Occurrence of Bezold-Jarisch Reflex During Hyperinsulinemic Glucose Clamp

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In two subjects undergoing a high-dose hyperinsulinemic-euglycemic clamp, we witnessed the sudden onset of bradycardia and hypotension associated with pallor, nausea and vomiting, diaphoresis, lethargy, extreme weakness, impending doom, and near syncope. In both cases, the insulin infusion was discontinued immediately at the onset of the symptoms, normal saline was infused, and the bed placed in the reverse trendelenburg position, with resolution of symptoms in 5–10 min and restoration of baseline hemodynamics in 10–15 min.

T.J. was a 36-yr-old healthy, normally glucose-tolerant white male with mild untreated hypertension with a body mass index (BMI) of 24.1 kg/m^2. J.H. was a 41-yr-old obese white male (BMI 31.8 kg/m^2), with a 2-yr history of non-insulin-dependent diabetes mellitus, previously treated with sulfonylureas but who had recently been treated with insulin (HbA_{1c} 8.7%). Both subjects had no history of syncopal attacks and were on no medications on the day of the study.

The hyperinsulinemic-euglycemic glucose clamp studies were performed as previously described (1). The mean arterial pressure (MAP) was monitored via a 16-gauge three and one-half inch (Angiocath, Deseret, Sandy, UT) catheter inserted in the femoral artery and connected to a hemodynamic monitor (VSMI Physio-Control, Redmond, WA) via a pressure transducer. Heart rate (HR) was monitored via precordial leads. Potassium phosphate was infused to achieve a K^+ infusion rate of 0.0038 meq $\cdot$ kg^{-1} $\cdot$ min^{-1}, which prevented significant hypokalemia (<3.2 meq/L) in both cases.

At baseline, T.J. had a MAP of 105 mmHg, a HR of 84 bpm, and a fasting serum glucose level of 5.4 mM. Fifteen to 20 min after the start of a square-wave insulin infusion of 600 mu $\cdot$ m^{-2} $\cdot$ min^{-1} (15,800 pM), the HR increased to 115 bpm, and MAP fell to 90 mmHg. Forty minutes into the insulin infusion, T.J. began to complain of nausea and feeling "faint". He began sweating profusely and became pale and lethargic. His MAP and HR reached a nadir of 60 mmHg and 52 bpm, respectively. The glucose infusion rate at that time was 30.5 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}, and the arterial serum glucose level was 6.2 mM. After recovery, he remained somewhat weak but was alert.

At baseline, J.H. had a MAP of 90 mmHg, an HR of 63 bpm, and the fasting serum glucose level was 8 mM. Four and one-half hours after the onset of a square-wave insulin infusion at 120 mu $\cdot$ m^{-2} $\cdot$ min^{-1} (2010 pM), the MAP had decreased to 84 mmHg, HR had increased to 73 bpm, and the mean serum glucose level was 5.2 mM. The insulin infusion rate was then increased to 600 mu $\cdot$ m^{-2} $\cdot$ min^{-1} (17,940 pM). Forty-five minutes later, J.H. complained of not feeling well and thought he was experiencing hypoglycemia. He began to sweat and became pale and drowsy. At this time, the serum glucose level was 5.8 mM, and his MAP and HR had dropped to 44 mmHg and 45 bpm, respectively, and the glucose infusion rate was 31 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}. Although the subject remained conscious, he was lethargic and weak.

The syndrome of bradycardia-hypotension, also known as the *Bezold-Jarisch* Reflex (2), is thought to occur as a result of parasympathetic overdrive and sympathetic inhibition and triggered by intracardiac, intracoronary, or extracardiac baroreceptors in response to a critical fall in MAP or ventricular filling (2). The Bezold-Jarisch Reflex can be induced by profound hypovolemic shock (3), inferior-wall myocardial infarction (1), prolonged tilting (4), and by coronary vasodilation (5).

Although hyperinsulinemia has been implicated in the pathogenesis of hypertension (6–8), note that insulin is a potent physiological vasodilator (1,9), thus capable of reducing vascular resistance and MAP. As judged by these case reports, it appears that insulin is able to acutely lower MAP even in hypertensive and obese diabetic subjects.

The mechanism or mechanisms underlying the induction of the Bezold-Jarisch Reflex during insulin infusion is unknown. It is possible that high dosages of insulin produce profound vaso-

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dilation at the level of the arterial and venous circulation. This would result in a fall in vascular resistance and an increase in venous pooling. This, in turn, would lead to a decrease in ventricular filling pressure below a critical level, which then triggers the reflex.

It is unlikely that the high K^+ PO^4 infusion rate was causally related to the occurrence of the Bezold-Jarisch Reflex because we previously witnessed similar near-syncopal episodes during high-dosage insulin clamps when the K^+ PO^4 infusion used was one-fourth the current rate, and we witnessed the reflex in only ~2% of our recent "high-dosage" clamps.

Regardless of the underlying mechanism, investigators utilizing the "high-dosage" hyperinsulinemic glucose clamp technique should be aware of the occurrence of this syndrome and not confuse it with a hypoglycemic reaction.

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Stress Buffering Effect of Psychological Support in a Diabetic Camp

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Several studies have indicated that patients with insulin-dependent diabetes mellitus (IDDM) may differentially respond to stress with fluctuation in blood glucose (BG) concentration (1,2). Although this response may be idiosyncratic to specific patient groups (3,4), it is clear that the effect of psychological stress is an important aspect of diabetic regulation (1–4). One source of potential stress, and hence glycemic regulation, is the camping experience so often recommended for diabetic children. During camp, children are presumably taught various strategies for managing their BG to enhance control of the disease (5). However, if stress is a source of significant BG disregulation, the stress experienced by campers may contradict this purpose. Few studies have addressed this question.

Forty patients with IDDM (16 male, 24 female; mean age 144 mo, range 108–189 mo) attending an American Diabetes Association camp were identified on the basis of their glycosylated hemoglobin (GHb) levels (5) (11.2–17.5%) before being randomly assigned to specially trained counselors (2–3 each) based on sex and proximity within the camp cabins. Counselors were instructed to form close, supportive relationships with their charges and to meet with each individually on a daily basis for at least 10 min. No specific suggestions for patient education

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