript{O\textsubscript{2max}})] glucoregulation differs. A rapid and massive increase (~8-fold) in Ra and a rise in glycemia occur, but plasma insulin (IRI) either remains constant or decreases slightly, and glucagon (IRG) increases less than twofold (26, 37, 38, 39). It seems unlikely that these small changes, even insofar as they reflect portal vein concentrations, would be sufficient for IRG/IRI to play the leading glucoregulatory role in IE. Furthermore, the Ra 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 were even decreased (37).

A “feedforward” mechanism for the regulation of hepatic glucose output during IE has been proposed (20, 45), which conceptually may be better suited to maintaining homeostasis during such extreme physiological conditions. We (24, 26, 37–39) and others (4, 20) have proposed that the rapid and marked catecholamine response of IE could be such a mechanism. Plasma norepinephrine (NE) and epinephrine (Epi) concentrations can both increase ~15-fold, and we have repeatedly demonstrated highly significant correlations of both with Ra during IE (24, 26, 37–39). We recently found that the patterns of plasma catecholamines, Rd, and their correlations also persist in subjects infused with glucose (24) or studied in the postprandial state (27). These are situations in which endogenous Ra suppression from hyperinsulinemia must be overcome, the latter being the situation under which most IE is actually performed. These responses differ from those at lower-intensity exercise in which attenuation or complete prevention of the endogenous Ra increment occurs with exogenous glucose infusion (2, 17, 18, 41, 45).

Catecholamine infusions stimulate Ra in both dogs (8, 12, 40) and humans (5, 10, 15, 19, 30–34). Most of these studies involved only Epi and were done at rest. Although some (5, 30) produced Epi levels comparable to those of IE, the 1.5- to 2.5-fold increments in Ra were considerably smaller. The increment in Ra from Epi was much greater than that from NE infusion in both humans (32) and dogs (8). This is consistent with

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hepatic denervation and adrenomedullation studies in animals that have suggested the greater importance of Epi than NE in stimulating R₄ (23, 44). One study of Epi infusion during exercise was performed on celiac ganglion-blocked and ilet cell-clamped human subjects exercising at 74% VO₂max. Epi was doubled by the infusion to concentrations typical of IE and was associated with a further increment in R₄ over that of the exercise alone (19). A recent study (15) with Epi infusion during 40% VO₂max exercise suggested that Epi contributes to but does not fully account for the R₄ increment of IE. Glucose disposal (Rₐ) however, is ordinarily inhibited by Epi (35). Epi infusions at rest in both dogs (12) and humans (5, 30–32) caused little change in Rₐ, but because glucose concentrations increased, this resulted in a 20–40% decline in metabolic clearance rates (MCR). Studies of Epi infusion during exercise in humans (15, 16, 19) have yielded differing R₄ results.

Therefore, to further test the hypothesis that catecholamines are the primary mediators of the R₄ response to IE by defining the metabolic effects of Epi during exercise, we studied fit lean young males undergoing 40 min of postabsorptive exercise at 50% VO₂max with and without infusion of 0.1 µg·kg⁻¹·min⁻¹ of epinephrine from 30 to 40 min. Results of these studies have been presented in part in abstract form (25).

**METHODS**

Participants were seven lean weight-stable fit men aged 19–31 yr (Table 1). All engaged in regular activity such as running, cycling, soccer, and/or rowing, combined in some with resistance training. Screening before the study included medical history, physical examination, hemogram, blood biochemistry, urinalysis, hepatitis B and HIV serology, electrocardiogram, and chest roentgenogram. Subjects were informed of the purpose of the study and of the possible risks, and they gave signed consent as prescribed by the institutional human ethics committee.

VO₂max was determined at a preliminary visit with breath-by-breath analysis during an incremental workload test (20 W/min) on an electrically braked cycle ergometer (Collins Metabolic Cart, Collins, Braintree, MA). Oxygen uptake (VO₂, STPD), carbon dioxide output (VCO₂, STPD), ventilation (Ve, l/min, BTPS), respiratory exchange ratio (RER), and heart rate were measured. The studies with glucose turnover measurements began between 0800 and 0900 with subjects in the 12-h overnight fasting state without having undergone any significant exercise in the preceding 24 h. Twenty-gauge intravenous cannulas were placed in both arms. A priming bolus of 22 µCi of HPLC-purified [3-3H]glucose tracer (Du Pont-NEN, Billerica, MA) was followed by a constant infusion of 0.22 µCi/min in 0.9% saline, except where otherwise specified. Blood was sampled at six 10-min intervals before time 0 (beginning of exercise) to assure a steady state of plasma [3H]glucose specific activity (SA). The subjects then cycled for 40 min at 50% VO₂max followed by a 120-min recovery period. The exercise intensity level was achieved by using 45% of the maximum workload reached during the incremental workload test and by making minor adjustments so that a steady state at 50% VO₂max was reached early during the study. Experiments with and without Epi infusion (EPI vs. CON) were separated by ≥2 wk, and the subjects were unaware of which infusate was being received. In the EPI experiment, epinephrine HCl (Abbott Laboratories, Saint-Laurent, QC) in isotonic saline and 1 mg/ml of ascorbic acid (as antioxidant, Sabex, Boucherville, QC) was infused at 0.1 µg·kg⁻¹·min⁻¹ from 30 to 40 min of exercise. In the CON experiment, only ascorbic acid in saline was infused.

Glucose SA was maintained by increasing the tracer infusion threefold during the EPI infusion and then returning it to the preexercise rate at minute 40. The goal was to introduce labeled glucose into the circulation at a rate proportional to endogenous R₄, thereby attenuating changes in [³H]glucose SA to <25% during the rapid changes in glucose kinetics, as in previous experiments (24, 26, 27, 37–39). This assures the validity of glucose turnover calculations (11), even if there may be changes in pool fraction during this time. Blood samples were drawn at intervals shown by the data in the figures.

Samples for glucose turnover measurements were placed into tubes containing heparin and sodium fluoride and were processed as previously described (24). Heparinized plasma was collected with aprotinin (Trasylol, 10,000 kallikrein inhibitor U/ml, FBA, New York, NY) for subsequent IRI and IRG 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, kept on ice until centrifuged at 4°C, and then frozen at −20°C for later lactate and pyruvate assays.

Glucose was measured by the glucose oxidase method with a Glucose Analyzer II (Beckman, Fullerton, CA). Blood lactate and pyruvate were measured by enzymatic microfluorometric methods, and IRI and IRG were measured by RIA, as previously detailed (37). Assays that were performed on aprotinin-containing plasma were corrected for the plasma dilution introduced. Plasma NE and Epi were measured using a radioenzymatic technique (sensitivity <50 pmol/I) (9). The intra- and interassay coefficients of variation for all assays were <10% for the enzymatic assays they were <5%. R₄ and R₄ were calculated from the variable isotope infusion protocols according to the one-compartment model (29) using a glucose distribution space of 25% body wt and with a pool fraction of 0.65 representing the part in which the rapid changes of glucose and SA occur. Data were systematically smoothed by the OOPSEG (optimized optimal segments) program, which continually reconstructs and retests the curve until the residual differences between it and the data points are considered random and thus should represent

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Data are means ± SE; n, no. of subjects. BMI, body mass index; VO₂max, maximum oxygen uptake; CON, control study; EPI, epinephrine infusion study.
measurement error (3). Glucose MCR was calculated by dividing \(R_d\) by the plasma glucose concentration.

Baseline characteristics were analyzed by one-way ANOVA. Plasma glucose, SA, glucose turnover, MCR, lactate, pyruvate, catecholamine, and hormone results were analyzed by ANOVA for repeated measures. Interstudy differences found to be significant (\(P < 0.05\)) were subsequently analyzed by the Student-Newman-Keuls (SNK) \(t\)-test. Paired Student’s \(t\)-tests were used for analysis of some differences within the same study over time. Linear correlations were calculated with the Pearson correlation coefficient. Individual correlation coefficients were calculated by using all data points for each individual at which catecholamines and \(R_a\) were measured in the specified intervals. This correlation coefficient was then treated as a continuous variable on which means and standard error were calculated, and intergroup differences were assessed using one-way ANOVA, ANOVA for repeated measures, and the SNK tests. The SAS-STAT software package (SAS Institute, Cary, CA), SPSS-Windows Release 6.0 software package (SPSS, Chicago, IL), Microsoft Excel 5.0 Analysis ToolPak (GrayMatter International, Cambridge, MA), and Primer Biostats (McGraw-Hill, New York, NY) were used. Data are presented as means \(\pm\) SE.

RESULTS

No untoward effects were experienced, and subjects were not able to identify the CON vs. the EPI studies. Anthropometric measures, \(V_{O_2}\)max and workload data are presented in Table 1. Percent \(V_{O_2}\)max reached to a maximum of 0.96 \((P = 0.010\) vs. CON). Heart rate increased with EPI infusion (\(P < 0.001\), ANOVA) to higher than that in CON at minutes 35 and 40 (\(P = 0.05\), paired \(t\)-test) although not by repeated-measures ANOVA. Neither systolic nor diastolic blood pressure differed between studies at any time.

Plasma glucose concentrations (Fig. 2) were not different between studies at baseline, increasing slightly with exercise in both studies (maximum 7.0% in EPI, 6.3% in CON; \(P = 0.003\) for both). It rose abruptly (19.9%) from minute 30 to minute 40 in EPI (\(P < 0.001\)) to 6.15 \(\pm\) 0.17 mM, becoming higher than CON (5.22 \(\pm\) 0.25 mM) from 38 to 40 min (\(P = 0.038\)). Peak glycemia was reached at minute 5 of recovery (7.12 \(\pm\) 0.22 in EPI, 5.59 \(\pm\) 0.22 in CON), and it remained higher in EPI (\(P = 0.001\)) for 60 min. In CON, no significant change occurred during recovery. 

\(R_a\) (Fig. 3A) did not differ between studies at baseline or during the progressive 70% rise during the first 30 min of exercise. Although \(R_a\) remained at this level in CON (3.75 \(\pm\) 0.53 mg·kg\(^{-1}\)·min\(^{-1}\) at minute 28), it increased markedly to \(>8\) mg·kg\(^{-1}\)·min\(^{-1}\) within 2 min of the EPI infusion, reaching a maximum of 8.57 \(\pm\) 0.58 mg·kg\(^{-1}\)·min\(^{-1}\) at minute 38. It was higher than in CON during infusion and for the first 10 min of recovery (\(P < 0.001\)). \(R_a\) fell to baseline values at minute 20 of recovery in both. Although it remained constant thereafter in CON, it continued to decline in EPI to a nadir of 1.32 \(\pm\) 0.12 mg·kg\(^{-1}\)·min\(^{-1}\) at minute 50 of recovery, remaining less than in CON from minute 30 to minute 90 of recovery (\(P = 0.029\)).

Neither glucose \(R_d\) (Fig. 3B) nor MCR (Fig. 3C) differed between studies at baseline or during the first 30 min of exercise. \(R_d\) gradually rose by \(~70\%\) and MCR by \(~80\%). Values plateaued in CON, but in EPI, both increased markedly within 2 min of starting the infusion to a maximum \(R_d\) of 5.55 \(\pm\) 0.54 mg·kg\(^{-1}\)·min\(^{-1}\) at minute 32 (vs. 3.38 \(\pm\) 0.46 mg·kg\(^{-1}\)·min\(^{-1}\) at minute 30 in CON), and a maximum MCR of 6.16 \(\pm\) 0.64 ml·kg\(^{-1}\)·min\(^{-1}\) at minute 32 (vs. 4.08 \(\pm\) 0.89 ml·kg\(^{-1}\)·min\(^{-1}\) at minute 28 in CON). Both \(R_d\) (\(P = 0.006\)) and MCR (\(P = 0.018\)) were higher in EPI throughout the infusion. Both fell abruptly early in recovery and then remained at slightly higher than baseline levels for the first hour of recovery. Neither differed significantly from CON during the recovery period.
IRI (Fig. 4A) was not different between studies at baseline and remained constant throughout from minutes 0 to 30 and from minutes 30 to 40 of exercise. Although the early-recovery rise in IRI was much greater in EPI (70% vs. 11%, P = 0.003), the differences did not reach significance. IRG (Fig. 4B) was not different at baseline and remained constant during the first 30 min of exercise in both studies and from minutes 30 to 40 in CON. During the Epi infusion, it rose progressively by 29% (P = 0.001). It then fell in early recovery in EPI (P = 0.001). Although by paired t-tests the ratio was significantly higher in CON (P < 0.03) from minutes 10 to 60 of recovery (the period of hyperglycemia in EPI), it was not different by repeated-measures ANOVA (P = 0.089).

The plasma Epi (Fig. 5A) did not differ between studies at baseline (0.45 ± 0.05 in EPI, 0.42 ± 0.06 nM in CON) or during the first 30 min of exercise, during which it gradually doubled. Although in CON Epi did not change from minutes 30 to 40 of exercise (0.99 ± 0.10 nM at minute 35), in EPI it rose immediately and markedly to 9.15 ± 0.98 nM at minute 35 and 9.43 ± 0.75 nM at minute 40 (P < 0.001 vs. CON). Levels fell abruptly after the simultaneous termination of exercise and discontinuation of the infusion in EPI, such that baseline values were approached at minute 5 and
reached at minute 20 of recovery. In CON, baseline values were reached at minute 5. EPI subjects’ concentrations were thus higher for the first 20 min of recovery ($P < 0.004$). The changes in Epi (between the two studies for each subject) correlated significantly with the changes in Ra in all seven subjects when taken individually (mean $r^2 = 0.923$; range, $0.834–0.967$; $P < 0.01$ for all) from minute 30 of exercise to minute 20 of recovery (corresponding to the time when Epi levels were significantly higher in the EPI studies). Plasma NE (Fig. 5B) did not differ between studies at baseline; both rose during the first 10 min of exercise (gradually increasing about fourfold) or during its return to baseline during recovery.

Neither blood lactate (Fig. 6A) nor pyruvate (Fig. 6B) was different between groups at baseline; both rose during the first 10 min of exercise to a plateau, not differing between studies during the first 30 min. However, both lactate ($P = 0.018$ vs. CON) and pyruvate ($P = 0.042$ vs. CON) then underwent another rise during the Epi infusion, peaking at minute 40 and remaining higher ($P = 0.014$ for lactate, $P = 0.005$ for pyruvate) than in CON throughout recovery.

**DISCUSSION**

A feedforward mechanism for the regulation of hepatic glucose output during IE has been proposed (20, 45). Previous results from our group have been consistent, with plasma catecholamines being the primary mediators of this response (24, 26, 27, 37–39); however, this hypothesis remains controversial (6, 7, 15, 16, 19, 21). The principal aim of this study was to define the potential role of epinephrine in stimulating hepatic glucose output during IE by attempting to “convert” the Ra response of moderately intense exercise to that of IE with an infusion to reproduce IE epinephrine levels. The results confirm that epinephrine is able to produce appropriate metabolic responses when present in elevated circulating concentrations. After the typical modest glucoregulatory and catecholamine responses to 50% $\dot{V}O_{2\text{max}}$ exercise, the infused subjects showed a marked and rapid Ra increment in association with the marked increment in plasma epinephrine. 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.

Quantitative analysis and interpretation of the responses require reference to those of exercise at $>80\%$ $\dot{V}O_{2\text{max}}$. The plasma epinephrine levels achieved during this study ($\sim 9 \text{nM}$) were higher than we have observed at exhaustion ($\sim 4–7 \text{nM}$) with 87–100% $\dot{V}O_{2\text{max}}$ exercise. 

Fig. 5. Plasma epinephrine (A) and norepinephrine (B) during baseline, 40 min of 50% $\dot{V}O_{2\text{max}}$ exercise with and without epinephrine infusion from 30 to 40 min, and recovery periods. Data are presented as in Fig. 1.

Fig. 6. Blood lactate (A) and pyruvate (B) during baseline, 40 min of 50% $\dot{V}O_{2\text{max}}$ exercise with and without epinephrine infusion from 30 to 40 min, and recovery periods. Data are presented as in Fig. 1.
cise (24, 26, 37, 39). However, comparable levels were reported by others (8.73 nM) during short maximal bursts (2 min at 110% \( V_{O_{2\text{max}}} \)) (20), and we observed higher levels during \( \alpha \)-adrenergic blockade (38). Endogenous levels increased by only \( \sim 0.5 \) nM during the first 30 min of exercise, as expected for exercise of this intensity (22); therefore, considering only the increment induced by the infusion would still result in levels generally somewhat above the range of IE. We propose that our results are still physiologically relevant. A much lower epinephrine infusion yielding levels of only \( \sim 2 \) nM was shown to account for 32% of the rise in \( R_a \) from 40 to 80% \( V_{O_{2\text{max}}} \) (with an \( R_a \) increment only 3.7-fold baseline), implying an even greater contribution at higher exercise intensities (15). On the other hand, \( R_a \) peaked at \( \sim 12-14 \) mg·kg\(^{-1}\)·min\(^{-1}\) at 87% \( V_{O_{2\text{max}}} \), and 16.7 mg·kg\(^{-1}\)·min\(^{-1}\) at 90–100% \( V_{O_{2\text{max}}} \) (39), compared with \( \sim 8.5 \) mg·kg\(^{-1}\)·min\(^{-1}\) at minute 10 of epinephrine infusion in the present study, despite the high epinephrine levels. These peak values occurred at exhaustion at minute 14-15 of IE, whereas at minute 10 of exercise, \( R_a \) reached 8–10 mg·kg\(^{-1}\)·min\(^{-1}\). It can be argued that the exercise duration factor is unlikely to have accounted for the lower peak in EPI, because \( R_a \) reached this level within 2 min of commencing the infusion and showed little tendency to rise further. Another potential explanation of the lower \( R_a \) relates to partial depletion of hepatic glycogen stores during the initial 30 min of exercise. This effect would likely be minor, because only \( \sim 10\% \) of the 70–90 g of postabsorptive hepatic glycogen content (35) would have been consumed.

Therefore, although epinephrine caused a marked increment in \( R_a \), suggesting that it is a major contributor, there are likely to be additional contributors to the response, as was suggested recently (15). Norepinephrine is a likely candidate (7, 15, 24, 26, 27, 37–39); studies of norepinephrine infusion in dogs (8) and humans (32) showed stimulation of \( R_a \), although less than from equivalent infusion rates of epinephrine. These findings define only the potential potency of circulating norepinephrine, because peripheral infusions would not match the probable local concentrations and/or effects due to release at intrahepatic sympathetic nerve terminals. Another possibility is that combined epinephrine and norepinephrine effects are equal to or greater than the sum of the two individual effects. Yet another is that epinephrine (or total catecholamines) require(s) a yet-unidentified exercise intensity-dependent neuromuscular, mechanical, humoral, and/or blood flow setting for full effect. This latter hypothesis could explain why other studies of similar rates of epinephrine infusion (5, 30–34) at rest resulted in much lower \( R_a \) increments than we and others (19) found during exercise. In addition, timing of sampling for glucose kinetics may also have been a factor, because several of the resting studies first calculated \( R_a \) at 15 min or later after initiation of infusion. The effect of epinephrine on liver glycogenolysis is rapid and transient (135, 40), being attenuated by counterregulatory responses that would be unlikely to occur to any significant degree during exercise, so a greater early response could have been missed. A third factor is likely to be a contribution by the increase in the IRG-to-IRI molar ratio.

Although it is known that epinephrine can stimulate glucagon release, its effects on glucose turnover are independent of this effect (12). The 40% rise in IRG/IRI induced by the epinephrine infusion may be an underestimate of the portal venous changes in this ratio (42); nonetheless, the magnitude of this change is still too small to account for such a large \( R_a \) response (14, 43). In addition, it occurred with a time course inappropriate to explain the \( R_a \) response, as we have also found in other experiments without catecholamine infusions (26, 27). Although IRG/IRI increased progressively (Fig. 4C), the \( R_a \) response was a nearly instantaneous rise to nearly maximum followed by plateau (Fig. 3A). The analysis of time courses provides strong additional support for epinephrine as a primary mediator, because it too followed such a time course (Fig. 5A). This is consistent with our previous IE studies, in which both \( R_a \) and catecholamines followed a rapid progressive parallel increase. Changes in peripheral IRG/IRI, on the other hand, did not follow such a pattern, reaching statistically significant increases only at exhaustion (26, 27). Because proportionally more insulin than glucagon is taken up by the liver at rest, it is difficult to predict portal levels from peripheral plasma concentrations during exercise. The most compelling argument for the magnitude of portal IRG/IRI changes being minor contributors to \( R_a \) in IE is that, during our islet cell clamp study, their portal levels were likely equal to peripheral levels, and either they did not change or they decreased, yet the rapid and large \( R_a \) response was unaffected (37).

A number of experimental findings have been interpreted as inconsistent with the hypothesis of catecholamine mediation of \( R_a \) in IE (6, 7, 15, 16, 19, 21). Many of these may be explained by the absolute intensity of the exercise being lower than that which we hypothesized as the threshold above which the catecholamines become key regulators. For example, in the celiac ganglion blockade study (19), there was no attenuation of \( R_a \), despite the lowering of plasma epinephrine and norepinephrine levels in those not infused with epinephrine. However, the subjects were exercising at <75% \( V_{O_{2\text{max}}} \). \( R_a \) increased only threefold, and lactate levels peaked at only 5 mM, demonstrating a less-than-intense level of exercise in this experiment. Another study (21) showed no significant attenuation of \( R_a \) in subjects who had undergone liver transplantation, exercising at 82% \( V_{O_{2\text{max}}} \). However, the absolute intensity was quite low [only 68 vs. 123 W in their controls, 145 W in the current study, and 260 W in our subjects exercising at 87% \( V_{O_{2\text{max}}} \) (27)]. This was reflected in an \( R_a \) increment of only 2.1-fold matched by \( R_g \), resulting in constant plasma glucose levels; all these are markers of the metabolic response to low-to-moderate intensity exercise. A study of untrained subjects cycling for 30 min at 80% \( V_{O_{2\text{max}}} \) (6) showed no significant lesser
increment in $R_a$ during islet cell clamp, and because epinephrine rose only fourfold in the clamped subjects, the latter was felt not to be a significant factor in the preserved response. However, the duration of exercise, constant glycemia, matched $R_a$ and $R_d$ increments of only 3- to 3.5-fold, and the lesser epinephrine responses in both groups point to a lower absolute intensity of exercise than in our experiments. It does, however, suggest that our results may not be applicable to untrained individuals except possibly at the highest of exercise intensities. Another study showed a lack of attenuation of $R_a$ in dogs during “heavy” exercise with portal vein infusion of phenolamine and propranolol (7). Beyond potential species-related differences in the metabolic response to exercise, in that study, $R_a$ increased only 2.5- to 3-fold and lactate <2.5-fold. Two of the cited references (15, 16) present data supportive of our findings. In one (16), hepatic glucose output rose significantly early during the epinephrine infusion [when it would be expected to have its greatest effect (35)], despite the very low exercise capacity of the subjects $(V_{O2max} = 19 \text{ ml.kg}^{-1}.\text{min}^{-1})$. In the other (15), as previously mentioned, epinephrine accounted for a significant proportion of the response, despite a somewhat lower exercise intensity and much lower epinephrine levels than in our subjects exercised at 87% $V_{O2max}$ (24).

Our finding of increased glucose disposal during the epinephrine infusion is novel, as it is generally accepted that glucose uptake should be inhibited. Whereas in human studies of epinephrine infusion at rest (5, 30–32) $R_d$ changed little, and MCR declined 20–40%, results during exercise have varied.

One study (16) showed declines in both $R_a$ and MCR in adrenalectomized subjects (five female, one male) exercising at high relative (68 and 84% $V_{O2max}$) but very low absolute exercise intensities ($V_O2$ of 13.1 and 16.3 ml·kg$^{-1}$·min$^{-1}$) with and without epinephrine infusion. Another (15) showed no statistically significant change (though an upward trend) in $R_d$ and MCR during epinephrine infusion to plasma catecholamines of ~2 nM in subjects while exercising at 40% $V_{O2max}$. In our study, $R_a$ rapidly rose an additional 57% and MCR an additional 44% from their values at 50% $V_{O2max}$ (increments of 99 and 81% above resting values). Whereas the differences between our results and those of Ref. 15 could be due to epinephrine dose, those with Ref. 16 could relate to the very low absolute exercise intensity or to a training-dependent or sex-specific nature of the epinephrine-$R_d$ effect during exercise. It could be viewed as “advantageous” for epinephrine to have different effects on glucose disposal between intense exercise and severe nonexercise-related metabolic stresses. In vitro data could explain our observation, at least in part. Insulin and potassium depolarization (mimicking the initial phase of excitation-contraction coupling) increases glucose uptake via distinct pathways of GLUT-4 glucose transporter recruitment (28). Epinephrine has been shown to translocate GLUT-4 while increasing glucose transport in the absence of insulin but inhibiting glucose transport in the presence of insulin (13). It has also been shown that epinephrine inhibits glucose phosphorylation, which may become the rate-limiting step in glucose utilization under certain circumstances, much less during muscle contraction than during insulin stimulation (1). Another possible explanation for increased $R_d$ might be that, if adipose tissue blood flow were to have decreased as in IE, free fatty acid release would decrease, thereby favoring oxidation of glucose. The latter did occur during the epinephrine infusion according to the RER response. Finally, the possibility of a yet-undefined signaling mechanism between liver and muscle that causes increased glucose uptake when $R_a$ increases cannot be excluded, nor can an effect of epinephrine on muscular contractions (although $V_{O2}$ did not change during epinephrine infusion).

In summary, this study has shown that the $R_a$, $R_d$, glycemic, lactate, and RER responses to epinephrine infusion during moderate-intensity exercise can reproduce the pattern of those of intense exercise. This adds support to the view that the pronounced rise of plasma catecholamines during IE could be the primary driver behind the marked stimulation of hepatic glucose output. Our results suggest that epinephrine alone cannot account for the full increment of $R_a$ in IE. In addition, we have shown that the effect of epinephrine on glucose uptake and clearance during exercise appears to differ from its effect at rest, becoming stimulatory rather than inhibitory. This would enhance the body’s ability to shift to higher levels of muscular carbohydrate use during intense exercise, while still being consistent with epinephrine contributing to hyperglycemia during non-exercise-related stresses.

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