Euglycemic Hyperinsulinemia Alters the Response to Orthostatic Stress in Older Adults With Type 2 Diabetes

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Objective: Insulin has opposing influences on blood pressure by simultaneously increasing adrenergic activity and vasodilatating peripheral blood vessels. This study sought to determine if hyperinsulinemia affects tilt table responses in older adults with Type 2 diabetes not complicated by orthostatic hypotension.

Research design and methods: 22 older adults (mean age 71.7±1.1) with diet-controlled or oral hypoglycemic-controlled Type 2 diabetes were recruited. All subjects with orthostatic hypotension, diabetic nephropathy and sensory neuropathy were excluded. Subjects underwent euglycemic hyperinsulinemic clamp and placebo “sham clamp” sessions. Sequential euglycemic hyperinsulinemic clamps were performed for 2 hours at 40 mU/M^2/min (Low Dose) and 2 hours at 80 mU/M^2/min (High Dose) and each followed by a head-up tilt table test at 70 degrees for 10 minutes.

Results: There were no incidents of presyncope during the “sham clamp”, while there were 4 presyncopal events during both the Low Dose and High Dose tilts. Although the Low Dose clamp showed no difference in the response between sessions (2-way ANOVA), subjects demonstrated a significantly larger decrease in MAP (p=0.005) and DBP (p=0.08) during the High Dose tilt. Doppler measures of Middle Cerebral Artery velocity were no different between the two sessions at either dose.

Conclusions: The vasodilatatory response to insulin can unmask orthostatic intolerance in older adults with Type 2 diabetes, resulting in presyncopal symptoms. This could contribute to orthostatic hypotension in combination with other factors such as hyperthermia, hypovolemia and adverse effects from medications.
Orthostatic hypotension is common in older adults with diabetes, and is usually attributed to autonomic neuropathy or age-related co-morbidities. Insulin has profound cardiovascular properties, resulting in simultaneous adrenergic and vasodilatory responses that have opposing influences on blood pressure. Depending on the relative magnitude of sympathetic activation and vasodilation in older adults, insulin administration might be a contributing factor in orthostatic intolerance and syncope.

Epidemiological studies have demonstrated that the use of insulin is a risk factor for syncope in older adults and that insulin hypersensitivity is a predisposing factor for vasovagal syncope in young women. Previous work in young adults with Type 1 diabetes has shown that insulin has no impact on standing blood pressure unless their diabetes is already complicated by autonomic neuropathy. However, the aging process itself is associated with a reduction in adrenergic sensitivity. Insensitivity to an insulin-mediated increase in adrenergic activity could allow the vasodilatory response to predominate, and potentially uncover “latent” orthostatic hypotension in older adults with uncomplicated diabetes, similar to that demonstrated previously in young hyperthermic adults with diabetes.

In the current study, we examine in older adults with Type 2 diabetes (without baseline orthostatic hypotension) the impact of a hyperinsulinemia on arterial blood pressure and Doppler measures of cerebral blood flow during upright tilt. We hypothesized that in older adults with Type 2 diabetes, the cardiovascular effects of insulin would precipitate orthostatic intolerance not present at baseline.

**RESEARCH DESIGN**

**Subjects** (Table 1)—25 older adults (21 males and 4 females, mean age 71.7±1.1) were recruited ranging in age from 65 to 80. All subjects had to be over 65 years of age and were excluded if they had any history of syncope, presyncope, angina, myocardial infarction, stroke, hypertension, chronic pulmonary disease, or smoking in the last 5 years. Hypertension was defined as an average blood pressure (based on three measurements) with a systolic blood pressure greater than 160 mm Hg or a diastolic blood pressure greater than 90 mm Hg. Subjects were also excluded if they took beta-blockers, calcium channel blockers, or any other agent with the potential to influence autonomic function. Entry requirements included a normal blood pressure, a normal physical exam, normal resting electrocardiogram, and a normal hematocrit, fasting blood glucose, total cholesterol, and creatinine. All subjects had to have had a diagnosis of Type 2 diabetes for at least 5 years. On this basis we excluded 3 subjects (n=22).

With respect to diabetic complications, subjects were excluded if they had evidence of sensory neuropathy on physical exam (done by physician) as shown by the response to light touch, pain (pinprick) and vibration sense. Subjects with orthostatic hypotension at baseline were excluded during the initial screening visit, by a series of five orthostatic maneuvers. Each orthostatic maneuver consisted of changing position from lying to standing for 3 minutes, and was followed by a 5-minute rest period. Orthostatic hypotension was defined as a drop in systolic blood pressure greater than 20 mmHg during one of these maneuvers.

This study was approved by the Human Subjects Committee of the University of British Columbia, and all subjects gave written informed consent.

**Study Design**—Each subject underwent two sessions (insulin clamp and “sham clamp”) occurring in random order on different days (maximum time between sessions was 28 days). All study sessions were performed with the subject supine and occurred between 7 AM and noon for all subjects to avoid bias due to
circadian rhythms. Each subject was supine for 45 minutes prior to the start of data collection in order to reach steady state. Subjects were fasting, had refrained from the consumption of alcohol or caffeine, and had not exercised for the 24 hours prior to each session. Both the subject and the technician responsible for monitoring blood pressure, heart rate and cerebral Doppler measures were blinded to the session type. The study room was temperature-controlled (25 ± 1°C).

**Euglycemic Hyperinsulinemic Clamp**—During the insulin clamp session, each subject underwent an euglycemic hyperinsulinemic infusion initially at 40 mU/M²/min (Low Dose) and then at 80 mU/M²/min (High Dose), roughly corresponding to the peak insulin level that occurs after a 0.1 U/kg and 0.2 U/kg Novolin R subcutaneous injections of insulin (14). Each insulin infusion was administered for 2 hours which was then was followed by a 10 minute tilt (see below). Previous work has demonstrated that 2 hours of euglycemic hyperinsulinemia results in significant peripheral vasodilatation (6). In all studies, 18 gauge needles were inserted into an antecubital vein for infusion of glucose and into a contralateral hand vein for sampling of "arterialized" venous blood. Because there is a significant gradient between arterial and venous glucose values, the patient's hand is placed in a warming chamber which results in sufficient arteriovenous shunting to "arterialize" venous blood, avoiding arterial catheterization (15). A primed continuous infusion of insulin (40 mU/M²/min for Low Dose, 80 mU/M²/min for High Dose) was commenced using the euglycemic clamp technique and continued for 140 minutes (2 hours plus 10 minutes for the tilt table test). Blood glucose was maintained at basal levels (determined at the start of the first session) using the euglycemic clamp protocol (16). Plasma insulin was measured every 15 min as described previously (17).

**Tilt Table Protocol**—Each two hour euglycemic hyperinsulinemic clamp (at both Low and High Doses) was followed by a 70 degree head-up tilt for 10 minutes. During all clamps, and during each upright tilt heart rate, blood pressure and middle cerebral artery (MCA) velocity was measured continuously (see below) and an average determined for each minute. The tilt table was aborted prior to the 10 minutes if the subjects demonstrated presyncopal symptoms in association with at least a 30 mm Hg drop in blood pressure compared to baseline, or developed outright syncope.

**Data Collection and Processing:** Heart rate was monitored continuously using a 3 lead-electrocardiogram. Blood pressure was monitored using a Finometer (Finapres Medical Systems, The Netherlands). The Finometer measures beat-to-beat blood pressure noninvasively using infrared plethysmography through a finger-cuff. Use of the Finometer and infrared plethesmography for monitoring blood pressure changes has been well established as a noninvasive measure of beat-to-beat blood pressure (18) and has been extensively validated against intra-arterial blood pressure monitoring in older adults (19). The Finometer uses waveform filtering, level correction and an additional return-to-flow calibration to reconstruct brachial artery pressures (20).

Transcranial Doppler measures of MCA blood flow velocity was assessed during upright tilt following previously published methods (21). After a temporal ultrasonic bone window was confirmed, the right middle cerebral artery was insonated with a 2 MHz TCD probe (Spencer Technologies, US) using M-mode ultrasonography, which was fixed in place by a fixation device (Spencer Technologies, US). The electrocardiogram, blood pressure and transcranial Doppler signal were sampled at 1000 Hz (AD Instruments) and digitized for later analysis. Using
commercially available software, beat-to-beat measures of blood pressure (Beatscope, Finapres Medical Systems BV, The Netherlands), heart rate (Powerlab, AD Instruments) were calculated. With respect to MCA velocity measures, beat-to-beat measures of systolic (SBFV), diastolic (DBVF) and mean cerebral blood flow velocities (MBFV) were calculated as previously described both prior to and during each upright tilt(21). All variables were averaged for each one-minute data segment during upright tilting, and each segment of raw blood pressure, electrocardiogram and cerebral Doppler signal was manually examined for artifacts.

Measures of total peripheral resistance (TPR) for each heart beat was determined from the beat-to-beat blood pressure signal using commercially available software (Finapres Medical Systems, The Netherlands). This software uses an arctangent model (22) and has been validated for use in the older adult population(23). TPR was measured on a beat-to-beat basis and averaged for each one-minute data segment during upright tilting.

Statistical Analysis—All data analysis was done in a blinded fashion. Results are expressed as the mean ± standard error. Our sample size calculations for our primary outcome measures (systolic blood pressure, mean blood pressure, diastolic blood pressure, and TPR) assumed a power of 90% and a 1.25% level of significance. After a Bonferroni correction for multiple comparisons, we found that we required a sample size of at least 20 subjects to detect a 5 percent difference in our primary outcome measures, assuming a syncope-related incompletion rate of 5 subjects. Mean values for each variable were determined for each minute of upright tilt. A two-way ANOVA with repeated measures was used to compare the response to ten minutes of tilting between sessions (time*session) for all parameters(24). A value of p<0.0125 was considered significant, due to a Bonferroni correction for multiple comparisons(24).

RESULTS

Subject Characteristics (Table 1)—The subjects had an average age of 71.4±0.4 years. They all had reasonable control of their blood sugars as shown by their mean fasting blood glucose (6.5±0.1 mEq), 2-hour glucose tolerance test (11.4±0.2) and glycosylated hemoglobin (6.2±0.05 %). Mean weight (85.9±1.2 kg) and mean height (173.9±0.8 cm) resulted in a subject population that was mildly overweight but not obese(25) with a mean body mass index of 28.2±0.2 kg/m². None of the subjects had any new health issues or medication changes between the 2 sessions.

Effects of Euglycemic Hyperinsulinemic Clamps (Table 1)—The mean insulin levels were significantly different (p<0.001) between the insulin (903±121 pmol/L) and placebo (161±22 pmol/L) sessions during the Low Dose infusion. Similarly, the mean insulin levels were significantly different (p<0.001) between the insulin (1785±239 pmol/L) and placebo (163±23 pmol/L) sessions during the High Dose infusion.

Neither the Low Dose or the High Dose hyperinsulinemic clamps produced any significant changes in systolic (p=0.101), mean (p=0.111) or diastolic (p=0.105) blood pressure when compared with placebo (by 2-way AVOVA with repeated measures). Similarly, heart rate (p=0.491), SBFV (p=0.191), MBFV (p=0.837) and DBFV (p=0.769) did not demonstrate any significant change with the two doses of hyperinsulinemic clamps.

Hemodynamic Responses to Upright Tilting—4 subjects experienced presyncope during both the Low Dose and High Dose Tilts. The length of time on the tilt table ranged from 4.3 to 9.75 minutes for those that experienced presyncope. Presyncopal Low Dose subjects had a range of blood pressures from 91/52 (62) to 98/61 (72) and a range of heart rates from 65 to 90 beats per minute just prior to discontinuing the tilt table test. Presyncopal High Dose subjects had a range of blood pressures from 62/42 (48) to 86/51 (62) and a range of heart rates from 85 to 89 beats per
minute just prior to discontinuing the tilt table test.

When these subjects were excluded from the analysis there was no significant effect of insulin on the response of systolic (p=0.992), mean (p=0.962) or diastolic (p=0.959) blood pressure when compared with placebo (by 2-way AVOVA with repeated measures) during the Low Dose Tilt (See Table 1). During the High Dose Tilt subjects demonstrated a significantly larger drop in mean (p=0.005) and diastolic (p=0.008) blood pressure over time. As shown in Figure 1, this drop in blood pressure became significant during the 8th and 9th minutes (t8 and t9). The difference between the two sessions with respect to systolic blood pressure approached, but did not reach statistical significance (p=0.014) for the High Dose Tilt. Despite the increased orthostatic drop with insulin during the High Dose Tilt, there was no significant difference in the heart rate response (p=0.979, Low Dose; p=0.273, High Dose) between the insulin and saline sessions (Figure 2). As shown in Figure 3, there was also no significant difference in total peripheral resistance during the hyperinsulinemic clamp as compared to placebo (p=0.047) during the High Dose Tilt or Low Dose Tilt (p=0.897).

**MCA Velocity Measures During Upright Tilt**—Excluding subjects who were unable to complete the tilt due to presyncope, there was no difference in the response of SBFV (p=0.356), MBFV (p=0.616) or DBFV (p=0.391) to upright tilting between the insulin and saline sessions during the Low Dose tilt (Table 1). Similarly, there was no difference in the response of SBFV (p=0.805), MBFV (p=0.125) or DBFV (p=0.232) during the High Dose tilt (Table 1).

**CONCLUSIONS**

Our study demonstrated a significant impairment of the ability to maintain blood pressure under orthostatic stress during conditions of euglycemia hyperinsulinemia. Subjects during both doses of hyperinsulinemia demonstrated presyncope that was not found during the saline “sham clamp” sessions. This orthostatic intolerance was also dose-dependent, as shown by the fact that only the High Dose tilt (80 mU/M2/min) demonstrated lower blood pressures. Presyncope during hyperinsulinemic upright tilt was possibly due to a decrease in total peripheral resistance (although this did not reach statistical significance) and due to an impaired tachycardic response to tilt-induced hypotension.

The opposing effects of insulin on standing blood pressure are well established and are due to the conflicting effects of an adrenergic response (4) in conjunction with a direct vasodilatory response(5). A subcutaneous dose of insulin was shown in a small study of young subjects with Type 1 diabetes (7 subjects with autonomic neuropathy and 7 without autonomic neuropathy) to produce lower standing blood pressures only in the setting of baseline autonomic neuropathy-induced orthostatic hypotension(9). In those young subjects with autonomic neuropathy, the consequent sympathetic nervous system dysfunction allowed the vasodilatory response to insulin to predominate, resulting in lower standing blood pressures(9). Contrary to these results, the present study demonstrated orthostatic intolerance in older subjects with Type 2 diabetes, where subjects with orthostatic hypotension were excluded. The most likely explanation for this is that our subjects were much older than the subjects in previous studies. It is well established that the aging process itself results in adrenergic insensitivity(10). Insensitivity to an insulin-mediated increase in adrenergic activity could allow the vasodilatory response to predominate in older subjects, thereby uncovering orthostatic hypotension that was not present at baseline. This is supported by prospective epidemiological data demonstrating an association between insulin use and syncope in older adults(7). To our knowledge, no previous study has directly examined the effects of
hyperinsulinemia on tilt table responses in older adults with diabetes.

Adrenergic insensitivity as a potential mechanism underlying hyperinsulinemic-associated orthostatic intolerance in older adults is supported by several findings in the present study. First of all, older subjects with Type 2 diabetes demonstrated no significant difference in total peripheral resistance during upright tilt during the High Dose insulin session (there was a non-significant trend towards lower total peripheral resistance, as shown in Figure 3). In addition, there was no change in the heart rate response during upright tilt between the two sessions (see Figure 2) despite larger decreases in blood pressure with High Dose insulin infusion. This suggests age-associated insensitivity to the insulin-induced adrenergic response, both at the vascular and chronotropic levels.

Despite the fact that more episodes of syncope occurred during upright tilt with insulin infusion, there was no difference in the response of Doppler measures of MCA velocity when the two sessions were compared. This is likely due to the fact that for ethical reasons the tilt table tests were discontinued at the onset of presyncopal symptoms, as opposed to allowing the subjects to continue the test and proceed to an outright syncopal spell. The lack of a significant difference in Doppler measures of MCA velocity also indicates that cerebral autoregulation remained intact in the face of an orthostatic stress during euglycemic hyperinsulinemia.

**Clinical Implications**—As shown in Figure 1, insulin infusion resulted in a statistically significant worsening of orthostatic tolerance, resulting in presyncopal symptomatology in 4 patients during insulin. Although the observed exaggeration in the orthostatic drop with insulin would be unlikely to be a sole etiology for syncopal spells in older adults with diabetes, it could contribute to orthostatic hypotension in combination with other factors such as hyperthermia(11), hypovolemia and adverse effects from medications(2).

**Limitations**—Further research is needed to determine the clinical significance of insulin-mediated orthostatic hypotension in older adults with diabetes. Although our results were consistent with age-related adrenergic insensitivity as an explanatory mechanism, more research is needed to determine the underlying cause of this phenomenon. Some of our subjects could still have had a mild sensory neuropathy, since we used an insensitive method (physical exam maneuvers) to screen for this condition. Some of our subjects could also have had a mild autonomic neuropathy, since only orthostatic changes in blood pressure were used to screen for this condition.

**Summary**—We demonstrated that hyperinsulinemia results in symptomatic orthostatic intolerance in older adults with Type 2 diabetes. This was most likely due to an age-associated adrenergic insensitivity allowing the direct vasodilatory action of insulin to predominate.

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REFERENCES


The effect of euglycemic hyperinsulinemic clamps on heart rate (HR, bpm), systolic blood pressure (SBP, mm Hg), diastolic blood pressure (DBP, mm Hg), mean arterial pressure (MAP, mm Hg), systolic blood flow velocity (SBFV, m/sec), mean blood flow velocity (MBFV, m/sec), and diastolic blood flow velocity (DBFV, m/sec) at baseline and during the 10 minute tilt table response. The symbol * designates a significantly different response \((p<0.0125)\) between sessions as per two-way (time*session). A value of \(p<0.0125\) was considered significant, due to a Bonferroni correction for multiple comparisons. Analysis of Variance with repeated measures (ANOVA) is for the entire ten minutes of upright tilt. Tilt table values shown consist of that portion of the 10 minute tilt (during the 8th and 9th minute as delineated by t8 and t9) where blood pressure was significantly lower during insulin clamp than during the saline session. Analysis is on 18 subjects (4 were excluded due to inability to complete tilt table test).
FIGURE CAPTIONS

1. During the High Dose Tilt (80 mU/M2/min insulin infusion), subjects demonstrated a significantly larger drop in mean (MAP, p=0.005) and diastolic (DBP, p=0.008) blood pressure over time during the insulin session. The difference with respect to systolic blood pressure did not reach statistical significance (SBP, p=0.014). This drop in blood pressure became significant during the 8th and 9th minutes (t8 and t9). t0 to t9, each of the 10 minutes of the tilt table test. r1 and r2, the first 2 post-tilt recovery minutes. Black circles = SBP-Insulin; white circles SBP-Placebo; black triangles = MAP-Insulin; white triangles = MAP-Placebo; black squares = DBP-Insulin; white squares = DBP-Placebo.

2. Despite the drop in blood pressure seen during the High Dose Tilt, there was no significant difference in the heart rate response (p=0.979, Low Dose; p=0.273, High Dose) between the insulin and saline sessions (Figure #3). Black circles = Low Dose Insulin; white circles Low Dose Placebo; black triangles = High dose Insulin; white triangles = High Dose-Placebo.

3. There was no significant difference with respect to the change in total peripheral resistance during the hyperinsulinemic clamp as compared to placebo during either the High Dose (p=0.047) or Low Dose Tilt (p=0.897). Black circles = Low Dose Insulin; white circles Low Dose Placebo; black triangles = High dose Insulin; white triangles = High Dose-Placebo.

Figure 1--Blood Pressure Response to High Dose Tilt

![Blood Pressure Graph]

Legend:
- • SBP-Insulin
- ○ SBP-Placebo
- ● MAP-Insulin
- ○ MAP-Placebo
- ○ DBP-Insulin
- ● DBP-Placebo
Figure 2--Heart Rate Response to Low Dose and High Dose Tilts

Figure 3--Total Peripheral Resistance During Low and High Dose Tilts