High-Intensity Training Improves Plasma Glucose and Acid-Base Regulation During Intermittent Maximal Exercise in Type 1 Diabetes

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In individuals without diabetes, high-intensity exercise (HIE) training may reduce (1) the characteristic postexercise rise in plasma glucose with HIE (2–4) and reduces (5,6) the marked acid-base balance perturbations (5–8). In type 1 diabetes, continuous HIE induces sustained hyperglycemia (9,10), while very brief intermittent HIE may reduce hyperglycemia (11). Acid-base disturbances during exercise may be heightened in type 1 diabetes (12–14). Effects of HIE training on glycemia and acid-base balance during intermittent HIE in type 1 diabetes are unknown; thus, despite the potential clinical importance of such exercise, there is no evidence on which to base patient guidelines. The aim of the present study was thus to investigate the effects of HIE training on glycemia and acid-base regulation during intermittent HIE in type 1 diabetes.

RESEARCH DESIGN AND METHODS

— Eight subjects with type 1 diabetes (duration of diabetes 7.1 ± 4.0 years) and seven subjects without diabetes (control group), all of whom were healthy and took no medications (other than insulin in type 1 diabetic subjects), consented to participate. The study was approved by the human ethics committees of The University of Sydney and the South Sydney West Area Health Service. Control subjects closely matched those with diabetes for age (type 1 diabetes 25 ± 4 years and control 25 ± 4 years), BMI (25.4 ± 3.2 and 23.8 ± 5.0 kg/m^2, respectively), and $V\text{O}_{2\text{peak}}$ (42.7 ± 12.2 and 43.7 ± 6.2 ml · kg^{-1} · min^{-1}), as detailed in a related study that reported effects of sprint training on muscle sodium-potassium ATPase and on plasma potassium during maximal exercise (15).

Testing was conducted after overnight fasting. Type 1 diabetic subjects delayed their morning insulin. Subjects completed four 30-s maximal exercise bouts (EB1–4) (each separated by 4 min rest) on a cycle ergometer. Supervised high-intensity cycling training (5,15,16) was then conducted thrice-weekly for 7 weeks. The number of cycle bouts per training session progressed from 4 in week 1 to 6 in week 2, 8 in week 3, and 10 in weeks 4–7. After training, EB1–4 were repeated, with power output set to be identical to the pretraining test. Arterialised blood was sampled at rest, before and in the final seconds of EB1–4, and during recovery. Blood gases, insulin, glucose, and A1C were analyzed as previously described (15). With the exception of lactate, which was analyzed using a standard enzymatic technique (17), plasma ions were analyzed using an automated blood gas analyzer (Corning 865; Chiron Diagnostics). The plasma strong ion difference (SID) was calculated: SID (mmol/) = ([potassium] + [sodium]) − ([lactate] + [chloride]). Data were analyzed with repeated-measures ANOVA (SPSS version 10.0 for Windows). When significance was detected, pairwise comparison between means was performed by a contrast technique. Significance was accepted at $P < 0.05$. Results are reported as means ± SD.

RESULTS

— Exercise training did not alter A1C in type 1 diabetic subjects (preexercise 8.6 ± 0.8%, postexercise 8.1 ± 0.6%; $P = 0.09$). Resting plasma glucose was higher in type 1 diabetic subjects than in control subjects (13.3 ± 5.3 and 5.0 ± 0.3 mmol/l, respectively; $P < 0.001$), with no change after training. In type 1 diabetes, exercise induced a sustained rise in plasma glucose from rest (Δ[PG]) (Fig. 1*A*). In control subjects, Δ[PG] peaked at 4 min recovery and did not fall significantly thereafter. After training, Δ[PG] was markedly attenuated in both groups ($P = 0.001$) (Fig. 1*A*). Insulin did not differ between groups at rest or after training, however, fell slightly during exercise in type 1 diabetic subjects, in contrast to the rise in control subjects ($P < 0.001$). Plasma SID fell after EB1 and remained reduced throughout the remainder of the test ($P < 0.001$), mainly due to the rise in plasma lactate, with no group differences. After training, SID was higher ($P = 0.001$) in both groups (Fig. 1*B*). SID was greater in type 1 diabetic subjects than control subjects across all times and both days ($P < 0.05$) but was within the normal range. The dramatic rises in plasma [H^+] and lactate during HIE ($P < 0.001$) (Fig. 1*C* and *D*) were markedly attenuated after training ($P < 0.001$), with no group differences. After training, bicarbonate fell

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Abbreviations: HIE, high-intensity exercise; SID, strong ion difference.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

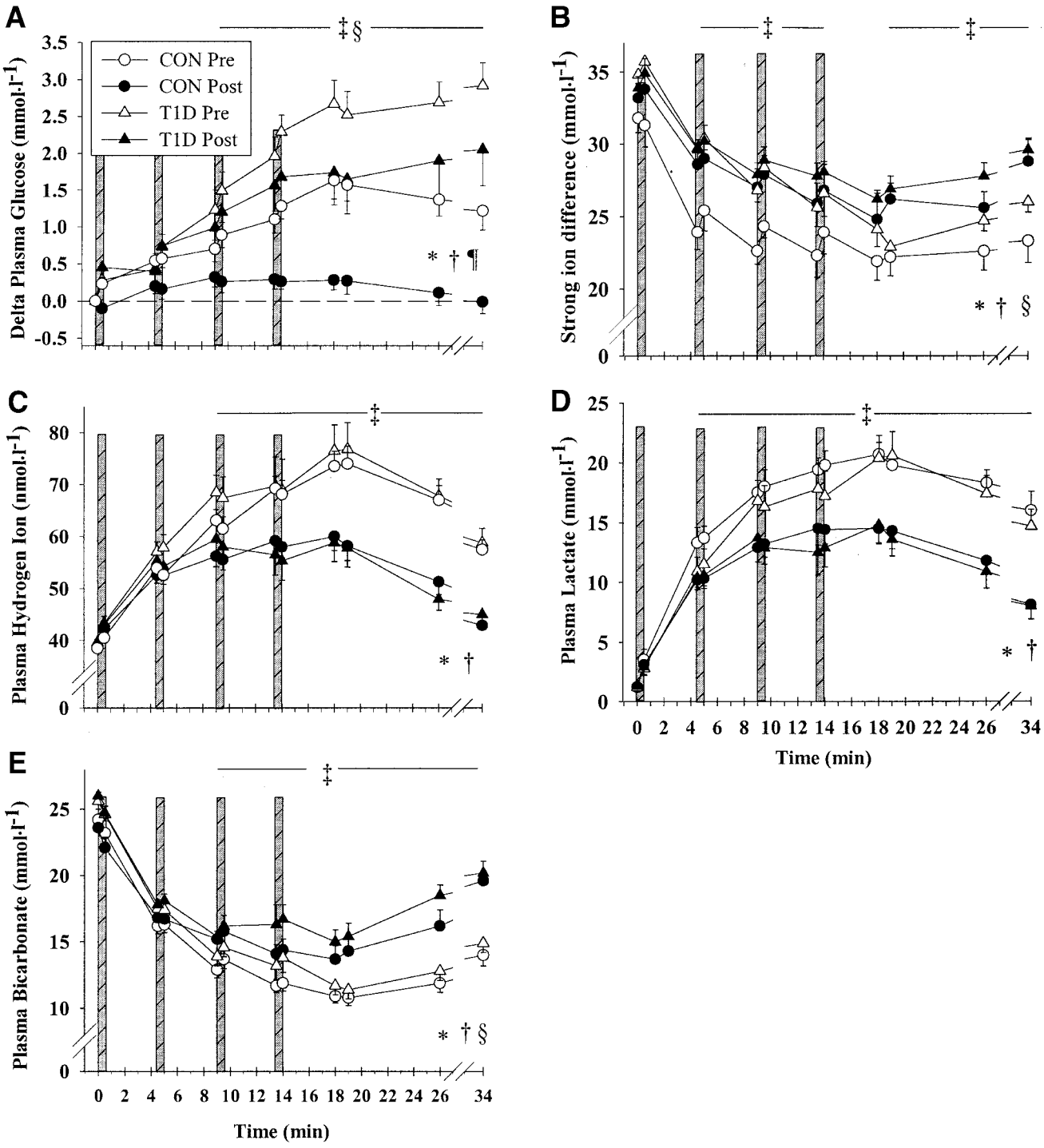

Figure 1—*Effects of intermittent maximal exercise (hatched bars) before and after intense intermittent exercise training in the type 1 diabetic (T1D) group and in the control (CON) group on the change (Δ) in plasma glucose concentration* (A)*, plasma strong ion difference* (B)*, plasma hydrogen ion concentration* (C)*, plasma lactate concentration* (D)*, and plasma bicarbonate concentration* (E)*. Data are means ± SE.* A: **P < 0.001, main effect of time; †P = 0.001, main effect of training status, pre- > posttraining; ‡P < 0.001, training status-by-time interaction, pre- > posttraining; §P < 0.001, time-by-group interaction, type 1 diabetic > control subjects; and ¶P < 0.001, type 1 diabetic > control subjects.* B: **P < 0.001, main effect of time; †P = 0.001, main effect of training status, post- > pretraining; ‡P < 0.01, training status-by-time interaction, post- > pretraining; and §P < 0.05, type 1 diabetic > control subjects.* C *and* D: **P < 0.001, main effect of time; †P < 0.001, main effect of training status, pre- > posttraining; and ‡P < 0.001, training status-by-time interaction, pre- > posttraining.* E: **P < 0.001, main effect of time; †P < 0.001, main effect of training status, post- > pretraining; ‡P < 0.001, training status-by-time interaction, post- > pretraining; and §P < 0.05, type 1 diabetic > control subjects.*

less ($P < 0.001$) (Fig. 1*E*) in both groups. Bicarbonate was greater ($P < 0.05$) and chloride lesser ($P < 0.01$) in type 1 diabetic subjects than control subjects across all times and both days, but both were within the normal range. PO_2 did not differ between days or groups. After training, PCO_2 returned more rapidly toward resting values during recovery ($P < 0.01$), with no group differences. PCO_2 was greater across both days and all times in type 1 diabetic subjects than in control subjects ($P < 0.01$); however, resting values were within the normal range.

CONCLUSIONS — This is the first study to examine the effects of intermittent HIE and training on glycemia and acid-base regulation in type 1 diabetes. Hyperglycemia during and after HIE in type 1 diabetes was likely due to a lack of physiological hyperinsulinemia (10). Interestingly, based on findings in rodent muscle (18), the high plasma lactate in both groups may have induced acute insulin resistance. This may have further contributed to the hyperglycemia in type 1 diabetes and likely explains the lack of fall in plasma glucose during recovery in control subjects, despite high insulin. After training, lower plasma glucose with similar insulin suggests less acute insulin resistance, improved clearance, and/or lower catecholamine stimulation. Plasma lactate was considerably lower after training, which may have lessened any acutely induced insulin resistance. This, and effects of HIE training on GLUT4 content and catecholamines during repeated HIE in type 1 diabetes, remains to be investigated.

Plasma acid-base status during HIE depends primarily on the SID and PCO_2; reduced SID and increased PCO_2 will increase $[H^+]$ and reduce bicarbonate (19,20). Less acid-base perturbation after training is consistent with the higher SID, due mainly to less rise in lactate, which is perhaps consequent to greater skeletal muscle oxidative metabolism (5). Plasma PCO_2, SID, and bicarbonate were greater and chloride lesser in type 1 diabetic subjects than in control subjects (though within normal range), while plasma $[H^+]$ did not differ between groups. The mechanism of greater PCO_2 in type 1 diabetic subjects cannot be determined from this study; however, higher PCO_2 may have induced chloride movement into cells via the chloride/bicarbonate exchange (20). This is consistent with lower plasma chloride and hence greater SID in type 1 diabetic subjects, which likely explains the similar acidosis between groups.

HIE training did not improve A1C (however, this may reflect a type II error) but did improve glycemia and acid-base regulation during intermittent HIE in patients with type 1 diabetes.

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References

1. Green HJ, Thomson JA, Houston ME: Supramaximal exercise after training-induced hypervolemia. II. Blood/muscle substrates and metabolites. *J Appl Physiol* 62:1954–1961, 1987
2. Hermansen L, Pruett EDR, Osnes JB, Giere FA: Blood glucose and plasma insulin in response to maximal exercise and glucose infusion. *J Appl Physiol* 29:13–16, 1970
3. Kjær M, Hollenbeck CB, Frey-Hewitt B, Galbo H, Haskell W, Reaven GM: Glucoregulation and hormonal responses to maximal exercise in non-insulin-dependent diabetes. *J Appl Physiol* 68:2067–2074, 1990
4. Marliss EB, Simantirakis E, Miles PDG, Purdon C, Gougeon R, Field C, Halter JB, Vranic M: Glucoregulatory and hormonal responses to repeated bouts of intense exercise in normal male subjects. *J Appl Physiol* 71:924–933, 1991
5. Harmer AR, McKenna MJ, Sutton JR, Snow RJ, Ruell PA, Booth J, Thompson MW, Mackay NA, Stathis CG, Crameri RM, Carey MF, Eager DM: Skeletal muscle metabolic and ionic adaptations during intense exercise following sprint training in humans. *J Appl Physiol* 89:1793–1803, 2000
6. McKenna MJ, Heigenhauser GJF, McKelvie RS, MacDougall JD, Jones NL: Sprint training enhances ionic regulation during intense exercise in men. *J Physiol* 501.3: 687–702, 1997
7. Kowalchuk JM, Heigenhauser GJF, Lindinger MI, Sutton JR, Jones NL: Factors influencing hydrogen ion concentration in muscle after intense exercise. *J Appl Physiol* 65:2080–2089, 1988
8. Lindinger MI, Heigenhauser GJ, McKelvie RS, Jones NL: Blood ion regulation during repeated maximal exercise and recovery in humans. *Am J Physiol* 262:R126–R136, 1992
9. Mitchell TH, Abraham G, Schiffrin A, Leiter LA, Marliss EB: Hyperglycemia after intense exercise in IDDM subjects during continuous subcutaneous insulin infusion. *Diabetes Care* 11:311–317, 1988
10. Purdon C, Brousson M, Nyveen SL, Miles PDG, Halter JB, Vranic M, Marliss EB: The roles of insulin and catecholamines in the glucoregulatory response during intense exercise and early recovery in insulin-dependent diabetic and control subjects. *J Endocrinol Metab* 76:566–573, 1993
11. Guelfi KJ, Jones TW, Fournier PA: Intermittent high-intensity exercise does not increase the risk of early postexercise hypoglycemia in individuals with type 1 diabetes. *Diabetes Care* 28:416–418, 2005
12. Unal M, Unal DO, Salman F, Baltaci AK, Mogulkoc R: The relation between serum leptin levels and max VO_2 in male patients with type 1 diabetes and healthy sedentary male subjects. *Endocrine Res* 30: 491–498, 2004
13. Crowther GJ, Milstein JM, Jubrais SA, Kushmerick MJ, Gronka RK, Conley KE: Altered energetic properties in skeletal muscle of men with well-controlled insulin-dependent (type 1) diabetes. *Am J Physiol* 284:E655–E662, 2003
14. Berger M, Berchtold P, Cüppers HJ, Drost H, Kley HK, Müller WA, Weigelmann W, Zimmermann-Telschow H, Gries FA, Krüskemper HL, Zimmermann H: Metabolic and hormonal effects of muscular exercise in juvenile type diabetics. *Diabetologia* 13:355–365, 1977
15. Harmer AR, Ruell PA, McKenna MJ, Chisholm DJ, Hunter SK, Thom JM, Morris NR, Flack JR: Effects of sprint training on extrarenal potassium regulation with intense exercise in type 1 diabetes. *J Appl Physiol* 100:26–34, 2006
16. McKenna MJ, Schmidt TA, Hargreaves M, Cameron L, Skinner SL, Kjeldsen K: Sprint training increases human skeletal muscle Na^+-K^+-ATPase concentration and improves K^+ regulation. *J Appl Physiol* 75:173–180, 1993
17. Annan W: A method for the determination of blood lactate and pyruvate using an LKB 8600 reaction rate analyzer. *Med Lab Tech* 32:287–294, 1975
18. Choi CS, Kim Y-B, Lee FN, Zabolotny JM, Kahn BB, Youn JH: Lactate induces insulin resistance in skeletal muscle by suppressing glycolysis and impairing insulin signaling. *Am J Physiol Endocrinol Metab* 283:E233–E240, 2002
19. Stewart PA: *How to Understand Acid-Base: A Quantitative Acid-Base Primer for Biology and Medicine*. New York, Elsevier/ North-Holland Biomedical Press, 1981
20. Jones NL: *Blood Gases and Acid-Base Physiology*. New York, Thieme, 1987