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

KENNETH M. MADDEN, MSC, MD
GALE TEDDER, RN
CHRIS LOCKHART, BSC
GRAYDON S. MENEILLY, MD

OBJECTIVE — Insulin has opposing influences on blood pressure by simultaneously increasing adrenergic activity and vasodilatating peripheral blood vessels. In this study, we sought to determine whether hyperinsulinemia affects tilt table responses in older adults with type 2 diabetes not complicated by orthostatic hypotension.

RESEARCH DESIGN AND METHODS — Twenty-two older adults (mean age 71.7 ± 1.1) with diet-controlled or oral hypoglycemic drug–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 h at 40 mU · m^{-2} · min^{-1} (low dose) and 2 h at 80 mU · m^{-2} · min^{-1} (high dose), and each was followed by a head-up tilt table test at 70°C for 10 min.

RESULTS — There were no incidents of presyncope during the sham clamp, whereas there were four presyncopal events during both the low-dose and high-dose tilts. Although the low-dose clamp showed no difference in the response between sessions (two-way ANOVA), subjects demonstrated a significantly larger decrease in mean arterial pressure ($P = 0.005$) and diastolic blood pressure ($P = 0.08$) during the high-dose tilt. Doppler measures of middle cerebral artery velocity were no different between the two sessions at either dose.

CONCLUSIONS — The vasodilatory 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.

Diabetes Care 31:2203–2208, 2008

Orthostatic hypotension is common in older adults with (1) and without diabetes (2) and is usually attributed to autonomic neuropathy or age-related comorbidities (3). Insulin has profound cardiovascular properties, resulting in simultaneous adrenergic (4) and vasodilatory (5,6) 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 (7) and that insulin hypersensitivity is a predisposing factor for vasovagal syncope in young women (8). 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 (9). However, the aging process itself is associated with a reduction in adrenergic sensitivity (10). 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 (11).

In the current study, we examined in older adults with type 2 diabetes (without baseline orthostatic hypotension) the impact of hyperinsulinemia (12) 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 AND METHODS

— Twenty-five older adults, ranging in age from >65 to 80 years (21 men and 4 women, mean age 71.7 ± 1.1 years) were recruited (Table 1). All subjects had to be aged >65 years, and subjects 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 measurement (based on three measurements) with a systolic blood pressure >160 mmHg or a diastolic blood pressure >90 mmHg. Subjects were also excluded if they took β-blockers, calcium channel blockers, or any other agent with the potential to influence autonomic function. Entry requirements included normal results for the following: blood pressure, physical examination, resting electrocardiogram, 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 three subjects ($n = 22$).

With respect to diabetes complications, subjects were excluded if they had evidence of sensory neuropathy on physical examination (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 ortho-

From the Division of Geriatric Medicine, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada.
Corresponding author: Kenneth M. Madden, kmmadden@interchange.ubc.ca.
Received 10 June 2008 and accepted 10 August 2008.
Published ahead of print at http://care.diabetesjournals.org on 20 August 2008. DOI: 10.2337/dc08-1058.

static maneuvers. Each orthostatic maneuver consisted of changing position from lying to standing for 3 min and was followed by a 5-min rest period. Orthostatic hypotension was defined as a drop in systolic blood pressure >20 mmHg during one of these maneuvers (13).

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

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 A.M. and noon for all subjects to avoid bias due to circadian rhythms. Each subject was supine for 45 min before the start of data collection to reach steady state. Subjects were fasting, had refrained from the consumption of alcohol or caffeine, and had not exercised for the 24 h before 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 a euglycemic-hyperinsulinemic infusion initially at 40 $mU \cdot m^{-2} \cdot min^{-1}$ (low dose) and then at 80 $mU \cdot m^{-2} \cdot min^{-1}$ (high dose), roughly corresponding to the peak insulin level that occurs after subcutaneous injections of insulin (0.1 and 0.2 unit/kg Novolin R) (14). Each insulin infusion was administered for 2 h and was then followed by a 10-min tilt (see below). Previous work has demonstrated that 2 h 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 (low dose 40 $mU \cdot m^{-2} \cdot min^{-1}$ and high dose 80 $mU \cdot m^{-2} \cdot min^{-1}$) was begun using the euglycemic-hyperinsulinemic clamp technique and continued for 140 min (2 h plus 10 min for the tilt table test). Blood glucose was maintained at basal levels (determined at the start of the first session) using the euglycemic-hyperinsulinemic clamp protocol (16). Plasma glucose was measured every 5 min and analyzed immediately using a YSI glucose analyzer (YSI Life Sciences, Yellow Springs, OH). Plasma insulin was measured every 15 min as described previously (17).

Tilt table protocol

Each 2-h euglycemic-hyperinsulinemic clamp (at both low and high doses) was followed by a 70° head-up tilt for 10 min. During all clamps and during each upright tilt heart rate, blood pressure and middle cerebral artery (MCA) velocity were measured continuously (see below), and an average was determined for each minute. The tilt table test was aborted before 10 min if the subjects demonstrated presyncopal symptoms in association with at least a 30 mmHg drop in blood pressure compared with baseline or developed outright syncope.

Data collection and processing

Heart rate was monitored continuously using a three-lead electrocardiogram. Blood pressure was monitored using a Finometer (Finapres Medical Systems, Amsterdam, the Netherlands). The Finometer measures beat-to-beat blood pressure noninvasively using infrared plethysmography through a finger cuff. Use of the Finometer and infrared plethysmography 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 MCA was insonated using M-mode ultrasonography with a 2-MHz TCD probe (Spencer Technologies, Seattle, WA), which was fixed in place by a fixation device (Spencer Technologies). The electrocardiogram, blood pressure, and transcranial Doppler signal were sampled at 1,000 Hz (AD Instruments) and digitized for later analysis. Beat-to-beat measures of blood pressure (Beatscope; Finapres Medical Systems) and heart rate (Powerlab; AD Instruments) were calculated using commercially available software. With respect to MCA velocity measures, beat-to-beat measures of systolic (SBFV), diastolic (DBVF), and mean cerebral blood flow (MBFV) velocities were calculated as described previously both before and during each upright tilt (21). All variables were averaged for each 1-min 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 were determined from the beat-to-beat blood pressure signal using commercially available software (Finapres Medical Systems). 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 1-min data segment during upright tilting.

Statistical analysis

All data analysis was done in a blinded fashion. Results are expressed as means ± SEM. 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% difference in our primary outcome measures, assuming a syncope-related incompletion rate of five 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 10 min of tilting between sessions (time × session) for all parameters (24). $P < 0.0125$ was considered significant with Bonferroni correction for multiple comparisons (24).

RESULTS — Characteristics of the subjects are shown in Table 1. The subjects had an average age of 71.4 ± 0.4 years. They all had reasonable control of their blood glucose as shown by their mean ± SEM fasting blood glucose (6.5 ± 0.1 mEq), 2-h glucose tolerance test (11.4 ± 0.2 mEq), and A1C (6.2 ± 0.05%). Weight (85.9 ± 1.2 kg) and height (173.9 ± 0.8 cm) indicated a subject population that was mildly over-

weight but not obese (25) with a BMI of 28.2 ± 0.2 kg/m^2. None of the subjects had any new health issues or medication changes between the two sessions.

Effects of euglycemic-hyperinsulinemic clamps

Mean ± SEM 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 (Table 1). Similarly, insulin levels were significantly different ($P < 0.001$) between the insulin (1,785 ± 239 pmol/l) and placebo (163 ± 23 pmol/l) sessions during the high-dose infusion.

Neither the low-dose or the high-dose euglycemic-hyperinsulinemic clamps produced any significant changes in systolic ($P = 0.101$), mean ($P = 0.111$), or diastolic ($P = 0.105$) blood pressure compared with placebo (by two-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 euglycemic-hyperinsulinemic clamps.

Hemodynamic responses to upright tilting

Four 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 min for those who experienced presyncope. Presyncopal low-dose tilt subjects had a range of blood pressures from 91/52 (mean 62) to 98/61 (72) mmHg and a range of heart rates from 65 to 90 bpm just before discontinuing the tilt table test. Presyncopal high-dose tilt subjects had a range of blood pressures from 62/42 (48) to 86/51 (62) mmHg and a range of heart rates from 85 to 89 bpm just before 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 compared with placebo (by two-way AVOVA with repeated measures) during the low-dose tilt (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 Fig. 1, this drop in blood pressure became significant during the 8th and 9th min (t8 and t9). The difference between the two sessions with

Table 1—*Effects of euglycemic-hyperinsulinemic clamps on subject hemodynamic and arterial baroreflex functions at baseline and during the 10-min tilt table response*

	Baseline	After low dose	After high dose	*P* value	Low-dose tilt		*P* value	High-dose tilt		*P* value
					t8	t9		t8	t9	
Heart rate (bpm)										
Insulin	56.5 ± 1.7	57.9 ± 1.9	60.0 ± 2.1	0.491	65.2 ± 2.6	64.0 ± 3.0	0.979	65.4 ± 2.5	65.3 ± 2.4	0.273
Saline	57.6 ± 2.7	57.13 ± 2.7	60.4 ± 2.9		64.4 ± 2.9	64.3 ± 2.5		68.7 ± 2.8	69.4 ± 2.7	
Systolic blood pressure (mmHg)										
Insulin	126.1 ± 6.4	142.6 ± 6.1	125.1 ± 3.9	0.101	126.3 ± 7.6	122.4 ± 9.5	0.992	124.4 ± 3.0	123.4 ± 3.0	0.014
Saline	131.4 ± 5.6	138.2 ± 5.1	135.9 ± 5.5		122.2 ± 8.2	121.4 ± 7.6		131.8 ± 4.0	130.6 ± 4.0	
Diastolic blood pressure (mmHg)										
Insulin	61.8 ± 2.3	70.0 ± 1.7	63.7 ± 1.9	0.105	63.1 ± 2.7	61.2 ± 3.3	0.959	59.9 ± 3.4	59.9 ± 3.7	0.008*
Saline	69.1 ± 2.2	69.8 ± 2.7	69.4 ± 2.8		63.1 ± 3.9	63.6 ± 3.5		68.7 ± 2.9	69.2 ± 2.9	
Mean arterial pressure (mmHg)										
Insulin	85.9 ± 3.4	96.1 ± 3.0	85.2 ± 2.3	0.111	84.6 ± 4.1	82.2 ± 5.3	0.962	81.2 ± 5.1	81.3 ± 5.4	0.005*
Saline	92.4 ± 3.0	95.2 ± 3.3	93.5 ± 3.5		84.0 ± 5.5	84.2 ± 4.8		91.2 ± 3.5	90.8 ± 3.4	
SBFV (m/s)										
Insulin	56.7 ± 3.2	56.8 ± 3.2	61.0 ± 3.4	0.191	53.2 ± 2.5	53.5 ± 2.6	0.356	60.6 ± 4.9	60.7 ± 4.7	0.805
Saline	62.3 ± 6.9	59.3 ± 6.4	57.5 ± 5.6		53.2 ± 5.5	54.1 ± 5.6		56.4 ± 5.3	57.2 ± 5.7	
MBFV (m/s)										
Insulin	35.1 ± 1.8	33.0 ± 2.0	34.6 ± 1.7	0.837	31.9 ± 2.2	31.7 ± 2.3	0.616	32.7 ± 2.7	31.7 ± 2.1	0.125
Saline	38.2 ± 4.1	34.9 ± 3.4	36.8 ± 3.1		32.3 ± 3.1	32.8 ± 3.1		33.5 ± 2.9	34.4 ± 2.7	
DBFV (m/s)										
Insulin	21.4 ± 1.4	20.9 ± 1.9	20.0 ± 1.3	0.769	19.4 ± 1.8	19.1 ± 1.9	0.391	18.7 ± 1.5	19.4 ± 1.8	0.232
Saline	24.0 ± 2.9	21.9 ± 2.1	21.5 ± 2.3		18.8 ± 1.6	18.9 ± 1.6		20.8 ± 1.8	20.9 ± 1.5	

Data are means ± SEM. *Significantly different response ($P < 0.0125$) between sessions as per two-way ANOVA (time × session). A value of $P < 0.0125$ was considered significant owing to a Bonferroni correction for multiple comparisons. ANOVA is for the entire 10 min of upright tilt. Tilt table values shown consist of that portion of the 10-min tilt (during the 8th and 9th min as delineated by t8 and t9) when blood pressure was significantly lower during the insulin clamp than during the saline session. Analysis is for 18 subjects (4 were excluded because of their inability to complete the tilt table test).

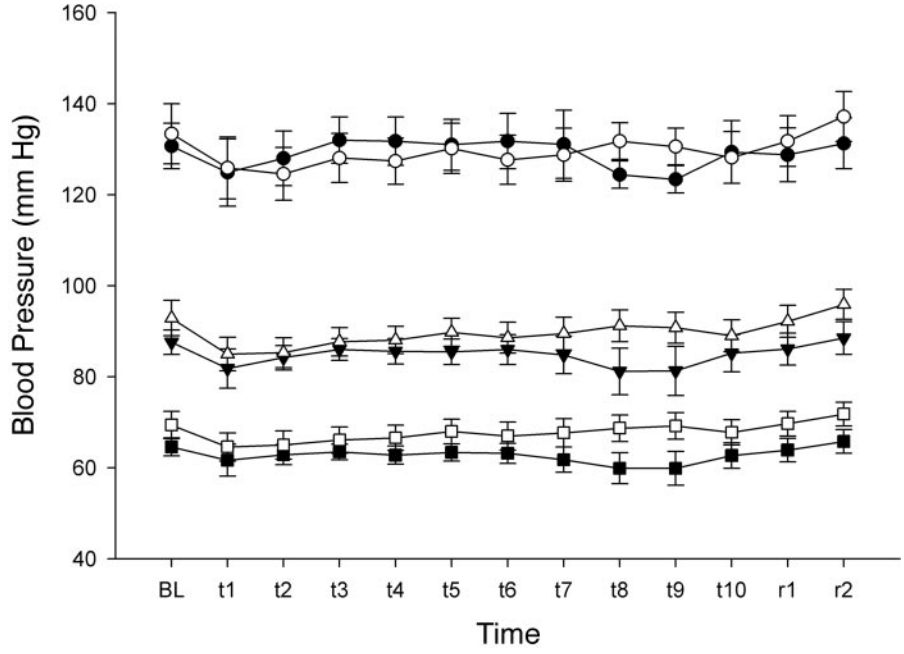

Figure 1—*Blood pressure response to high-dose tilt. During the high-dose tilt (80 mU · m^{-2} · min^{-1} insulin infusion), subjects demonstrated a significantly larger drop in mean arterial pressure (MAP) (P = 0.005) and diastolic blood pressure (DBP) (P = 0.008) over time during the insulin session. The difference with respect to systolic blood pressure (SBP) did not reach statistical significance (P = 0.014). This drop in blood pressure became significant during the 8th and 9th min (t8 and t9). t0 to t9, each of the 10 min of the tilt table test; r1 and r2, the first two post-tilt recovery minutes; ●, SBP-insulin; ○, SBP-placebo; ▲, MAP-insulin; △, MAP-placebo; ■, DBP-insulin; □, DBP-placebo.*

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 tile; $P = 0.273$, high-dose tilt) between the insulin and saline sessions (Fig. 2). As shown in Fig. 3, there was also no significant difference in total peripheral resistance during the euglycemic-hyperinsulinemic clamp compared with placebo ($P = 0.047$) during the high-dose tilt or low-dose tilt ($P = 0.897$).

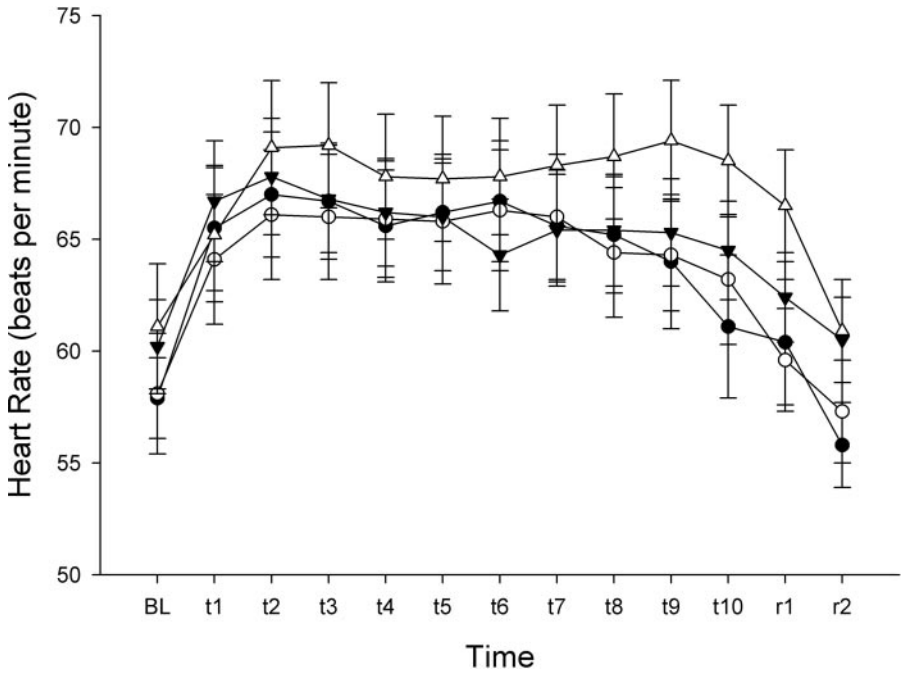

Figure 2—*Heart rate response to low- and high-dose tilts. Despite the drop in blood pressure seen during the high-dose tilt, there was no significant difference in the heart rate response (low-dose tilt P = 0.979; high-dose tilt P = 0.273) between the insulin and saline sessions (Fig. 3). ●, low-dose insulin; ○, low-dose placebo; ▲, high-dose insulin; △, high-dose-placebo.*

MCA velocity measures during upright tilt

Excluding subjects who were unable to complete the tilt test because of 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 significant impairment of the ability to maintain blood pressure under orthostatic stress during conditions of euglycemia hyperinsulinemia. Subjects demonstrated presyncope during both doses of hyperinsulinemia 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 · m^{-2} · min^{-1}) demonstrated lower blood pressures. Presyncope during euglycemic-hyperinsulinemic upright tilt was possibly due to a decrease in total peripheral resistance (although this did not reach statistical significance) or 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 (seven subjects with autonomic neuropathy and seven 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, in the present study, from which subjects with orthostatic hypoten-

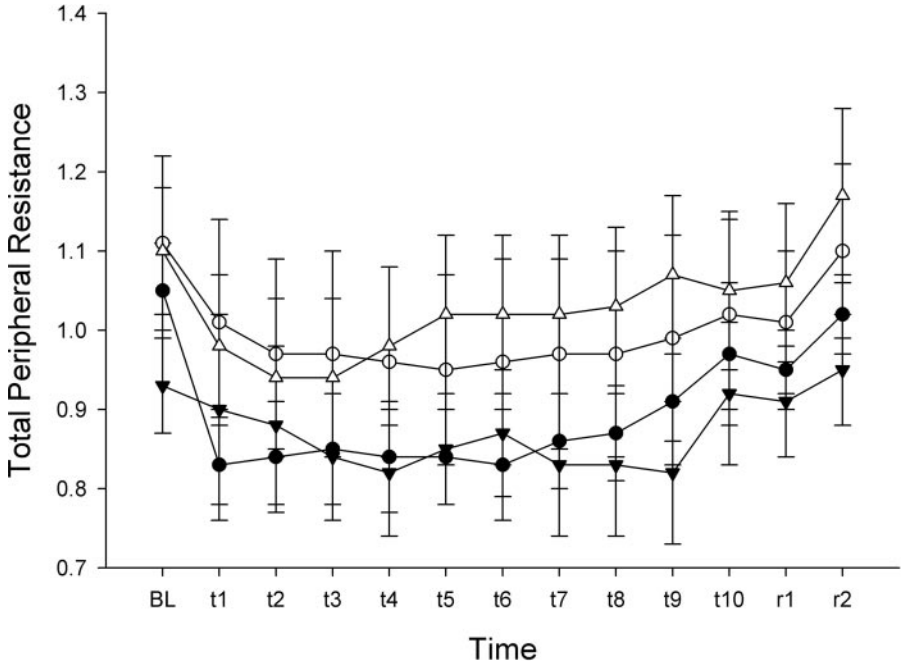

Figure 3—*Total peripheral resistance during low- and high-dose tilts. There was no significant difference with respect to the change in total peripheral resistance during the hyperinsulinemic clamp as compared with placebo during either the high-dose (P = 0.047) or low-dose tilt (P = 0.897). ●, low-dose insulin; ○, low-dose placebo; ▲, high-dose insulin; △, high-dose-placebo.*

sion were excluded, we demonstrated orthostatic intolerance in older subjects with type 2 diabetes. The most likely explanation for this result 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 hypothesis 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 hyperinsulinemia-associated orthostatic intolerance in older adults is supported by several findings in the present study. First, older subjects with type 2 diabetes demonstrated no significant difference in total peripheral resistance during upright tilt in the high-dose insulin session (there was a nonsignificant trend toward lower total peripheral resistance, as shown in Fig. 3). In addition, there was no change in the heart rate response during upright tilt between the two sessions (Fig. 2) despite larger decreases in blood pressure with the high-dose insulin infusion. This result 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 the 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 probably because of 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 presence of an orthostatic stress during euglycemic hyperinsulinemia.

Clinical implications

As shown in Fig. 1, insulin infusion caused a statistically significant worsening of orthostatic tolerance, resulting in presyncopal symptomatology in four patients during insulin. Although the observed exaggeration in the orthostatic drop with insulin would be unlikely to be a sole cause 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, as we used an insensitive method (physical examination maneuvers) to screen for this condition. Some of our subjects could also have had a mild autonomic neuropathy, as only orthostatic changes in blood pressure were used to screen for this condition.

In summary, we demonstrated that hyperinsulinemia results in symptomatic orthostatic intolerance in older adults with type 2 diabetes. This finding was most likely due to an age-associated adrenergic insensitivity allowing the direct vasodilatory action of insulin to predominate.

Acknowledgments— This research was supported by Canadian Institutes of Health Research Grant 145801 and by the Academic Enhancement Fund (Department of Medicine, University of British Columbia).

References

1. de Kanter M, Lilja B, Elmstahl S, Eriksson KF, Sundkvist G: A prospective study of orthostatic blood pressure in diabetic patients. *Clin Auton Res* 8:189–193, 1998
2. Gupta V, Lipsitz LA: Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 120:841–847, 2007
3. Vinik AI, Erbas T: Cardiovascular autonomic neuropathy: diagnosis and management. *Curr Diab Rep* 6:424–430, 2006
4. Tack CJ, Lenders JW, Willemsen JJ, van Druten JA, Thien T, Lutterman JA, Smits P: Insulin stimulates epinephrine release under euglycemic conditions in humans. *Metabolism* 47:243–249, 1998
5. Tack CJ, Smits P, Willemsen JJ, Lenders JW, Thien T, Lutterman JA: Effects of insulin on vascular tone and sympathetic nervous system in NIDDM. *Diabetes* 45: 15–22, 1996
6. Meneilly GS, Elliott T, Battistini B, Floras JS: N^G-Monomethyl-L-arginine alters insulin-mediated calf blood flow but not glucose disposal in the elderly. *Metabolism* 50:306–310, 2001
7. Lipsitz LA, Pluchino FC, Wei JY, Rowe

JW: Syncope in institutionalized elderly: the impact of multiple pathological conditions and situational stress. *J Chronic Dis* 39:619–630, 1986
8. Ruiz GA, Calvar C, Hermes R, Rivadeneira D, Bengolea V, Chirife R, Tentori MC, Gelpi RJ: Insulin sensitivity in young women with vasovagal syncope. *Am Heart J* 145:834–840, 2003
9. Porcellati F, Fanelli C, Bottini P, Epifano L, Rambotti AM, Lalli C, Pampanelli S, Scionti L, Santeusanio F, Brunetti P, et al.: Mechanisms of arterial hypotension after therapeutic dose of subcutaneous insulin in diabetic autonomic neuropathy. *Diabetes* 42:1055–1064, 1993
10. Stratton JR, Cerqueira MD, Schwartz RS, Levy WC, Veith RC, Kahn SE, Abrass IB: Differences in cardiovascular responses to isoproterenol in relation to age and exercise training in healthy men. *Circulation* 86:504–512, 1992
11. Petrofsky JS, Besonis C, Rivera D, Schwab E, Lee S: Impairment in orthostatic tolerance during heat exposure in individuals with type I and type II diabetes. *Med Sci Monit* 11:CR153–CR159, 2005
12. Patel NP, Pugh ME, Goldberg S, Eiger G: Hyperinsulinemic euglycemia therapy for verapamil poisoning: a review. *Am J Crit Care* 16:498–503, 2007
13. Ziegler D, Laux G, Dannehl K, Spuler M, Muhlen H, Mayer P, Gries FA: Assessment of cardiovascular autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. *Diabet Med* 9:166–175, 1992
14. Meneilly GS: A comparison of insulin aspart and regular insulin in elderly patients with type 2 diabetes. *Diabetes Obes Metab* 9:754–755, 2007
15. McGuire EA, Helderman JH, Tobin JD, Andres R, Berman M: Effects of arterial versus venous sampling on analysis of glucose kinetics in man. *J Appl Physiol* 41: 565–573, 1976
16. Andres R, Swerdloff R, Pozefsky T, Coleman D: Manual feedback technique for control of glucose concentration. In *Automation in Analytic Chemistry*. Skeggs LT Jr, Ed. New York, Medaid, 1966, p. 486–501
17. Egan JM, Meneilly GS, Habener JF, Elahi D: Glucagon-like peptide-1 augments insulin-mediated glucose uptake in the obese state. *J Clin Endocrinol Metab* 87:3768–3773, 2002
18. Imholz BP, Wieling W, van Montfrans GA, Wesseling KH: Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovasc Res* 38:605–616, 1998
19. Rongen GA, Bos WJ, Lenders JW, van Montfrans GA, van Lier HJ, van Goudoever J, Wesseling KH, Thien T: Comparison of intrabrachial and finger blood pressure in healthy elderly volunteers. *Am J Hypertens* 8:237–248, 1995
20. Guelen I, Westerhof BE, Van Der Sar GL, Van Montfrans GA, Kiemeneij F, Wesseling KH, Bos WJ: Finometer, finger pressure measurements with the possibility to reconstruct brachial pressure. *Blood Press Monit* 8:27–30, 2003
21. Lipsitz LA, Mukai S, Hamner J, Gagnon M, Babikian V: Dynamic regulation of middle cerebral artery blood flow velocity in aging and hypertension. *Stroke* 31: 1897–1903, 2000
22. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ: Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 74: 2566–2573, 1993
23. Sollers JJ 3rd, Merritt MM, Silver RA, Sadle TN, Ferrucci L, Thayer JF: Comparison of arterial compliance indices derived via beat-to-beat blood pressure waveforms: aging and ethnicity. *Biomed Sci Instrum* 42:518–523, 2006
24. Dawson-Saunders B, Trapp RG: *Basic and clinical biostatistics*. Toronto, Prentice Hall of Canada, 1994
25. Lau DC, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E: 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *CMAJ* 176:S1–S13, 2007