

# Insulin-Induced Decreases in Aortic Wave Reflection and Central Systolic Pressure Are Impaired in Type 2 Diabetes

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**OBJECTIVE** — To determine whether large arteries are resistant to insulin.

**RESEARCH DESIGN AND METHODS** — Insulin normally acutely decreases central systolic pressure by decreasing wave reflection in vivo. This effect occurs before any changes in peripheral vascular resistance or heart rate under normoglycemic conditions. We determined whether the ability of insulin to decrease central aortic pressure is altered in uncomplicated type 2 diabetes. The study subjects consisted of 16 type 2 diabetic patients (age  $54 \pm 2$  years, BMI  $29 \pm 1$  kg/m<sup>2</sup>) and 19 matched nondiabetic individuals ( $51 \pm 2$  years,  $29 \pm 1$  kg/m<sup>2</sup>) studied under normoglycemic-hyperinsulinemic conditions. Central aortic pressure waveforms were synthesized from those recorded in the periphery using applanation tonometry and a validated reverse transfer function to construct the central aortic pressure waveform every 30 min. This method allowed determination of aortic augmentation (the pressure difference between the first and second central systolic pressure waves) and the augmentation index (augmentation divided by pulse pressure).

**RESULTS** — Whole-body insulin sensitivity was 31% lower ( $P < 0.05$ ) in the type 2 diabetic patients than in the normal subjects. Basally, before the insulin infusion, augmentation averaged  $8.9 \pm 1.3$  and  $11.1 \pm 1.2$  mmHg (NS) and the augmentation index averaged  $23.1 \pm 2.1$  and  $27.5 \pm 2.1\%$  (NS) in the normal subjects and diabetic patients, respectively. After 30 min of hyperinsulinemia, augmentation decreased significantly to  $6.1 \pm 1.1$  mmHg ( $P < 0.001$ ) in the normal subjects but remained unchanged at  $9.1 \pm 1.1$  mmHg (NS) in type 2 diabetic patients. At 30 min, the augmentation index had decreased significantly ( $30 \pm 7\%$  decrease) to  $17.9 \pm 2.6\%$  in the normal subjects but remained at  $24.4 \pm 2.4\%$  in the diabetic patients ( $13 \pm 4\%$  decrease,  $P < 0.05$  for change vs. normal subjects). Central systolic pressure decreased significantly by 30 min in the normal subjects but only after 120 min in the type 2 diabetic patients. There were no significant changes in heart rate, pulse pressure, or forearm blood flow during the first 120 min of the insulin infusion.

**CONCLUSIONS** — Insulin resistance in type 2 diabetes involves a delay in the ability of insulin to decrease central aortic pressure. This defect could predispose these patients to develop systolic hypertension.

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Patients with type 2 diabetes are at high risk of developing cardiovascular disease, which is inadequately explained by classic risk factors (1). Re-

garding hypertension, recent evidence from the Systolic Hypertension in the Elderly Program and the Framingham Heart Study have suggested that the pulsatile

component of the hemodynamic load of the heart is a better predictor of cardiovascular events than either systolic or diastolic pressure (2,3). In these trials, the pulsatile component was assessed from measurements of pulse pressure, a surrogate for arterial stiffening. With increasing stiffness, pulse wave velocity increases, causing an early return of pressure waves from reflectance sites. An increase in the tone of small muscular arteries, which may occur independent of changes in peripheral vascular resistance, has a similar effect (4) and will increase or augment central systolic pressure and the afterload of the left ventricle and decrease diastolic pressure and coronary blood flow (5). Recently, the augmentation index was shown to increase the risk of cardiovascular death in patients with end-stage renal failure 18.4-fold, independent of aortic stiffness as measured by pulse wave velocity, age, and diastolic blood pressure (6). The degree of augmentation of the central systolic pressure wave can be recorded noninvasively using applanation tonometry of the radial artery, a validated transfer function, and pulse wave analysis (7).

Type 2 diabetic patients appear to have stiffer arteries than age-, sex-, and weight-matched nondiabetic subjects, as determined by pulse wave analysis (8), pulse wave velocity (9,10), the ratio of pulse pressure to stroke volume (11), or the stiffness index  $\beta$  (12). In cross-sectional studies, insulin sensitivity, as measured using the euglycemic clamp technique (13,14) or by determining fasting insulin concentrations (15), has been found to correlate with stiffness indexes (12,13,15) or changes in stiffness indexes by insulin (14). In the Atherosclerosis Risk in Communities Study, the association between fasting insulin and arterial stiffness was independent of other risk factors including age, smoking status, BMI, total cholesterol, triglycerides, HDL cholesterol, and hypertension (15). We have recently shown that insulin acutely

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

Table 1—Characteristics of the study groups

	Normal subjects	Type 2 diabetic patients
M/F	13/6	12/4
Age (years)	51 ± 2	54 ± 2
Weight (kg)	87 ± 3	88 ± 4
Height (cm)	174 ± 2	174 ± 2
BMI (kg/m <sup>2</sup> )	28.9 ± 0.9	29.1 ± 1.1
Body fat (%)	28 ± 2	28 ± 1
Systolic blood pressure (mmHg)	125 ± 4	129 ± 4
Diastolic blood pressure (mmHg)	80 ± 2	79 ± 2
Waist-to-hip ratio	0.95 ± 0.02	1.00 ± 0.02
Smoking (+/−)	4/15	4/12
Fasting plasma glucose (mmol/l)	5.7 ± 0.1	11.6 ± 0.7*
Fasting serum-free insulin (mU/l)	11 ± 2	11 ± 2
Fasting serum C-peptide (nmol/l)	0.8 ± 0.1	1.1 ± 0.2
HbA <sub>1c</sub> (%)	5.7 ± 0.1	8.3 ± 0.2*
Serum cholesterol (mmol/l)	4.8 ± 0.2	5.2 ± 0.3
Serum HDL cholesterol (mmol/l)	1.3 ± 0.1	1.1 ± 0.1
Serum triglycerides (mmol/l)	1.2 ± 0.1	1.8 ± 0.2†
Serum creatinine (μmol/l)	85 ± 3	83 ± 2
Urinary albumin excretion rate (μg/min)	10 ± 2	9 ± 3
Duration of diabetes (years)	—	7 ± 1

Data are means ± SE unless otherwise indicated. \* $P < 0.001$ ; † $P < 0.001$  for type 2 diabetic patients vs. normal subjects.

delays wave reflection and thereby moves the reflected pressure wave toward diastole in normal subjects (16). This effect precedes any vasodilatory effect of insulin in peripheral resistance vessels (17). In subsequent studies, this action of insulin was shown to be blunted in obese insulin-resistant subjects and in insulin-resistant type 1 diabetic patients (17,18). Therefore, we wished to determine whether a similar defect in the ability of insulin to acutely diminish wave reflection characterizes patients with type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Subjects

A total of 16 type 2 diabetic patients and 19 nondiabetic subjects participated in the study. Physical and biochemical characteristics of the study groups are shown in Table 1. Except for diabetes, all participants were healthy, as judged by history and physical examination, an electrocardiogram, and routine laboratory tests (creatinine, liver enzymes, complete blood count, and urinalysis). Subjects with hypertension or cardiovascular disease (determined by an electrocardiogram and history and physical examination)

were excluded from the study. Other major systemic diseases were excluded by laboratory tests and by history and physical examination. The diabetic patients were recruited from diabetes outpatient clinics in the Helsinki area and had to meet, in addition to the above criteria, the following criteria: 1) age 40–70 years, 2) treatment with sulfonylurea alone or in combination with metformin, 3) no active retinopathy requiring laser treatment, and 4) no history of ketoacidosis. Written informed consent was obtained after the purpose, nature, and potential risks had been explained to the subjects. The experimental protocol was approved by the Ethical Committee of the Department of Medicine, Helsinki University Central Hospital.

### Study protocol

Insulin action on glucose uptake, limb blood flow, and arterial stiffness were determined under normoglycemic-hyperinsulinemic conditions using the euglycemic insulin clamp technique (insulin infusion rate, 2 mU · kg<sup>-1</sup> · min<sup>-1</sup>) (19). The insulin clamp was performed after an overnight fast starting at 8:00 A.M. as previously described (20). The subjects were advised not to take any medication

the previous evening or in the morning of the study. Before and during the insulin infusions, metabolic and hemodynamic measurements (recording of the pulse wave, heart rate, blood flow, and vascular resistance) were performed at 30-min intervals as detailed below. We did not perform a time control study because we have previously shown that the measured parameters remain unchanged during a 6-h saline infusion (16).

### Pulse wave analysis

The technique of pulse wave analysis was used to determine central aortic pressure and the augmentation index as previously described in detail (7,16). All measurements were made from the radial artery by applanation tonometry using a Millar tonometer (SPC-301; Millar Instruments, Houston, TX) basally and every 30 min during the insulin infusions. Data were collected directly into a desktop computer and processed with the Sphygmo-Cor Blood Pressure Analysis System (BPAS-1; PWV Medical, Sydney, Australia), which allows continuous online recording of the radial artery pressure waveform. The integral system software was used to calculate an average radial artery waveform and to generate the corresponding ascending aortic pressure waveform using a transfer factor (21,22). Wave transmission properties in the upper limbs (in contrast to the descending aorta and lower limbs) change little with age, disease, and drug therapy in adults (23). The transfer factor has been validated recently for the present device by comparing the derived augmentation index to that measured simultaneously invasively by recording central pressure in 62 patients undergoing coronary bypass surgery (24). The aortic waveform was then subjected to further analysis for calculation of aortic augmentation (the pressure difference between the second and first systolic pressure peaks), the augmentation index, and central blood pressure. The augmentation index was calculated by dividing augmentation with pulse pressure (7,25).

### Forearm blood flow and peripheral vascular resistance

Forearm blood flow was measured every 30 min with venous occlusion plethysmography (Model EC-4; Hokanson, Bellevue, WA), a rapid cuff inflator (Rapid Cuff Inflator model E20; Hokanson), and

computerized analysis of flow curves (MacLab/4e; AD Instruments, Castle Hill, Australia), as previously described (20). Peripheral vascular resistance was calculated by dividing mean arterial pressure in the brachial artery by forearm blood flow.

### Other measurements

Fat-free mass and the percent of body fat were determined using bioelectrical impedance analysis (BioElectrical Impedance Analyzer System model BIA-101A; RJL Systems, Detroit, MI). Serum-free insulin concentrations were measured before and at 30-min intervals during the insulin infusion by double-antibody radioimmunoassay (Pharmacia Insulin RIA kit; Pharmacia, Uppsala, Sweden) after precipitation with polyethylene glycol. Plasma glucose concentrations were measured in duplicate using the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). HbA<sub>1c</sub> was measured by high-performance liquid chromatography using a fully automated Glycosylated Hemoglobin Analyzer System (BioRad, Richmond, CA).

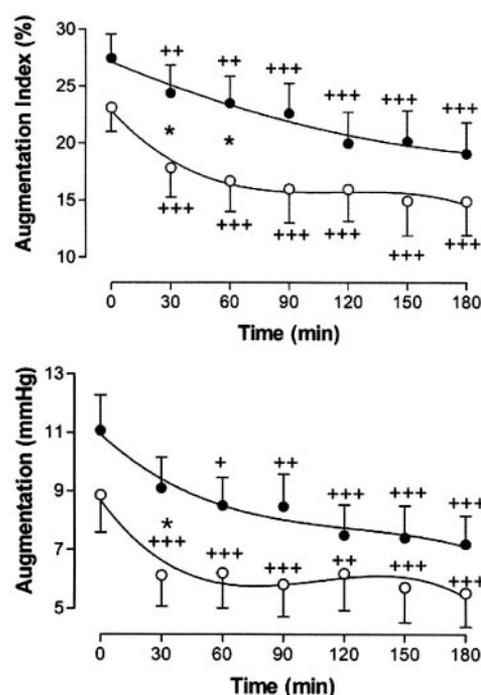
### Statistical analysis

Analysis of group, time, and group times time effects between normal subjects and type 2 diabetic patients was made using ANOVA for repeated measures. Correlation analyses were performed using Spearman's nonparametric correlation coefficient. The best fit characterizing the relationship between hemodynamic parameters over time was determined by comparing the goodness of fit of linear and multiple nonlinear equations using GraphPad Prism v. 2.01 (GraphPad Software, San Diego, CA). The results are expressed as means  $\pm$  SE. *P* values  $< 0.05$  were considered statistically significant.

## RESULTS

### Glucose and insulin concentrations and insulin sensitivity

Fasting plasma glucose and serum-free insulin concentrations are given in Table 1. During the insulin infusions, serum-free insulin concentrations averaged  $170 \pm 7$  mU/l in the normal subjects and  $167 \pm 7$  mU/l in the patients with type 2 diabetes (NS). During the last hour of hyperinsulinemia, plasma glucose averaged  $5.1 \pm 0.1$  mmol/l in the normal subjects and  $5.3 \pm 0.1$  mmol/l in the patients with type 2 diabetes (NS). Whole-body insulin



**Figure 1**—The augmentation index and augmentation during 180 min of hyperinsulinemia.  $\circ$ , Normal subjects;  $\bullet$ , type 2 diabetic patients. \**P*  $< 0.05$  for the difference of change in the augmentation index or augmentation between the groups. +*P*  $< 0.05$ , ++*P*  $< 0.01$ , +++*P*  $< 0.001$  for change vs. 0 min.

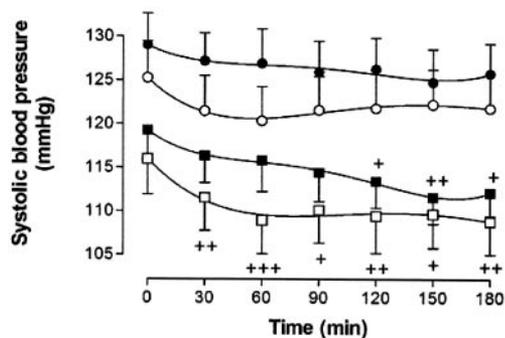
sensitivity of glucose metabolism (*M* value 150–180 min) was 31% lower in patients with type 2 diabetes ( $4.8 \pm 0.6$  mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>) than in the normal subjects ( $7.0 \pm 0.6$  mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>, *P*  $< 0.05$ ).

### Augmentation and the augmentation index

Augmentation averaged  $8.9 \pm 1.3$  mmHg at baseline in the normal subjects and decreased significantly within 30 min to  $6.1 \pm 1.1$  mmHg (*P*  $< 0.001$  vs. basal), and after 180 min, it decreased to  $5.5 \pm 1.2$  mmHg (*P*  $< 0.001$  vs. basal). The augmentation index averaged  $23.1 \pm 2.1\%$  at 0 min and decreased significantly (by 30%) after 30 min to  $17.9 \pm 2.6\%$  (*P*  $< 0.001$  vs. basal) and after 180 min to  $14.9 \pm 3.0\%$  (Fig. 1). The decrease during the first hour also could not be attributed to a decrease in peripheral vascular resistance because both forearm blood flow ( $1.8 \pm 0.2$  vs.  $1.7 \pm 0.1$  ml  $\cdot$  dl<sup>-1</sup>  $\cdot$  min<sup>-1</sup>, 0 vs. 60 min, NS) and peripheral vascular resistance ( $64 \pm 7$  vs.  $54 \pm 4$  mmHg  $\cdot$  ml<sup>-1</sup>  $\cdot$  dl<sup>-1</sup>  $\cdot$  min<sup>-1</sup>, respectively; NS) remained unchanged.

Basally, before the insulin infusion, augmentation and the augmentation index were comparable between type 2 diabetic patients and normal subjects. In contrast to the normal subjects, however, augmentation did not decrease signifi-

cantly after insulin administration in the diabetic patients during the first 30 min. Mean augmentation averaged  $11.1 \pm 1.2$  mmHg basally and  $9.1 \pm 1.1$  mmHg after 30 min (NS vs. basal) (Fig. 1). The first significant decrease in augmentation was observed at 60 min in the patients with type 2 diabetes ( $8.5 \pm 1.0$  mmHg) (*P*  $< 0.05$  vs. basal). Minimum augmentation was reached after 180 min of insulin infusion, when it averaged  $7.2 \pm 1.0$  mmHg (*P*  $< 0.001$  vs. basal) (Fig. 1). The percent change in augmentation was significantly smaller in the patients with type 2 diabetes than in the normal subjects at 30 min ( $-17 \pm 6$  vs.  $-36 \pm 7\%$ , *P*  $< 0.05$ ). Basally, the augmentation index averaged  $27.5 \pm 2.1\%$  in the diabetic patients. The augmentation index decreased to  $24.4 \pm 2.2\%$  at 30 min (*P*  $< 0.01$  vs. basal) and reached a minimum of  $19.1 \pm 2.7\%$  at 180 min (*P*  $< 0.001$  vs. basal). There was a significantly smaller percent change in the augmentation index in the diabetic patients than in normal subjects at 30 min ( $-13 \pm 4$  vs.  $-30 \pm 7\%$ , *P*  $< 0.05$ ) and at 60 min ( $-16 \pm 5$  vs.  $-39 \pm 9\%$ , *P*  $< 0.05$ ). The decrease was significantly lower in the diabetic group than in the nondiabetic group (*P*  $< 0.05$  for group effect) after ANOVA for repeated measures, with the change of the augmentation index as the dependent variable and basal augmentation index as a covariate.



**Figure 2**—Peripheral (○, ●) and aortic (□, ■) systolic blood pressure in normal subjects (○, □) and type 2 diabetic patients (●, ■). +P < 0.05, ++P < 0.01, +++P < 0.001 for change vs. 0 min.

There were no significant correlations between insulin sensitivity and augmentation or the augmentation index or their changes by insulin in either group.

### Central and peripheral systolic blood pressure

As expected from the change in augmentation and the augmentation index (Fig. 1), systolic aortic blood pressure decreased significantly in the normal subjects by 30 min, whereas there was no significant change in systolic aortic blood pressure at this time point in the type 2 diabetic patients (Fig. 2). Aortic systolic blood pressure remained significantly lower than that at baseline for the entire period of hyperinsulinemia in the normal subjects (Fig. 2). In the type 2 diabetic patients, a significant decrease in aortic systolic blood pressure was not observed until 120 min of hyperinsulinemia (Fig. 2). Brachial systolic pressure did not change significantly in either group (Fig. 2).

### Other hemodynamic parameters

Heart rate remained unchanged in both groups during the 180-min period of insulin infusion (data not shown). A small (21%) increase in peripheral blood flow was observed at 180 min in the normal subjects ( $1.8 \pm 0.2$  vs.  $2.2 \pm 0.2$  ml · dl<sup>-1</sup> · min<sup>-1</sup>,  $P < 0.05$ ), and this increase was associated with a significant decrease in brachial artery diastolic pressure at 150 min ( $-2.7 \pm 1.0$  mmHg,  $P < 0.05$ ) and 180 min ( $-3.7 \pm 0.9$  mmHg,  $P < 0.01$ ) compared with basal diastolic pressure ( $80 \pm 2$  mmHg). Forearm blood flow and diastolic pressure remained unchanged in the type 2 diabetic patients (data not shown).

**CONCLUSIONS**— In the present study, we determined whether insulin re-

sistance in type 2 diabetes involves a defect in the action of insulin to diminish wave reflection and central blood pressure. We found the type 2 diabetic patients to be resistant not only to the action of insulin to stimulate glucose uptake but also to its ability to decrease central aortic pressure augmentation and the augmentation index. The decrease in pressure wave reflection in the normal subjects was accompanied by a significant and rapid decrease in aortic systolic blood pressure. The ability of insulin to decrease wave reflection and the augmentation index was delayed in the type 2 diabetic patients and therefore could have contributed to the lack of decrease in aortic systolic blood pressure by insulin in this group.

The basal augmentation index was also higher in the type 2 diabetic patients than in the normal subjects, although this difference did not reach statistical significance. The decrease in the augmentation index by insulin was, however, significantly blunted in type 2 diabetic patients, even when adjusted for the higher basal augmentation index. Nevertheless, although the change in the augmentation index by insulin remained significantly different after adjusting for the basal augmentation index, it could have contributed to the observed difference between the two groups. One may argue that the remaining transient defect that was observed at a supraphysiological insulin concentration (insulin infusion rate,  $2$  mU · kg<sup>-1</sup> · min<sup>-1</sup>) is of questionable physiological significance. While this may be true, this hemodynamic defect in insulin action is no less impressive than the defect in insulin stimulation of peripheral blood flow, when first described in type 2 diabetes (26). In the latter study, the insulin doses ( $3$ – $30$  mU · kg<sup>-1</sup> · min<sup>-1</sup>) were higher, and the duration of

insulin infusions (6 h) was even longer than in the present study.

The augmentation index depends, at least in part, on pulse wave velocity in the aorta and large arteries because an increase in pulse wave velocity results in earlier return of the reflected wave, which will increase left ventricular afterload and decrease diastolic filling, provided the pressure of the reflected wave exceeds that of the first wave (4,23,27). The augmentation index can, however, also be altered independent of aortic pulse wave velocity by vasoactive drugs such as nitroglycerin (4,28). Low doses of nitroglycerin decrease wave reflection and diminish left ventricular load independent of changes in peripheral vascular resistance and aortic compliance (28). The decrease in wave reflection by nitroglycerin has therefore been attributed to a change in the tone of muscular conduit arteries rather than to changes in elastic properties of the aorta. In the present study, peripheral vascular resistance and heart rate remained unchanged during the time period when the changes in augmentation occurred (Fig. 1). Aortic pulse wave velocity was not measured. The decrease in wave reflection by insulin in the normal subjects could thus have been due to an acute decrease in the tone of muscular arteries greater than those controlling peripheral vascular resistance or to a change in elastic properties of the aorta, although given the rapid time course, this possibility seems unlikely. Analogously, the delayed effect of insulin on wave reflection in the type 2 diabetic patients could have been due to failure of insulin to acutely decrease the tone of muscular arteries or to alter elastic properties of the aorta. Regardless of the vascular location of the defect in the insulin-induced decrease in aortic augmentation, it appears to be harmful because the augmentation index predicts cardiovascular death even better and independent of aortic pulse wave velocity (6).

There was no change in peripheral blood flow in the type 2 diabetic patients, whereas a small increase was observed in the normal subjects at 180 min. These data are in keeping with previous studies, where defects in insulin stimulation of peripheral blood flow have not been found in type 2 diabetic patients at physiological insulin concentrations, whereas defects were found in one study that used supraphysiological insulin concentrations and

where the insulin infusions lasted at least 400 min (29). The present data showing that insulin decreases wave reflection and central systolic blood pressure before inducing any vasodilatation in the periphery in type 2 diabetic patients are consistent with our previous data. In these studies, defects in insulin-induced decreases in wave reflection but not in peripheral blood flow were observed 30–60 min after the start of an insulin infusion, which increased serum insulin concentrations to a physiological range (61–69 mU/l) in young obese (17) and type 1 diabetic (18) insulin-resistant subjects. In the present study, insulin sensitivity of glucose metabolism within the group of type 2 diabetic patients was not correlated with insulin action on the augmentation index, although we have found such a relationship in previous studies in both nondiabetic men (14) and a group of obese subjects (17). The previously studied nondiabetic group included a total of 50 men with BMIs ranging from 19 to 45 kg/m<sup>2</sup> and age from 18 to 60 years (14) and a larger variation in basal augmentation index, its change by insulin, and insulin action on glucose metabolism than in the present study. Compared with the study comparing obese and nonobese age- and sex-matched subjects with respect to insulin action on glucose metabolism and the augmentation index (17), the differences between the present BMI-, age-, and sex-matched groups were smaller. This result implies that obesity may be a stronger determinant of insulin action on the augmentation index than type 2 diabetes, i.e., hyperglycemia. As before (14,16,17) and in contrast to large-scale epidemiological studies (15), we did not find insulin sensitivity to correlate with the basal augmentation index.

The mechanism underlying insulin-induced decreases in augmentation and the augmentation index is unknown. In resistance arteries, insulin-induced vasodilatation in vivo can be abolished by coinfusion of N<sup>G</sup>-monomethyl-L-arginine but not by other vasoconstrictors, such as norepinephrine (29). Insulin has also been shown to potentiate acetylcholine but not sodium nitroprusside-induced vasodilatation in human resistance arteries in vivo (30). In contrast to the latter data, acute hyperinsulinemia was recently suggested to decrease rather than enhance the ability of shear-stress but not glyceryl trinitrate to induce vasodilatation of bra-

chial and femoral arteries (31), i.e., arterial beds that are possible sites of wave reflection and insulin action. Therefore, hypothetically, chronic hyperinsulinemia, which precedes type 2 diabetes by years, could have contributed to the blunted effect of insulin to diminish the augmentation index in the type 2 diabetic patients. Consistent with the idea that endothelium-dependent rather than endothelium-independent vasodilatation of conduit arteries is blunted in type 2 diabetic patients, photoplethysmographic assessment of pulse wave reflection has revealed impaired endothelium-dependent  $\beta_2$ -adrenergic vasodilatation (a process that is in part nitric oxide dependent) (32) in patients with type 2 diabetes. Photoplethysmographic assessment of pulse wave reflection showed a normal response to glyceryl trinitrate in patients with type 2 diabetes (32). These data imply that the defect found in the present study is perhaps more likely to be due to impaired endothelial than smooth muscle function, but separate mechanistic studies are needed to resolve this issue.

In diabetic and nondiabetic patients with hypertension, both diastolic and systolic blood pressure are often elevated, although recent data from the Framingham Heart Study and the Third National Health and Nutrition Examination Survey show that two-thirds of hypertensive subjects actually have systolic hypertension (33–35). The present data demonstrating that the ability of insulin to decrease aortic systolic pressure is blunted in type 2 diabetic patients cannot explain why diastolic pressure is increased but provides one potential link between insulin resistance and systolic hypertension. The data obviously do not exclude the possibility that insulin resistance affects blood pressure via other mechanisms, such as via excessive activation of the sympathetic nervous system (36,37).

To conclude, insulin resistance in patients with clinically uncomplicated type 2 diabetes extends to arteries larger than those controlling peripheral vascular resistance and is characterized by failure of insulin to normally decrease wave reflection and central systolic pressure. Given that two-thirds of all individuals with hypertension suffer from systolic hypertension (33,35,38), it is possible that the defect in insulin action on wave reflection could provide one mechanism that con-

tributes to systolic hypertension in insulin-resistant type 2 diabetic patients.

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