Marked Resistance of the Ability of Insulin to Decrease Arterial Stiffness Characterizes Human Obesity

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We tested the hypothesis that insulin has effects on large artery stiffness in addition to its slow vasodilatory effect on resistance vessels in skeletal muscle, and whether such an effect might be altered in obesity. Eight nonobese (aged 25 ± 1 years, BMI 22.7 ± 0.4 kg/m^2) and eight obese (aged 27 ± 2 years, BMI 30.6 ± 0.9 kg/m^2) men were studied under normoglycemic-hyperinsulinemic (sequential 2-h insulin infusions of 1 [step 1] and 2 [step 2] mU · kg^{-1} · min^{-1}) conditions, and another seven men participated in a saline control study. Central aortic pressure waves were synthesized from those recorded in the periphery using applanation tonometry and a validated reverse transfer function every 30 min. This allowed determination of augmentation (the pressure difference between early and late systolic pressure peaks) and the augmentation index (augmentation divided by pulse pressure), a measure of arterial stiffness. Whole-body glucose uptake was reduced by 48 (step 1) and 41% (step 2) (P < 0.01) in the obese subjects versus the nonobese subjects. Basal forearm blood flow averaged 2.5 ± 0.2 and 2.6 ± 0.2 ml · dl^{-1} · min^{-1} in the obese and nonobese subjects, respectively (NS). Insulin induced a significant increase in forearm blood flow after 2.5 h (3.6 ± 0.4 ml · dl^{-1} · min^{-1}, P < 0.05 vs. basal) in the nonobese subjects and after 4 h in the obese subjects (3.2 ± 0.2, P < 0.05). In contrast to these slow changes in peripheral blood flow, augmentation and the augmentation index decreased significantly in the nonobese subjects after 1 h (–3.0 ± 1.6 mmHg and –10.0 ± 5.4%, respectively, P < 0.001 vs. basal), but remained unchanged until 3 h in the obese subjects. Percent fat (r = 0.86, P < 0.0001) and whole-body glucose uptake (r = –0.72, P < 0.01) correlated with the change in the augmentation index by insulin. These data demonstrate temporal dissociation in insulin's vascular actions. Insulin's effect to decrease arterial stiffness in nonobese subjects (a decrease in wave reflection) is observed under physiological conditions and precedes a slow vasodilatory effect in the periphery. In the obese subjects, insulin's normal effect to decrease central wave reflection is severely blunted. The degree of impairment in this novel vascular action of insulin is closely correlated with the degree of obesity and insulin action on glucose uptake. ***Diabetes*** **48:821–827, 1999**

Different parts of the arterial tree have distinct hemodynamic functions. Terminal arteries and arterioles control peripheral vascular resistance and blood flow, while conduit vessels serve as a pressure-buffering and blood-carrying system (1). Insulin is known to decrease peripheral vascular resistance by increasing blood flow in skeletal muscle (2). However, this action of insulin has a slow time course and requires prolonged exposure of tissues to insulin (3). Its physiological significance has therefore been questioned (3).

Insulin's vasodilatory effect on peripheral resistance vessels appears to be mediated via insulin stimulation of endothelial cell nitric oxide (NO) synthesis (4,5). The function of conduit arteries is also NO-dependent (6), and can be regulated independent of peripheral blood flow and vascular resistance. For example, agents such as nitroglycerin decrease stiffness of conduit arteries without affecting peripheral blood flow or vascular resistance (7). Changes in arterial stiffness cause profound changes in the arterial pulse waveform, which reflects pressure changes in arteries during the cardiac cycle (Fig. 1). The second systolic peak of the pressure wave is caused by reflection of the initial systolic pressure wave back from the lower body (8). Decreases in both stiffness and peripheral vascular resistance delay return of the reflected wave. This will decrease the contribution of the reflected wave to central systolic pressure and increase its contribution to diastolic pressure. Such a change is advantageous because it increases coronary perfusion and decreases central systolic pressure in individuals with stiff arteries (9).

In the present study, we examined *1*) whether insulin has effects on large artery function, in addition to or independent of its effects on resistance vessels in normal subjects; *2*) whether the time course of insulin's effects on large artery function differ from its effect on peripheral vascular resistance; and *3*) whether such an action of insulin is altered in obesity, a condition characterized by insulin resistance and impaired NO-mediated vasodilatation (10,11). For this purpose, we used the technique of pulse wave analysis, which allows noninvasive measurement of central pressure and the central aortic wave-

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AV-difference, difference between arterialized and deep venous blood.

form (12). The analysis involves use of the principle of applanation tonometry to accurately record peripheral arterial waveforms and use of a validated integral transfer function to determine aortic pressure and the aortic waveform, augmentation (the pressure difference between the first and second systolic pressure peaks), and the augmentation index (augmentation divided by pulse pressure) (12).

RESEARCH DESIGN AND METHODS

Subjects. A total of 23 men were studied. Of these, eight nonobese and eight obese men participated in studies addressing insulin's vascular effects (Table 1), while another group of seven nonobese men participated in a saline control study (vide infra). The subjects were healthy as judged by medical history and physical examination, electrocardiogram, and routine laboratory tests. Their fasting plasma glucose and glycosylated HbA_{1c} concentrations were in the normal range (Table 1). The subjects were not taking any medications. For 2 days before the studies, the subjects consumed a weight-maintaining diet containing at least 200 g of carbohydrate per day. Written informed consent was obtained after the purpose, nature, and potential risks of the study 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 protocols. Insulin's actions on glucose uptake and blood vessel function were determined under normoglycemic hyperinsulinemic conditions, which were created using the insulin clamp technique (13). Each study consisted of two sequential 2-h insulin infusions at rates of 1 (step 1) and 2 (step 2) $mU \cdot kg^{-1} \cdot min^{-1}$. The insulin clamp study was performed after an overnight fast, starting at 7:30 A.M. Three 18-gauge catheters (Venflon; Viggo-Spectramed, Helsingborg, Sweden) were inserted as previously described (14). Insulin and glucose were infused in a catheter inserted in the left antecubital vein. The left hand was kept in a heated chamber (65°C), and arterialized venous blood was withdrawn from a heated dorsal hand vein. The third catheter was inserted retrogradely into a median antecubital vein for measurement of glucose concentrations in venous blood–draining forearm muscles (14). Before and during the insulin infusions, metabolic and hemodynamic measurements (pulse wave analysis, heart rate, forearm glucose extraction, blood flow, and vascular resistance) were performed at 30-min intervals as detailed below. A control study was also performed in seven normal men (aged 25 ± 1 years, BMI 23.1 ± 0.5 kg/m^2), in whom pulse wave analysis and measurements of forearm blood flow, heart rate, and blood pressure were performed for 4 h during infusion of saline instead of glucose and insulin.

Pulse wave analysis. The technique of pulse wave analysis was used to determine central aortic pressure and the augmentation index (12). All measurements were made from the radial artery, with the wrist slightly extended and supported on a pillow, by applanation tonometry using a Millar tonometer (SPC-301; Millar Instruments, Houston, TX). Data were collected directly into a desktop computer and processed with recently developed software (SphygmoCor Blood Pressure Analysis System BPAS-1; PWV Medical, Sydney, Australia), which allows continuous on-line recording of the radial artery pressure waveform. The radial waveform was assessed visually to ensure that artifacts from movement and respiration were minimized. Pulse wave analysis were made twice basally, with a 30 min interval, and every 30 min during insulin infusions. The mean of three measurements, each consisting of 15–20 sequentially recorded radial artery waveforms, was used to calculate augmentation (the difference between the second and first systolic pressure peaks) and other parameters at the given time point. The integral system software was used to calculate an average radial artery waveform and to generate the corresponding ascending aortic pressure waveform using a previously validated transfer factor (Fig. 1) (12,15,16). The aortic waveform was then subject to further analysis for calculation of augmentation, the augmentation index, and central blood pressure. The augmentation index is calculated by dividing augmentation by pulse pressure (Fig. 1) (12,17,18). As suggested by O'Rourke and Gallagher (12), the radial blood pressure was calibrated against the sphygmomanometrically determined brachial pressure, ignoring the small degree of amplification between the brachial and radial sites.

Forearm blood flow, glucose extraction, and peripheral vascular resistance. Forearm blood flow was measured every 30 min with venous occlusion plethysmography using a mercury in silastic rubber strain-gauge apparatus (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) (14). Peripheral vascular resistance was calculated by dividing mean arterial pressure in the brachial artery by blood flow. Glucose extraction was calculated from the glucose concentration difference between arterialized and deep venous blood (glucose AV-difference).

Other measurements. Fat free mass and the percentage of body fat were determined using bioelectrical impedance analysis (BioElectrical Impedance Analyzer System model #BIA-101A; RJL Systems, Detroit, MI) (19). Serum free insulin was measured before and at 30-min intervals during the insulin infusions. Serum free insulin was determined by double antibody radioimmunoassay (Pharmacia Insulin RIA kit; Pharmacia, Uppsala, Sweden) after precipitation with polyethylene glycol (20). The plasma glucose concentration was measured in duplicate by the glucose oxidase method (21), using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). HbA_{1c} was measured by high-performance liquid chromatography, using a fully automated Glycosylated Hemoglobin Analyzer System (BioRad, Richmond, CA).

Statistical analysis. Statistical comparisons between nonobese and obese subjects were made using analysis for repeated measures followed by the Bonferroni's test. 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 ± SE. P values <0.05 were considered to be statistically significant. Reproducibility of augmentation and augmentation index cannot be directly assessed using the coefficient of variation, since the mean of both parameters oscillates around zero. We, therefore, calculated the coefficient of variation, as suggested by Hayward et al. (22), from augmentation values defined as the ratio of the pressure at the second systolic peak to the pressure at the first systolic peak because this definition gives a continuous positive value (22). Bland-Altman plots were used to assess the dependence of reproducibility on the mean (23).

RESULTS

Glucose and insulin concentrations and glucose uptake. Fasting plasma glucose and serum free insulin concentrations are given in Table 1. During the insulin infusions, serum free insulin concentrations averaged 62 ± 3 (step 1) and 134 ± 5 (step 2) mU/l in the nonobese subjects, and 69 ± 5 (step 1) and 157 ± 13 (step 2) mU/l in the obese subjects (NS for nonobese vs. obese). Plasma glucose averaged 5.2 ± 0.1 (step 1) and 5.2 ± 0.1 (step 2) mmol/l in the nonobese subjects and 5.1 ± 0.1 (step 1) and 5.0 ± 0.1 (step 2) mmol/l in the obese subjects (NS). Whole-body glucose uptake was 48% lower during step 1 (3.7 ± 0.6 vs. 7.1 ± 0.6 $mg \cdot kg^{-1} \cdot min^{-1}$, $P < 0.01$ for obese vs. nonobese) and 41% lower during step 2 (7.4 ± 0.9 vs. 12.5 ± 1.1, $P < 0.01$) in the obese subjects than the nonobese subjects. The decrease in whole-body glucose uptake was paralleled by a comparable and temporarily similar defect in forearm glucose uptake (Fig. 2). During the first step, i.e., during the 1 $mU \cdot kg^{-1} \cdot min^{-1}$ insulin infusion, the decrease in insulin-stimulated glucose uptake could be attributed to a decrease in glucose extraction (AV-difference) (Fig. 2), since during the first 2 h, forearm blood flow (Fig. 3) and peripheral vascular resistance (Table 2) were comparable between the groups.

Augmentation and the augmentation index. Pulse wave analysis showed that augmentation, i.e., the pressure difference between the second and first systolic pressure peaks, decreased significantly during the first hour (Fig. 3) in the nonobese subjects. Mean augmentation averaged –0.5 ± 1.2 mmHg basally, –3.3 ± 1.2 mmHg during step 1 ($P < 0.001$ vs. basal), and –4.8 ± 1.2 mmHg during step 2 ($P < 0.001$ vs. basal; NS vs. step 1) in the nonobese subjects. This decrease during step 1 could not be attributed to a decrease in peripheral vascular resistance, since both forearm blood flow (Fig. 3), mean arterial pressure, and peripheral vascular resistance remained unchanged (Table 2). The augmentation index, i.e., the ratio between augmentation and pulse pressure, was also already significantly decreased at 1 h (Fig. 3). The augmentation index averaged –2.4 ± 3.9% basally, –11.1 ± 4.3% during step 1 ($P < 0.001$ vs. basal), and –13.1 ± 3.4% during step 2 ($P < 0.001$ vs. basal; NS vs. step 1) (Fig. 3).

In the obese subjects, in contrast to the nonobese subjects, augmentation did not decrease with insulin during the first hour (Fig. 3). A significant decrease in augmentation was not observed until after 3 h (Fig. 3). As in the nonobese

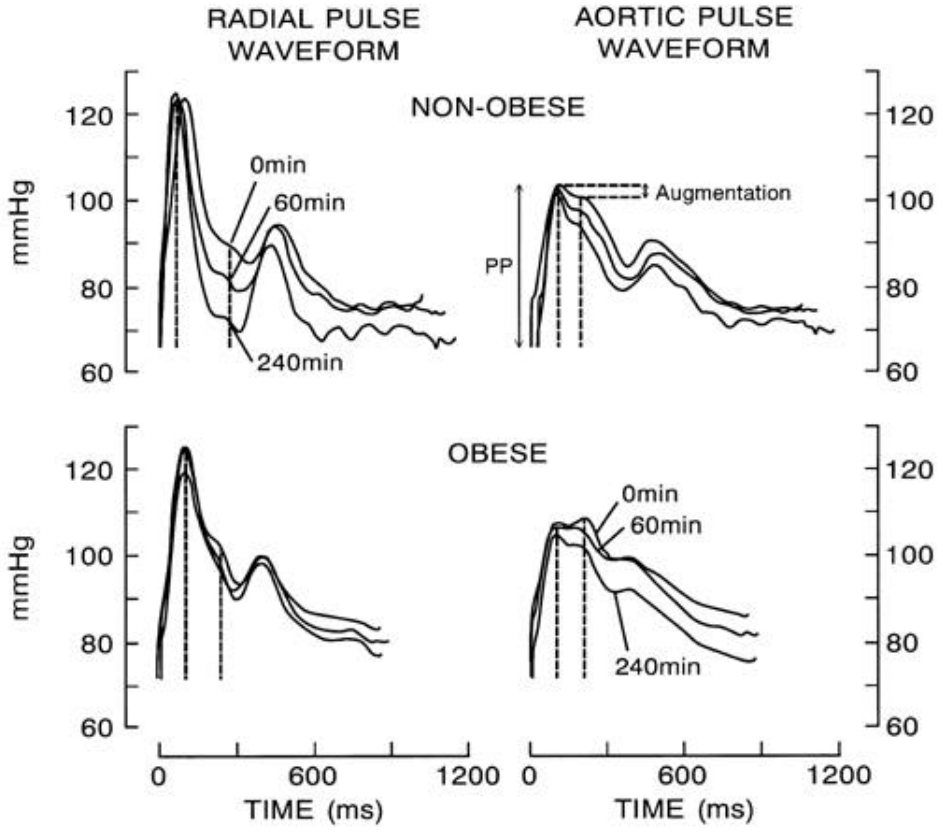

FIG.1. Examples of the effect of insulin on radial and aortic pressure waveforms in nonobese and obese subjects at various time points, as measured using applanation tonometry and pulse wave analysis. The pressure measurements were performed from the radial artery. The aortic waveform was generated using a validated transfer factor (12,15,16). The aortic waveform was then subjected to further analysis for calculation of augmentation, the augmentation index, and central blood pressure. The augmentation index is calculated by dividing augmentation by pulse pressure (PP).

subjects, blood flow, pulse pressure (Fig. 3), mean arterial pressure, and peripheral vascular resistance (Table 2) remained unchanged during step 1. Mean augmentation averaged 2.5 ± 0.8 mmHg basally, 2.1 ± 0.7 mmHg during step 1 (NS vs. basal in the obese subjects), and 1.5 ± 1.0 mmHg during step 2 ($P < 0.05$ vs. basal; NS vs. step 1). The augmentation index averaged 7.1 ± 1.8% basally, 6.1 ± 2.1% during step 1 (NS vs. basal), and 3.4 ± 2.6% during step 2 ($P < 0.05$ vs. basal; NS vs. step 1). The first significant decrease in the augmentation index was detected after 3 h (3.5 ± 2.4%, $P < 0.05$ vs. basal) in the obese subjects (Fig. 3). The changes in augmentation and augmentation index were significantly different between the nonobese and obese subjects from 1 h onward (Fig. 3). Percent fat ($r = 0.86$, $P < 0.0001$) and whole-body glucose uptake ($r = –0.72$, $P < 0.01$) were significantly correlated with the change in the augmentation index by insulin during step 1 (Fig. 4). Both augmentation and the augmentation index remained unchanged during the saline control study (data not shown). The coefficient of variation of the augmentation index averaged 5 ± 1% during the saline control study. The individual mean augmentations ranged from –6.3 to 6.5 mmHg and standard deviations between 0.6 and 1.4 mmHg. Bland-Altman plots did not reveal any trend for the difference to be dependent on the mean value.

Peripheral blood flow. Forearm blood flows were comparable between the obese and nonobese subjects basally and during the first step, i.e., during the first 2 h of hyperinsulinemia (Fig. 3, Table 2). The first significant increase in blood flow in the nonobese subjects was observed after 2.5 h (Fig. 3). In the obese subjects, the first significant increase was observed after 4 h (Fig. 3). Both absolute flow during the highest insulin dose (step 2) and the increase in forearm blood flow above basal were significantly lower in the obese subjects than in the nonobese subjects from 2.5 h onward (Fig. 3). Forearm blood flow remained unchanged during the saline control study (data not shown).

Peripheral and central blood pressure and other hemodynamic parameters. Peripheral and central diastolic blood pressure decreased significantly in the nonobese subjects after 3 h. In the obese subjects, neither peripheral nor central diastolic blood pressure was significantly decreased by insulin (Table 2). Peripheral systolic blood pressure increased significantly during step 2, while central systolic blood pressure remained unchanged in both groups (Table 2).

TABLE 1
Physical characteristics of the subjects

	Nonobese	Obese
n	8	8
Age (years)	25 ± 1	27 ± 2
Weight (kg)	71.8 ± 1.4	98.5 ± 3.3*
Height (cm)	178 ± 2	179 ± 2
BMI (kg/m^2)	22.7 ± 0.4	30.6 ± 0.9*
Body fat (%)	12.0 ± 0.8	26.5 ± 0.8*
Fasting plasma glucose (mmol/l)	5.3 ± 0.1	5.6 ± 0.1
Fasting serum insulin (mU/l)	4 ± 1	10 ± 2†
HbA_{1c} (%)	5.0 ± 0.2	5.2 ± 0.1
Serum cholesterol (mmol/l)	4.3 ± 0.3	5.2 ± 0.5
Serum HDL cholesterol (mmol/l)	1.6 ± 0.1	1.4 ± 0.2
Serum LDL cholesterol (mmol/l)	2.4 ± 0.2	3.1 ± 0.4
Serum triglycerides (mmol/l)	0.7 ± 0.1	1.5 ± 0.2‡

Data are means ± SE. *$P < 0.001$; †$P < 0.05$; ‡$P < 0.01$.

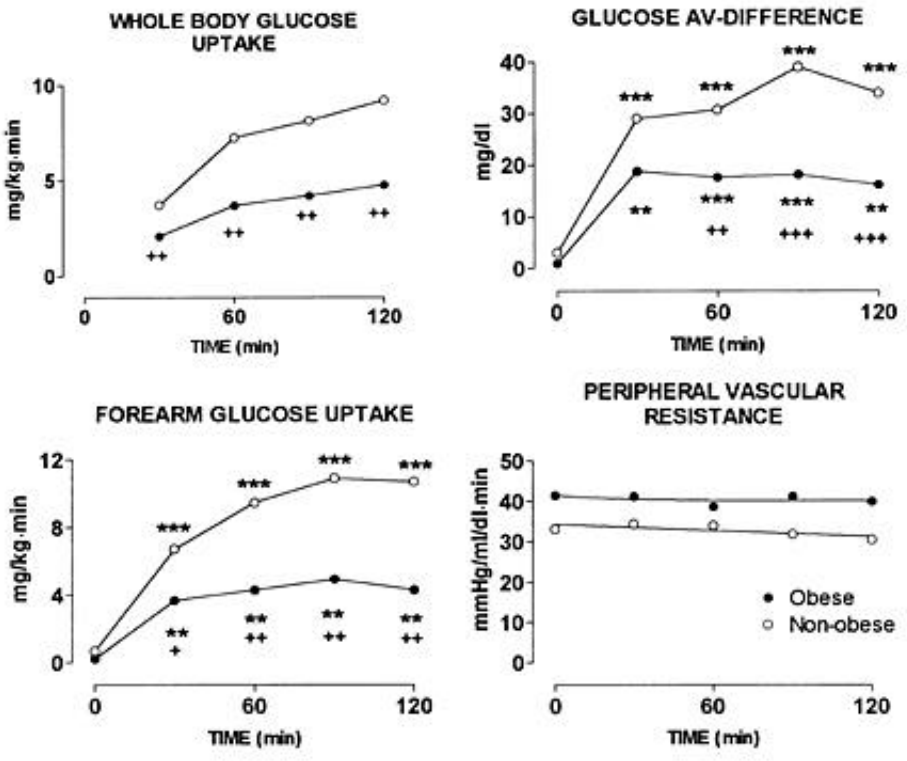

FIG. 2. Whole body glucose uptake, glucose AV-difference, forearm glucose uptake, and peripheral vascular resistance in the nonobese and obese subjects plotted as a function of time during step 1 (insulin infusion rate 1 mU · kg^{-1} · min^{-1}) of euglycemic hyperinsulinemia. For whole-body glucose uptake, the open (○) and filled (●) circles denote mean glucose uptake during the preceding 30 min for nonobese and obese subjects. *P < 0.05, **P < 0.01, ***P < 0.001 for change vs. 0 min. ^{+}P < 0.05, ^{++}P < 0.01, ^{+++}P < 0.001 for nonobese vs. obese subjects.

Pulse pressure increased and peripheral vascular resistance decreased significantly in both groups during step 2 (Fig. 3, Table 2) The increase in pulse pressure and the decrease in peripheral vascular resistance were significantly blunted in the obese subjects compared with the nonobese subjects during step 2 (Fig. 3, Table 2). Heart rate remained unchanged for the first 1.5 h in the nonobese subjects and until 4 h in the obese subjects. The increase in heart rate during step 2 was significantly lower in the obese subjects than in the nonobese subjects (Table 2). Both heart rate and blood pressure remained unchanged during the saline control study (data not shown).

DISCUSSION

The present study demonstrates temporal dissociation between insulin's different vascular effects in nonobese healthy subjects. Consistent with previous studies (2,3,14), insulin slowly increased forearm blood flow and decreased peripheral vascular resistance. These effects required a pharmacological dose of insulin (2 mU · kg^{-1} · min^{-1}) and 2.5–3 h to become significant. In contrast, a physiological dose of insulin decreased wave reflection (augmentation) in the aorta significantly within 1 h (Fig. 3). Because peripheral blood flow and vascular resistance remained unchanged during the first 2 h, and insulin does not change, or even increases, vascular resistance in other vascular beds (24,25), the decrease in augmentation reflects diminished stiffness of arteries larger than those controlling peripheral vascular resistance (7). In the obese subjects, three defects in insulin action were observed. First, glucose extraction was resistant to stimulation by a physiological concentration of insulin (Fig. 2). Second, supraphysiological insulin concentrations did not normally stimulate peripheral blood flow (Fig. 3) or decrease peripheral vascular resistance (Table 2). And third, physiological insulin concentrations failed to normally decrease augmentation in the aorta (Fig. 3). The magnitude of the latter defect was closely correlated with whole-body glucose uptake, implying that insulin resistance in obesity involves not only resistance of glucose uptake but also a defect in the ability of insulin to diminish arterial stiffness.

We used pulse wave contour analysis recorded by applanation tonometry from the radial artery to assess insulin's effects on large vessel function (12). Radial artery pressure waveforms measured with tonometry have been shown to equal those measured intra-arterially in a large group of normal subjects (26). Although changes in the aortic pressure waveform can be inferred from changes in the contour of the radial pressure wave, accurate assessment of the aortic pressure waveform necessitates either direct measurements in the aorta, or use of a transfer function to calculate aortic pressure based on measurements in the radial artery. Several studies have now demonstrated that a single generalized transfer function can be used to accurately determine central from peripheral pressure in normal subjects and in patients with a variety of diseases (12,15,16).

In the present study, in the nonobese normal subjects, insulin rapidly decreased wave reflection, as measured from the decrease in augmentation and augmentation index. Virtually all wave reflection as seen from the heart comes from the lower aorta (12), but summation of reflection from more distal arteries also contributes to wave reflection (27). Drugs that dilate arterioles and lower peripheral vascular resistance have only modest effects on wave reflection and augmentation and do not change the augmentation index, i.e., the ratio between augmentation and pulse pressure (12). In contrast, drugs that dilate small arteries rather than arterioles, such as small doses of nitrates (7), decrease augmentation and the augmentation index without changing peripheral vascu-

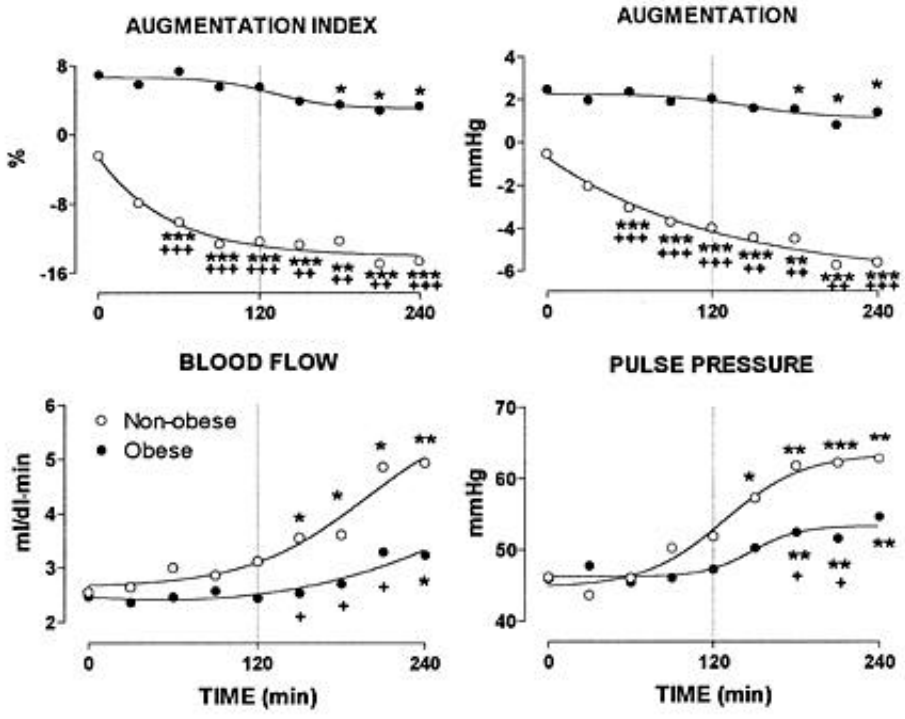

FIG. 3. The augmentation index, augmentation, forearm blood flow, and pulse pressure plotted as a function of time during sequential insulin infusions of 1 (0–120 min) and 2 (120–240 min) mU · kg^{-1} · min^{-1}. Normoglycemia was maintained using the euglycemic insulin clamp technique. *P < 0.05, **P < 0.01, ***P < 0.001 for change in parameter at a given time point vs. 0 min. ^{+}P < 0.05, ^{++}P < 0.01, ^{+++}P < 0.001 for difference between nonobese and obese subjects.

lar resistance (27). This effect of nitrates on the pulse wave contour is similar to that observed with insulin in the present study. Although the present study provides no mechanistic information of insulin's effect on arterial function, it is of interest that insulin has been shown to cause peripheral vasodilatation via an NO-dependent mechanism (4,5) and that dilatation of human conduit arteries (6,28) and arterial compliance (29) are also NO-dependent processes.

The slow insulin-induced increase in peripheral blood flow in the normal subjects is consistent with multiple previous studies (3). This slow phenomenon was contrasted by the relatively rapid decrease in the augmentation index, suggesting temporal hierarchy in insulin's vascular actions. Such hierarchy could have multiple causes, which cannot be determined from the present study but could involve variation in the sensitivity of different size vessels to insulin, or heterogeneity of insulin signaling pathways among vessels. There are, to our knowledge, no data comparing insulin's effects on arteries of various sizes, but there is reason to believe such differences do exist. For example, the contribution of NO to endothelium-dependent vasodilatation depends on the size of the artery (6). This has even been shown for human vessels, in which the contribution of NO to endothelium-dependent vasorelaxation is significantly larger in arteries, such as the gastroepiploic artery, than in distal microvessels (6).

A decrease in the augmentation index reflects diminished stiffness, but does not necessarily imply a change in stiffness at the level of the aorta (7). For example, glyceryl trinitrate does not alter aortic compliance, but clearly decreases wave reflection without changing peripheral resistance (7). This effect of glyceryl trinitrate reflects decreased stiffness at the level of conduit arteries rather than the aorta (7). Importantly, most ultrasound techniques and magnetic resonance imaging techniques measure compliance of the aorta, while

TABLE 2
Hemodynamic characteristics of the subjects

	Basal		Step 1		Step 2	
	Nonobese	Obese	Nonobese	Obese	Nonobese	Obese
Heart rate (beats/min)	53 ± 3	63 ± 3*	56 ± 3	65 ± 3	59 ± 4§	64 ± 3
Brachial systolic blood pressure (mmHg)	113 ± 3	127 ± 3*	115 ± 2	126 ± 3*	121 ± 2‖**	131 ± 3*§#
Brachial diastolic blood pressure (mmHg)	67 ± 3	81 ± 2†	67 ± 3	79 ± 3*	60 ± 3‖**	78 ± 3†
Aortic systolic blood pressure (mmHg)	98 ± 2	111 ± 3†	97 ± 2	110 ± 4†	98 ± 2	112 ± 3†
Aortic diastolic blood pressure (mmHg)	69 ± 3	80 ± 3‡	68 ± 3	80 ± 3†	61 ± 3‖**	80 ± 3†
Pulse pressure (mmHg)	46 ± 3	46 ± 2	48 ± 3	47 ± 1	61 ± 3¶††	52 ± 2*‖**
Mean arterial pressure (mmHg)	83 ± 3	96 ± 3†	83 ± 2	95 ± 3†	81 ± 2§#	96 ± 3†
Blood flow (ml · dl^{-1} · min^{-1})	2.6 ± 0.2	2.5 ± 0.2	3.0 ± 0.3	2.5 ± 0.2	4.0 ± 0.5‖**	2.9 ± 0.2*
Peripheral vascular resistance (mmHg · ml^{-1} · dl^{-1} · min^{-1})	33 ± 3	41 ± 3	33 ± 3	40 ± 2	25 ± 3‖**	35 ± 2*‖**

Data are means ± SE. *P < 0.05, †P < 0.01, ‡P < 0.001 nonobese vs. obese; §P < 0.05, ‖P < 0.01, ¶P < 0.001 vs. basal; #P < 0.05, **P < 0.01, ††P < 0.001 vs. step 1.

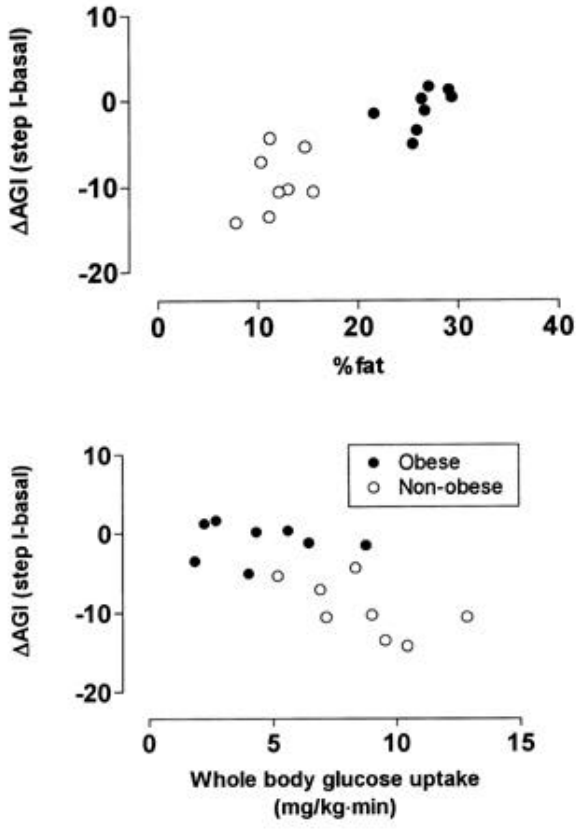

FIG. 4. Relationship between percent fat (upper panel) and whole-body glucose uptake (lower panel) and the change in the augmentation index (ΔAGI) during the 1 mU · kg^{-1} · min^{-1} insulin infusion.

pulse wave analysis has the advantage of reflecting compliance of the entire vasculature (30). Even if aortic compliance remains unchanged, diminished wave reflection at the level of the aorta has several beneficial hemodynamic effects. The delay in the return of the reflected wave will augment left ventricular filling, and thereby coronary blood flow (30). If augmentation is positive, i.e., the second systolic wave has a higher pressure than the initial systolic wave, a decrease in augmentation will also lower central aortic pressure. Augmentation and the augmentation index are positively correlated with age (12). In middle-aged and older subjects, augmentation is positive, i.e., the height of the reflected wave exceeds that of the first systolic peak. In the present study, all subjects were young, and basal augmentation was negative or slightly positive. This explains why aortic blood pressure did not decrease during the first 2 h despite a highly significant decrease in augmentation (Table 2).

In the obese subjects, multiple defects in insulin action were observed. First, as shown previously, glucose extraction was resistant to stimulation by insulin (10,31,32). This defect cannot be ameliorated by increasing blood flow (10) and is therefore a defect that is distinct from defects in insulin's vascular actions. Despite this, and consistent with previous studies (11,32), insulin stimulation of blood flow was blunted in the obese subjects, in whom an increase in blood flow was not observed until after 4 h of insulin infusion. In addition to this defect, the ability of insulin to decrease aortic wave reflection, as determined from augmentation and the augmentation index, was severely blunted in the obese subjects. Thus, in obese subjects, a decrease was not detected until after 3 h at a serum insulin concentration of 155 mU/l, in contrast to the nonobese subjects, in whom insulin significantly decreased augmentation within 1 h and at a concentration of 64 mU/l. Because this defect was observed under conditions where peripheral vascular resistance was unchanged, the failure of insulin to decrease augmentation is consistent with diminished arterial stiffness in obese subjects. The defect in stiffness was not observed in the basal state, but became evident only during insulin stimulation, suggesting that the defect may be a consequence of impaired insulin action. On the other hand, both obese human subjects (10,11) and obese animals (33) are characterized by a defect in endothelium-dependent vasodilatation. Thus, it is possible that the defect was not specific to insulin and that insulin merely acted to unmask a defect in large artery endothelial function.

Basal heart rate was significantly higher in the obese subjects than the nonobese subjects. This finding is consistent with data by Vollenweider et al. (34), who showed muscle sympathetic nervous activity to be increased, possibly as a consequence of hyperinsulinemia per se, in obese subjects compared with nonobese subjects. In the present study, insulin failed to increase heart rate in the obese subjects as it did in the nonobese subjects, a defect that could reflect lack of insulin-induced peripheral vasodilatation and reflex sympathetic activation. Alternatively, because insulin is known to activate the sympathetic nervous system even in the absence of changes in peripheral vascular resistance (35–37), it is also possible that the lack of a change in heart rate was a consequence of impaired insulin stimulation of the sympathetic nervous system.

In conclusion, the present study demonstrates that insulin's vascular effects extend to arteries that do not regulate peripheral blood flow. We found that normal insulin action on large vessels is to decrease arterial stiffness and that this effect precedes insulin's slow vasodilatory effects in the periphery. This effect of insulin is severely blunted in obesity and could provide a mechanism that links insulin resistance to cardiovascular disease.

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