Hyperglycemia Affects Cardiovascular Autonomic Nerve Function in Normal Subjects

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OBJECTIVE — To evaluate the effect of acute hyperglycemia on autonomic nerve function in normal subjects.

RESEARCH DESIGN AND METHODS — Six healthy volunteers ages 19–32 years underwent paired studies during euglycemia (blood glucose 5.1 ± 0.04 mmol/l) and hyperglycemia (blood glucose 15.7 ± 0.48 mmol/l) induced by intravenous infusion of glucose and maintained for 150 min. The order of the two studies was randomized. In each experiment, supine heart rate, heart rate variation with respiration, ratio of the maximum to minimum R-R interval after standing ("30:15" ratio), systolic blood pressure response to standing, and diastolic blood pressure response to sustained handgrip were measured. Data were analyzed using repeated measures analysis of variance.

RESULTS — The supine heart rate was greater ($P = 0.04$) and the "30:15" ratio less ($P = 0.03$) during hyperglycemia than during euglycemia. Hyperglycemia had no significant effect on any of the other cardiovascular reflex tests.

CONCLUSIONS — These observations indicate that acute hyperglycemia affects autonomic nerve function in healthy humans.

Peripheral and autonomic neuropathy occur frequently in patients with diabetes, and the risk of these complications is reduced by optimal glycemic control (1). Autonomic nerve function is usually evaluated using noninvasive cardiovascular reflex tests (2). Recent studies indicate that short-term changes in blood glucose concentration may influence autonomic nerve function. For example, in patients with IDDM, gastric emptying is slower during hyperglycemia than during euglycemia (3) and is accelerated during hypoglycemia (4). In normal subjects, the secretion of pancreatic polypeptide is suppressed by acute hyperglycemia, consistent with a reduction in vagal activity (5). In patients with IDDM, acute hyperglycemia slows peripheral nerve conduction velocity (6). Somewhat surprisingly, the effects of acute hyperglycemia on autonomic nerve function have not been previously evaluated. We have therefore assessed the effects of hyperglycemia on cardiovascular autonomic function in normal subjects.

RESEARCH DESIGN AND METHODS

Subjects

Six healthy volunteers (five women, one man), mean age 24 years (range 19–32) and mean BMI 21.6 (range 18.9–26.4), were studied. In each subject, studies were performed during euglycemia and hyperglycemia in a single-blind randomized order. The two studies were separated by at least 1 week.

Evaluation of autonomic nerve function

Autonomic nerve function was evaluated using the following standardized cardiovascular reflex tests (2).

Heart rate variation with respiration (test of parasympathetic function). Each subject was instructed to breathe in over 5 s and out over 5 s, over a 1-min period. The difference between maximum and minimum heart rate was calculated (2).

Heart rate response to standing "30:15" ratio (test of parasympathetic function). Each subject was asked to stand quickly from a supine position. The ratio of the maximum R-R interval, occurring at or around the 30th beat, and the minimum R-R interval, occurring at or around the 15th beat after standing, was calculated (2).

Systolic blood pressure response to standing (test of sympathetic function). Systolic blood pressure was measured at baseline and at 1 and 2 min after standing from a supine position (2), using a semiautomated noninvasive blood pressure monitor (Critikon Dinamap 8100, Johnson and Johnson).

Blood pressure response to sustained handgrip (test of sympathetic function). A handgrip dynamometer was constructed using a standard blood pressure cuff and mercury sphygmomanometer. Each subject was initially asked to exert maximum handgrip force to determine the grip pressure that represented maximum exertion and was subsequently asked to maintain 30% of maximum handgrip for 5 min while blood pressure was recorded at 1-min intervals (2). Because two subjects were able to maintain handgrip for only 4 of the 5 min, when comparing the effect of euglycemia and hyperglycemia, only readings obtained at 0, 1, 2, 3, and 4 min were analyzed.

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Protocol

Each study commenced at 0900 after an overnight fast and abstinence from alcohol, caffeine, smoking, and heavy exercise for at least 24 h. With the subject recumbent, an intravenous cannula was placed in an antecubital vein of the left arm for blood sampling. A second cannula was placed in the right forearm for intravenous infusions. In the study performed during hyperglycemia, 25% glucose was given as an initial 150-ml bolus, followed by an infusion at a variable rate to maintain the blood glucose concentration at ~15 mmol/l for the subsequent 150 min. In the study performed during euglycemia, 0.9% sodium chloride was given as an initial 150-ml bolus, followed by an infusion at a rate of 100 ml/h for 150 min. The resting supine heart rate, the heart rate variation with respiration, the heart rate response to standing, and the systolic blood pressure response to standing were measured immediately before commencement of the infusions (baseline) and subsequently every 15 min for 2 h. The resting supine heart rate was calculated as the mean of 30 R-R intervals recorded while subjects were supine before standing for measurement of the "30:15" ratio. The diastolic blood pressure response to sustained handgrip was evaluated twice between 120 and 150 min. Venous blood samples were taken at baseline and subsequently at least every 10 min for 150 min. Blood glucose concentrations were initially measured using a portable blood glucose meter (Medisense Companion 2 Glucometer, Medisense, Waltman, MA), and the accuracy of these measurements was subsequently confirmed using a hexokinase technique.

Statistical analysis

Data were evaluated using repeated measures analysis of variance with contrasts (to compare specific time points) and linear regression analysis and are shown as means ± SE. A P value of <0.05 was considered significant.

RESULTS — The studies were well tolerated in all subjects, and no subject reported a need to urinate. The mean blood glucose was 5.1 ± 0.04 mmol/l during saline infusion and 15.7 ± 0.48 mmol/l in the studies performed during hyperglycemia. A total of 406 ± 4 ml was infused in the studies performed during euglycemia and 693 ± 42 ml in the studies performed during hyperglycemia ($P < 0.01$).

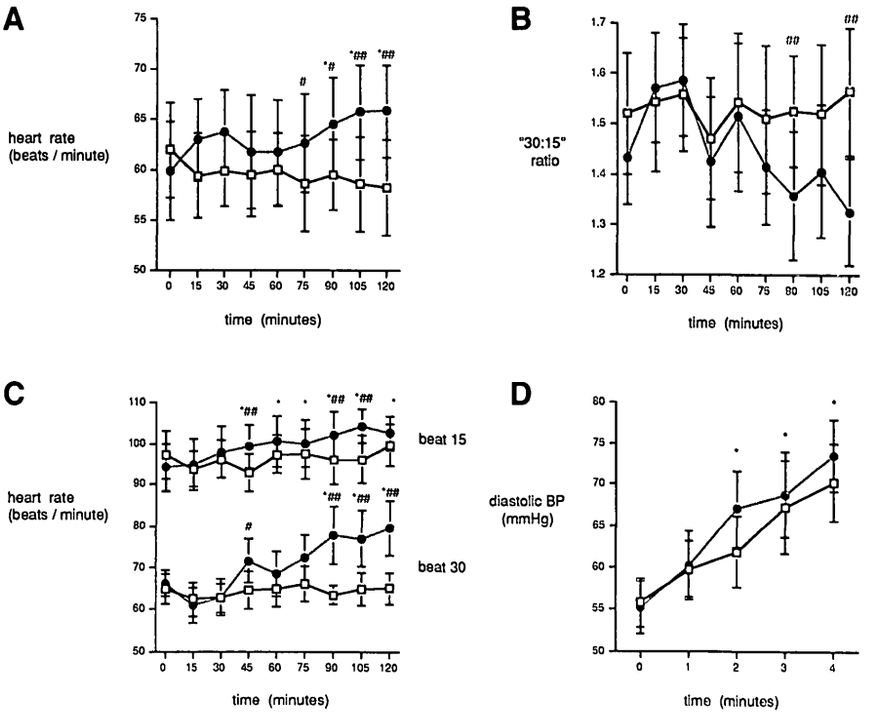

Figure 1—*Supine resting heart rate (A); heart rate response to standing, "30:15" ratio (B); heart rate at beat 15 ("15") and beat 30 ("30") after standing (C); and diastolic blood pressure response to submaximal handgrip (D) during hyperglycemia (●) and euglycemia (□). Data are means ± SE. *P < 0.05 cf. baseline; #P < 0.05, hyperglycemia vs. euglycemia; ##P < 0.01 hyperglycemia vs. euglycemia.*

Heart rate

Supine heart rate did not change significantly during saline infusion but increased during hyperglycemia ($P = 0.02$). The heart rate was greater ($P = 0.04$) during hyperglycemia than during euglycemia (Figure 1*A*). During hyperglycemia, the change in heart rate from baseline did not correlate significantly with the volume of fluid infused.

Parasympathetic function

The "30:15" ratio did not change significantly during saline infusion but decreased ($P = 0.003$) during hyperglycemia. The "30:15" ratio was less ($P = 0.03$) during hyperglycemia than during euglycemia (Fig. 1*B*). The change in the "30:15" ratio reflected an increase ($P = 0.02$) in heart rate at or around beat 15 associated with a greater increase ($P = 0.001$) in heart rate at or around beat 30 during hyperglycemia when compared with euglycemia (Fig. 1*C*). The heart rate variation with deep breathing did not change during either euglycemia ($P = 0.44$) or hyperglycemia ($P = 0.98$), and there was no difference between the two studies (data not shown).

Sympathetic function

There was no significant difference ($P = 0.49$) between euglycemia and hyperglycemia in the systolic blood pressure response to standing (data not shown). Submaximal handgrip resulted in a progressive increase ($P < 0.01$) in diastolic blood pressure, but there was no difference in the response between euglycemia and hyperglycemia (Fig. 1*D*).

CONCLUSIONS — We have demonstrated that acute hyperglycemia increases the supine heart rate and affects cardiovascular autonomic nerve function in normal subjects. The increase in heart rate during hyperglycemia may reflect reduced parasympathetic activity or stimulation of β-adrenergic mechanisms. However, since the "30:15" ratio is a specific test of vagal parasympathetic function and is unaffected by age or resting heart rate (2), our observations strongly suggest that hyperglycemia suppresses vagal function. Our study was designed to evaluate the effects of hyperglycemia on tests of cardiovascular autonomic function that

are used clinically. The absence of an effect of hyperglycemia on the second test of parasympathetic function, the heart rate response to deep breathing, may reflect the substantial interindividual variation in this test, given that only a relatively small number of subjects was studied. We were also unable to demonstrate any effect of acute hyperglycemia on the two tests of sympathetic function, but the latter are relatively insensitive (2). It must therefore be recognized that a more subtle effect of hyperglycemia on sympathetic function cannot be excluded.

Potential mechanisms by which acute hyperglycemia may affect nerve function have been reviewed (7). Hyperglycemia is associated with the activation of the polyol pathway, with resultant accumulation of sorbitol and depletion of myoinositol that lead to a reduction in Na^+-K^+-ATPase activity, which may result in the slowing of peripheral nerve conduction (7). Growth factors, endoneurial hypoxia, and glycosylation end products may also be important (7). Hyperglycemia may also have a central action to reduce vagal efferent activity (8). During euglycemia, hyperinsulinemia does not affect heart rate in healthy subjects (9), suggesting that the more rapid heart rate during hyperglycemia observed in our study is unlikely to be the consequence of secondary hyperinsulinemia. This conclusion is supported by studies indicating that insulin is not responsible for the effects of hyperglycemia on gastrointestinal motility (3,10). The increase in resting heart rate during hyperglycemia is also unlikely to reflect an increase in plasma catecholamine concentrations (11).

While the volume of glucose given in studies performed during hyperglycemia was greater than the amount of saline infused during euglycemia, because of the interindividual variation in the amount of intravenous glucose required to maintain hyperglycemia, the rates of infusion of both saline and glucose were below the threshold at which volume expansion has been reported to affect heart rate responses (12,13). It is also possible, but unlikely, that a relative increase in plasma osmolality during hyperglycemia may have resulted in altered nerve function.

In view of our observations, the effects of hyperglycemia on cardiovascular autonomic nerve function in patients with diabetes require evaluation. It will also be appropriate to determine whether changes in blood glucose concentration within the physiological range affect autonomic nerve function, as suggested by recent studies (10). The potential effects of the blood glucose concentration may need to be taken into account when autonomic nerve function is evaluated in patients with diabetes.

References

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Ewing DJ, Clarke BF: Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 285:916–918, 1982
3. Horowitz M, Fraser RJ: Disordered gastric motility in diabetes mellitus. *Diabetologia* 37:543–551, 1994
4. Schvarcz E, Palmer M, Aman J, Lindkvist B, Beckman KW: Hypoglycaemia increases gastric emptying rate in patients with insulin-dependent diabetes mellitus. *Diabetic Med* 10:660–663, 1993
5. Schwartz TW: Pancreatic polypeptide: a hormone under vagal control. *Gastroenterol* 85:1411–1425, 1983
6. Sindrup SH, Ejlertsen B, Gjessing H, Svendsen A, Froland A: Peripheral nerve function during hyperglycemic clamping in insulin-dependent diabetic patients. *Acta Neurol Scand* 79:412–418, 1989
7. Greene DA, Sima AAF, Stevens MJ, Feldman EL, Lattimer SA: Complications: neuropathy, pathogenetic considerations. *Diabetes Care* 15:1902–1925, 1992
8. Hirano T, Niijima A: Effects of 2-deoxy-D-glucose, glucose and insulin on efferent activity in gastric vagus nerve. *Experientia* 36:1197–1198, 1980
9. Airaksinen C, Lahtela JT, Ikaheimo MJ, Sotaniemi EA, Takkunen JT: Intravenous insulin has no effect on myocardial contractility or heart rate in healthy subjects. *Diabetologia* 28:649–652, 1985
10. Hasler WL, Soudah HC, Dulai G, Chung O: Mediation of hyperglycemia-evoked gastric slow-wave dysrhythmias by endogenous prostaglandins. *Gastroenterol* 108:727–736, 1995
11. Rowe JW, Young JB, Minaker KL, Stevens AL, Pallotta J, Landsberg L: Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. *Diabetes* 30:219–225, 1981
12. Vatner SF, Zimpfer M: Bainbridge reflex in conscious, unrestrained, and tranquilized baboons. *Am J Physiol* 240:H164–H167, 1981
13. Muir AL, Flenley DC, Kirby BJ, Sudlow MF, Guyatt AR, Brash HM: Cardiorespiratory effects of rapid saline infusion in normal man. *J Appl Physiol* 38:786–793, 1975