Insulin Causes Endothelial Dysfunction in Humans
Sites and Mechanisms

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Background—Insulin resistance is often accompanied by hyperinsulinemia and may predispose to atherosclerosis. Endothelium plays a central role in atherogenesis. The in vivo effects of hyperinsulinemia on endothelial function of large conduit arteries are unknown.

Methods and Results—Twenty-five healthy subjects were enrolled for study. In study A (n=9), subjects underwent both a time-control saline study and a euglycemic low-dose insulin (insulin ≈110 pmol/L) clamp for 6 hours. Study B (n=5) was identical to study A except that the euglycemic clamp was performed at high physiological insulin concentrations (≈440 pmol/L). In study C (n=7), subjects underwent two 4-hour euglycemic insulin (≈110 pmol/L) clamps with and without the concomitant infusion of an antioxidant (vitamin C). In study D (n=4), two saline time-control studies were performed with and without the concomitant infusion of vitamin C. In all studies, both at baseline and throughout the experimental period, endothelium-dependent (flow-mediated) and endothelium-independent (nitroglycerin-induced) vasodilation was assessed in femoral and brachial arteries by echo Doppler. Both low (study A) and high physiological (study B) hyperinsulinemia abolished endothelium-dependent vasodilation, whereas endothelium-independent vasodilation was unaffected. Vitamin C fully restored insulin-impaired endothelial function without affecting endothelium-independent vasodilation (study C). Vitamin C had no effects on endothelium-dependent or endothelium-independent vasodilation during saline control studies (study D).

Conclusions—Modest hyperinsulinemia, mimicking fasting hyperinsulinemia of insulin-resistant states, abrogates endothelium-dependent vasodilation in large conduit arteries, probably by increasing oxidant stress. These data may provide a novel pathophysiological basis to the epidemiological link between hyperinsulinemia/insulin-resistance and atherosclerosis in humans. **(*Circulation*. 2002;105:576-582.)**

Key Words: insulin ■ endothelium ■ atherosclerosis

The metabolic syndrome (otherwise named syndrome X or insulin resistance syndrome) is a cluster of metabolic and cardiovascular abnormalities whose common denominator is thought to be insulin resistance.[1] It is suspected to play a major role in triggering and sustaining atherogenesis.[2,3] However, most of the epidemiological evidence is not based on the reference tool to assess insulin sensitivity, that is, the insulin clamp,[4] rather on circulating insulin levels,[5] which are a good proxy of insulin resistance.[6,7] It was suggested long ago that hyperinsulinemia per se exerts a detrimental effect on the vasculature by virtue of its growth factor–like effects,[8] but most recent evidence shows that insulin exerts desirable actions on the vasculature,[9] primarily by amplifying endothelium-dependent vasodilation,[10] increasing endothelial constitutive nitric oxide synthase (ecNOS) gene expression[11] and activity,[12] and, therefore, nitric oxide (NO) bioavailability,[13] which in turn exerts a wide array of antiatherogenic actions.[14,15] Thus, the connection between insulin resistance and vascular disease would be ascribed to an absolute or relative deficiency of insulin action on the vessel wall through the phosphatidyl-inositol-3-kinase (PI3K) pathway, which activates ecNOS and has an antiapoptotic effect,[16,17] and a pathogenic role of compensatory (or primary) hyperinsulinemia in the endothelial dysfunction found in insulin-resistant states[13,18–20] would be ruled out.

However, in young individuals with no known risk factors for cardiovascular disease, endothelium-dependent vasodilation in the forearm microcirculation (acetylcholine-induced), in the brachial artery, and in the femoral artery are heterogeneous.[21] Thus, the favorable effects of insulin on the endothelium of the limb microcirculation[9,10,13] may not be extrapolated to other vessels. Endothelial function is endowed with special relevance because (1) endothelium is involved in several stages of atherogenesis[22]; (2) all classic and most

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TABLE 1. Demographic, Anthropometric, Cardiovascular, and Humoral Parameters of the Study Subjects

	Study A	Study B	Study C	Study D
n (M/F)	9 (6/3)	5 (4/1)	7 (3/4)	4 (2/2)
Age, y	24±1	24±1	22±1	24±1
BMI, kg/m^2	22.1±0.9	24.7±0.9	22.5±0.74	21.2±0.13
T-Chol, mmol/L	4.26±0.23	3.95±0.36	4.40±0.19	4.32±0.31
HDL-Chol, mmol/L	1.38±0.05	1.39±0.25	1.51±0.15	1.62±0.08
Triglycerides, mmol/L	0.86±0.12	0.75±0.14	0.80±0.14	0.74±0.09
SBP, mm Hg	116±2.5	121±3.0	115±2.6	110±5
DBP, mm Hg	65.0±1.6	63.3±2.1	62.2±1.8	62.4±2.3
MAP, mm Hg	80.5±2.1	80.5±2.3	78.7±1.9	75.7±2.4
Heart rate, bpm	67±1.4	61±3.7	62.2±2.0	65±3.4

T-Chol indicates total cholesterol; HDL-Chol, HDL cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; and MAP, mean arterial pressure.

nonclassic risk factors of cardiovascular disease are associated with endothelial dysfunction[18,23]; and (3) endothelial dysfunction precedes and predicts clinical macrovascular disease in human atherogenesis[24] and should be considered a target of therapy.[18] Because atherosclerosis affects conduit arteries, the effects of insulin on large arteries are of special relevance to shed some more light on the pathogenic links between the insulin resistance syndrome and atherosclerosis.

The present investigation therefore was undertaken to study the effects of modest hyperinsulinemia, mimicking fasting compensatory hyperinsulinemia of insulin-resistant states, on endothelium-dependent, flow-mediated vasodilation in the brachial and in the common femoral arteries of young healthy humans. Because insulin was found to impair endothelial function, we further tested whether vitamin C, an antioxidant, could counteract insulin effects on these vessels, a finding that would implicate increased oxidative stress as a mediator of insulin action in the human large vasculature.

Methods

Subjects

Twenty-five young (between 20 and 29 years old), healthy, nonsmoking, unrelated individuals were recruited for study. Body weight was stable in all subjects for at least 3 months before the study. Each subject gave written informed consent before participating in the study, which was approved by the Human Investigation Committee of the Verona City Hospital.

Each subject participated in one of four protocols (see below), consisting of two separate sessions. Demographic and anthropometric features of the study subjects are shown in Table 1.

Insulin Versus Saline Studies

Study A: Low Insulin Versus Saline Study

Nine subjects participated in this protocol. All studies were conducted in a temperature-controlled (22±1°C) room. Each subject was studied twice at 1- to 8-week intervals. Each study lasted 450 minutes (−90 minutes to 360 minutes). On both occasions, subjects were admitted at 7:30 AM to the Metabolic Research Unit after an overnight fast and having refrained from caffeine-containing beverages for at least 12 hours. An antecubital vein and a wrist vein (the latter retrogradely) were cannulated in the right arm. The latter was arterialized with the "hot box technique," as previously described.[7] Blood pressure and heart rate were measured every 3 to 5 minutes with Cardiocap II (Datex) for the following 30 minutes to provide baseline cardiovascular parameters values.

At time −60 minutes and at time −40 minutes, endothelium-dependent, flow-mediated vasodilation was assessed in random order in the left brachial artery and in the right common femoral artery, as previously described.[21,25] High-resolution echo Doppler (Esaote Biomedica AU4), with a 10-MHz linear vascular probe with axial resolution of 0.1 mm, was used to measure flow velocity and arterial diameter in the two arteries at a fixed site, as previously described.[21,25] A sphygmomanometer cuff was inflated below the knee at 250 mm Hg and deflated after 6 minutes of distal ischemia, when peak flow velocity in the femoral artery was recorded. Femoral artery diameter was measured before and 0.5, 2, 4, 6, and 8 minutes after deflating the cuff, as previously described.[21,25] To assess brachial artery motility, a pediatric sphygmomanometer cuff was inflated around the left wrist at 250 mm Hg and deflated after 2 minutes of distal ischemia. Flow velocity and arterial diameter were recorded with the same timing as in the femoral artery. Previous studies have shown that these vascular responses are endothelium- and NO-dependent in the radial artery.[26,27] At time −20 minutes, nitroglycerin (GTN, 0.3 mg sublingual), an NO donor, was administered. Femoral and brachial artery diameters were measured 3 and 5 minutes after GTN administration.

At time 0 minutes, either a 0.9% normal saline infusion or a euglycemic insulin (1.2 nmol of regular insulin per square meter of body surface area [BSA] as a prime plus 60 pmol per minute per square meter of BSA as a continuous infusion) clamp was started and continued for 360 minutes, as previously described.[4,28] During the saline study, no glucose was administered. At time 80 minutes (2nd hour), 200 minutes (4th hour), and 310 minutes (6th hour), flow-mediated vasodilation in the femoral and brachial arteries was assessed as described above. At time 350 minutes (6th hour), GTN-induced vasodilation was assessed as described above. Blood pressure and heart rate were measured every 20 to 30 minutes throughout the study. Blood samples were collected at timed intervals throughout the study to measure plasma glucose and serum insulin concentrations. Blood was spun at 4000*g* for 15 minutes at 4°C, and plasma/serum was quickly separated and stored at −20°C until assay.

Study B: High Insulin Versus Saline Study

Five subjects participated in this study. All maneuvers were identical to study A, except that the dose of the prime continuous intravenous insulin infusion was higher (4.8 nmol/m^2 BSA and 240 pmol/min per m^2 BSA for prime and continuous infusions, respectively) than in study A to achieve insulin levels in the high physiological range. Brachial artery vascular responses were assessed only in 3 subjects, who also were the only ones undergoing the time-control saline infusion experiment.

TABLE 2. Humoral, Hemodynamic, and Vascular Parameters in Study A

	Study Hours							
	Basal	1st	2nd	3rd	4th	5th	6th	*P*
Glucose, mmol								
Saline	4.7±0.2	4.5±0.1	4.5±0.1	4.4±0.1	4.4±0.1	4.3±0.1	4.3±0.1	0.0001
Low INS	4.8±0.2	4.8±0.1	4.8±0.1	4.7±0.2	4.8±0.2	4.8±0.1	4.9±0.2	
Insulin, pmol								
Saline	32±4	37±3	32±5	28±4	28±4	27±3	28±4	0.0001
Low INS	36±3	108±6	114±4	111±5	116±6	114±7	121±12	
MAP, mm Hg								
Saline	80±4	82±2	80±2	79±2	79±3	83±2	82±2	0.29
Low INS	81±3	82±3	84±3	84±4	79±5	86±4	86±3	
Heart rate, bpm								
Saline	69±2	65±3	60±3	63±2	62±2	65±3	72±3	0.85
Low INS	66±2	61±1	61±2	61±2	63±3	64±2	68±3	
Br Art Diam, mm								
Saline	3.9±0.2	nd	4.0±0.2	nd	4.0±0.2	nd	4.0±0.2	0.79
Low INS	4.0±0.2	nd	4.1±0.2	nd	4.1±0.2	nd	4.0±0.2	
BAFI, cm/s								
Saline	18.3±3.7	nd	20.2±6.5	nd	26.9±4.3	nd	25.4±3.3	0.40
Low INS	17.3±2.6	nd	21.2±3.5	nd	21.9±2.3	nd	24.2±3.6	
Fem Art Diam, mm								
Saline	8.4±0.4	nd	8.5±0.4	nd	8.4±0.4	nd	8.4±0.4	0.01
Low INS	8.4±0.5	nd	8.6±0.5	nd	8.7±0.5	nd	8.6±0.5	
FAFI, cm/s								
Saline	27.0±5.2	nd	26.1±3.8	nd	29.5±4.3	nd	29.7±5.0	0.16
Low INS	25.9±3.5	nd	27.1±2.1	nd	31.9±3.5	nd	33.2±5.1	

MAP indicates mean arterial pressure; Br Art Diam, left brachial artery diameter before eliciting endothelium-dependent vasodilation; BAFI, increase in flow velocity in the brachial artery after deflating the sphygmomanometric cuff at the wrist; Fem Art Diam, right common femoral artery diameter before eliciting endothelium-dependent vasodilation; FAFI, increase in flow velocity in the femoral artery after deflating the sphygmomanometric cuff under the knee; INS, insulin; and nd, not determined.

P is for comparison between saline and low-insulin study by 2-way ANOVA for repeated measures.

Insulin and Vitamin C Studies

Study C: Insulin Versus Insulin Plus Vitamin C

Seven subjects participated in this protocol. They underwent two euglycemic insulin clamp studies at a time interval of 4 to 7 weeks. The order of the studies was randomized. Endothelium-dependent and endothelium-independent vasodilations were assessed in the basal period as described in study A. All other maneuvers in the baseline period were identical to study A. At time 0 minutes, a euglycemic insulin clamp (prime, 1.2 nmol/m^2 BSA; continuous infusion, 60 pmol/min per m^2 BSA) was initiated and continued until 240 minutes. On one occasion, insulin infusion was accompanied by an infusion of 0.9% saline. On the other occasion, a prime (2 g) continuous (0.5 g per hour) intravenous infusion of vitamin C (Bracco) dissolved in 0.9% saline was administered. At time 190 minutes (4th hour), endothelium-dependent vasodilation was assessed in the right femoral and left brachial arteries in random order, as described above. At 230 minutes, endothelium-independent vasodilation was assessed, as described above. Blood samples were collected as in study A. Monitoring of hemodynamic parameters was identical to study A.

Study D: Saline Versus Saline Plus Vitamin C

Four subjects participated in this protocol. They were studied twice at a time interval of 4 to 7 weeks. The order of the studies was randomized. All maneuvers were identical to study C except that insulin infusion was substituted by 0.9% saline infusion on both occasions.

Analytical Methods

Plasma glucose concentration was determined in duplicate by the glucose oxidase method on a Beckman Glucose Analyzer II (Beckman Instruments). Serum insulin concentration was measured by a chemiluminescence-based immunoassay (Immunolite, Diagnostic Product Corp). Serum lipids were assayed by standard in-house methods.

Calculations

Tissue insulin sensitivity during the insulin clamp was quantified by calculating the *M* value, as previously described.[4,28] The *M* value is expressed in micromoles per minute per kilogram of body weight (BW).

A global quantitative index of endothelium-dependent, flow-mediated vasodilation was obtained by computing the average percent change in vessel diameter over the 8 minutes of observation after cuff deflation.[21,25] A global quantitative index of endothelium-independent, GTN-mediated vasodilation was obtained by computing the average percent increase in vessel diameter over the 5 minutes of observation after GTN administration.

Statistical Analysis

All data are presented as mean±SEM. Comparisons to assess insulin or vitamin C effects were carried out by 2-way or 1-way ANOVA for

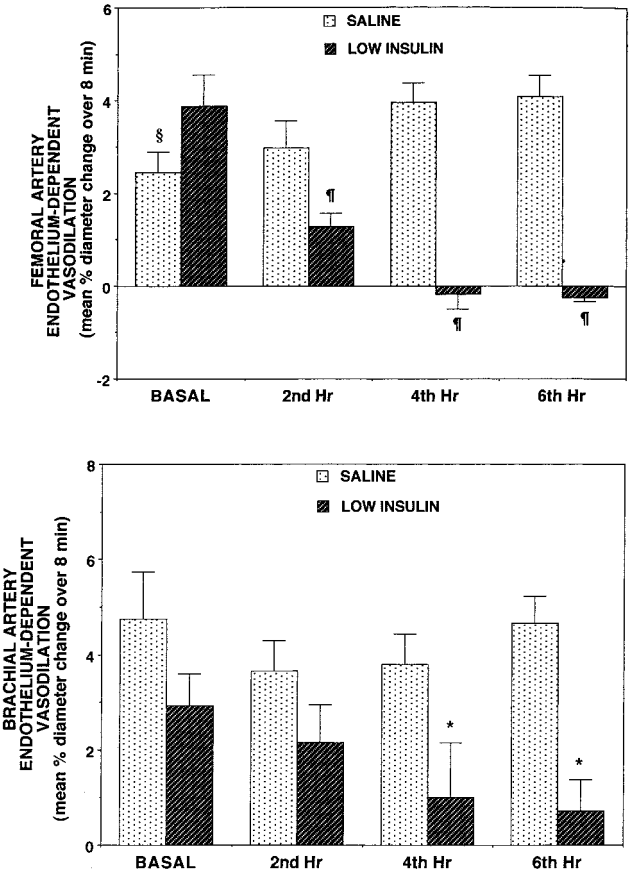

Figure 1. Endothelium-dependent vasodilation in femoral (top) and brachial (bottom) arteries during study A. ¶$P<0.001$, Low insulin vs saline, and *$P<0.02$, low insulin vs saline by 2-way ANOVA for repeated measures. §$P<0.02$, Basal vs subsequent assessments by ANOVA for repeated measures in the saline study.

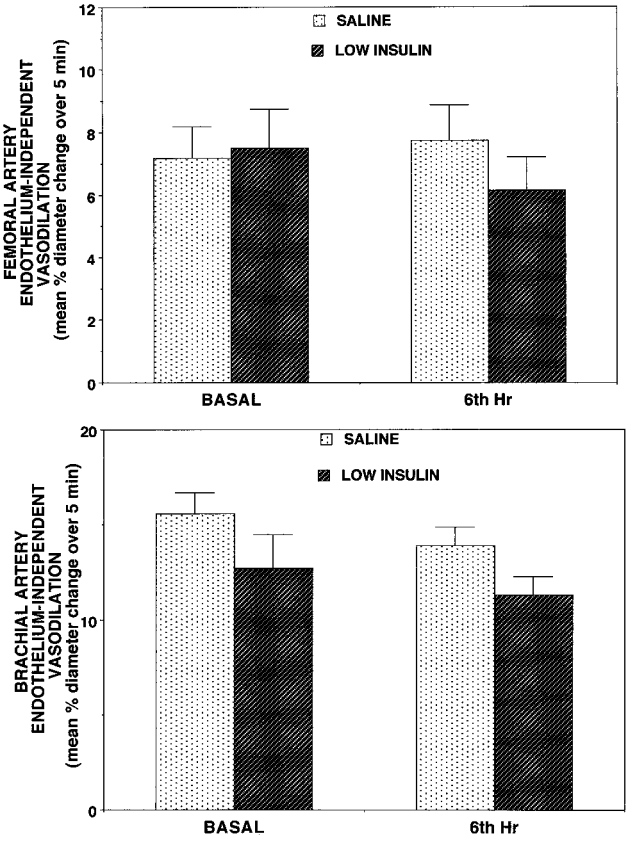

Figure 2. Endothelium-independent vasodilation in femoral (top) and brachial (bottom) arteries during study A.

repeated measures, in which baseline assessment of the variable of interest was inserted as a covariate to allow for day-to-day variability. Other comparisons were carried out by paired or unpaired Student's *t* test as most appropriate. All analyses were performed with SPSS 10.0 software. Statistical significance was declared at $P<0.05$.

Results

Insulin Versus Saline Studies

Plasma glucose and serum insulin concentrations and cardiovascular parameters of study A (low insulin versus saline) are presented in Table 2. The *M* value was 13.7 μmol/min per kg BW in the 2nd hour and reached 21.7±2.2 μmol/min per kg BW in the 6th hour. Femoral but not brachial artery diameter increased during the low insulin but not during the saline study (Table 2; $P=0.01$ low insulin versus saline). In contrast to the saline study, during the insulin clamp studies endothelium-dependent vasodilation decreased progressively in both arteries, down to being virtually annulled between the 4th and the 6th hours (Figure 1). Endothelium-independent vasodilation was not affected by insulin (Figure 2).

In study B (saline versus high insulin), during the saline experiment plasma glucose and serum insulin decreased similarly to study A (data not shown). During the high insulin experiment, serum insulin was raised to ≈440 pmol/L, whereas plasma glucose was kept constant at ≈4.7 mmol/L. The *M* value was 30.4±0.83 μmol/min per kg BW in the 2nd hour and reached 47.8±3.9 μmol/min per kg BW in the 6th hour ($P<0.01$ versus study A). No significant changes in blood pressure, heart rate, brachial/femoral artery diameters, and increases in flow velocity in response to distal ischemia could be documented between saline and high insulin studies (data not shown). Also in this study, insulin infusion caused a progressive decline in the endothelium-dependent vasodilation of both arteries (femoral artery, from 2.76±0.59% at baseline to −0.76±0.28% in the 6th hour of insulin clamp, $P<0.01$; brachial artery, from 5.52±1.4% at baseline to 0.17±1.14% in the 6th hour of the insulin clamp), whereas endothelium-independent vasodilation was unaffected (data not shown).

Insulin and Vitamin C Studies

Glucose and insulin concentrations of study C (insulin versus insulin plus vitamin C) are presented in Table 3. The *M* values in the 2nd and 4th hours were similar to those seen in study A and showed no influence of vitamin C (2nd hour, 14.2±1.8 and 13.1±1.3 μmol/min per kg BW without and with vitamin C infusion, respectively; 4th hour, 18.6±2.2 and 18.8±1.9 μmol/min per kg BW without and with vitamin C, respectively; P=NS for both). No significant changes in vascular and hemodynamic parameters were associated with vitamin C infusion (Table 3). As in study A, endothelium-

TABLE 3. Humoral, Hemodynamic, and Vascular Parameters in Study C

	Study Hours					
	Basal	1st	2nd	3rd	4th	*P*
Glucose, mmol						
INS	4.9±0.1	5.0±0.1	4.8±0.1	5.0±0.1	4.9±0.1	0.10
INS + VIT C	4.9±0.2	4.7±0.2	4.8±0.1	4.8±0.2	4.8±0.1	
Insulin, pmol						
INS	42±4	107±13	108±7	104±8	108±8	0.35
INS + VIT C	44±5	103±6	110±7	98±8	111±9	
MAP, mm Hg						
INS	80±3	77±3	77±2	76±2	75±3	0.85
INS + VIT C	78±2	79±3	77±3	76±3	75±3	
Heart rate, bpm						
INS	64±3	56±3	58±2	64±3	63±3	0.74
INS + VIT C	60±2	57±1	59±3	57±2	61±3	
Br Art Diam, mm						
INS	4.0±0.2	nd	nd	nd	4.1±0.2	0.61
INS + VIT C	4.0±0.2	nd	nd	nd	4.1±0.2	
BAFI, cm/s						
INS	27.7±5.9	nd	nd	nd	19.4±5.9	0.08
INS + VIT C	23.9±5.6	nd	nd	nd	30.0±7.9	
Fem Art Diam, mm						
INS	8.5±0.3	nd	nd	nd	8.5±0.3	0.69
INS + VIT C	8.5±0.3	nd	nd	nd	8.5±0.3	
FAFI, cm/s						
INS	29.4±9.0	nd	nd	nd	28.5±4.7	0.80
INS + VIT C	29.1±6.8	nd	nd	nd	26.6±6.0	

VIT C indicates vitamin C. All other abbreviations as in Table 2.

P is for comparison between insulin and insulin plus vitamin C study by 2-way or 1-way ANOVA for repeated measures, as appropriate.

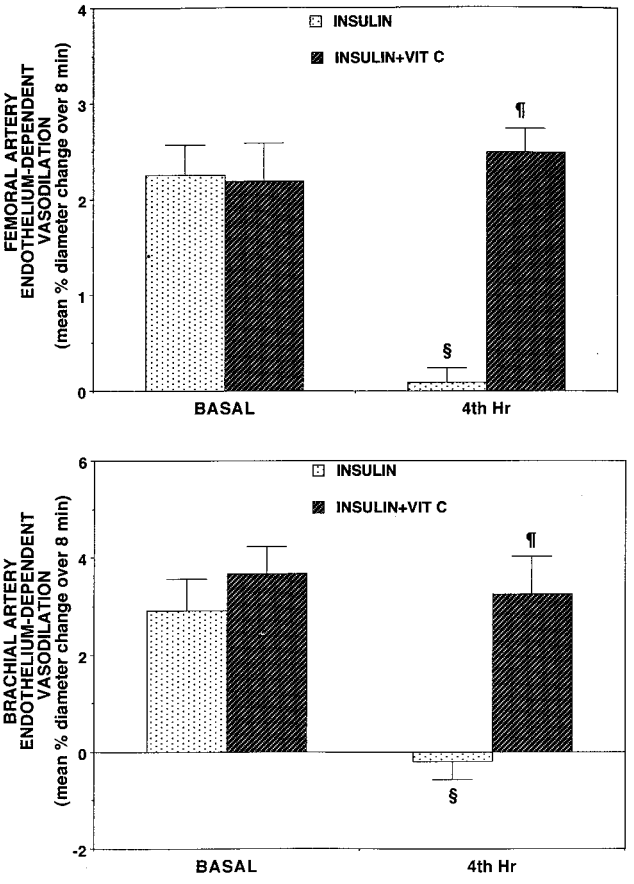

Figure 3. Endothelium-dependent vasodilation in femoral (top) and brachial (bottom) arteries during study C. ¶$P<0.001$, Insulin+Vitamin C vs insulin alone by 1-way ANOVA for repeated measures. §$P<0.01$, 4th hour insulin vs correspondent basal value by paired Student's *t* test.

dependent vasodilation was completely abrogated in the 4th hour of the insulin clamp (Figure 3), but it was fully restored by vitamin C infusion (Figure 3; $P<0.01$ insulin plus vitamin C versus insulin alone for both femoral and brachial artery). Endothelium-independent vasodilation was unaffected by vitamin C infusion during the insulin clamp (Figure 4).

In study D (saline versus saline plus vitamin C), vitamin C did not affect either endothelium-dependent (femoral artery, 2.77±1.0% and 1.80±0.3% without and with vitamin C, respectively; brachial artery, 3.81±1.82% and 2.94±0.94% without and with vitamin C, respectively; P=NS for both) or endothelium-independent (femoral artery, 6.70±1.3% and 6.24±1.2% without and with vitamin C, respectively; brachial artery, 12.3±2.9% and 15.3±1.7% without and with vitamin C, respectively; P=NS for both) vasodilation. Metabolic and hemodynamic parameters were similar with and without vitamin C infusion (data not shown).

Discussion

In this study, we assessed the effects of modest, prolonged hyperinsulinemia similar to that observed in insulin-resistant conditions after an overnight fast (Table 2)[29] on flow-mediated NO-dependent vasodilation in large conduit arteries. Over the 6 hours of the insulin clamp but not during the saline time-control studies, in both femoral and brachial artery we observed a progressive decline in endothelium-dependent vasodilation, which was virtually abrogated after 4 hours (Figure 1). No changes in endothelium-independent, GTN-induced vasodilation were observed (Figure 2), indicating that the endothelium was the target of insulin's detrimental action on vasomotility. The same effect was observed at an insulin concentration typical of the postprandial period (study B). Thus, the detrimental effect of insulin on endothelium is maximal at just less than 120 pmol/L, indicating a very steep dose-response curve, and is not reversed by higher insulin concentrations. To the best of our knowledge, this is the first evidence in humans that insulin causes severe endothelial dysfunction in large conduit arteries, which are prone to develop atherosclerosis.

Our findings are at variance with a large number of in vitro studies in which insulin exerts beneficial effects on endothelium by activating the PI3K/Akt pathway,[16,17] replenishing cellular tetrahydrobiopterin, a cofactor of ecNOS,[30] increasing transcription and activity of ecNOS[11,12] and inhibiting apoptosis.[17] Furthermore, several laboratories, including ours,[31] have shown that insulin causes vasodilation in the limb microcirculation by an endothelium-dependent and NO-

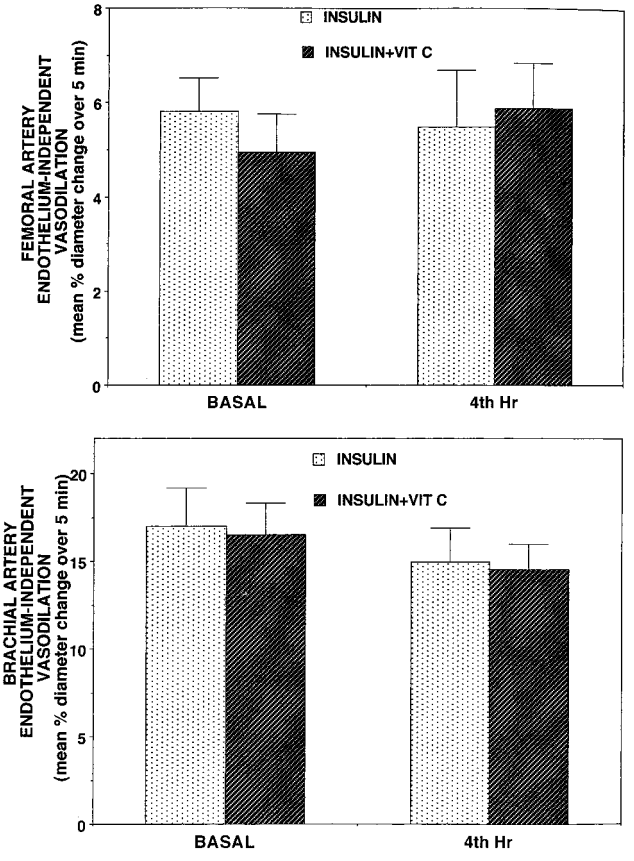

Figure 4. Endothelium-independent vasodilation in femoral (top) and brachial (bottom) arteries during study C.

dependent mechanism.[32,33] Some in vitro studies used pharmacological insulin concentrations.[12,16,17] At those doses but not at the concentrations achieved in our study, insulin can bind and activate the IGF-I receptor, so that those effects may not be insulin specific. Indeed, IGF-I can enhance endothelial NOS activity and NO production.[12] Furthermore, in our study the detrimental effects of insulin on endothelial function were fully evident only after 4 hours of hyperinsulinemia (Figure 1), suggesting that a prolonged exposure is needed to unveil this facet of insulin action. Endothelial responses are heterogeneous in humans and show vessel-specific susceptibility to potential determinants of endothelial function, such as ACE genotype.[21] Thus, our data point out that the endothelium of large arteries is exquisitely sensitive to detrimental insulin effects in vivo.

The mechanisms through which insulin impairs endothelial function are not clear. Since in most conditions characterized by endothelial dysfunction increased oxidant stress appears to be involved,[34] in study C we tested the hypothesis that vitamin C, an effective antioxidant, could counteract the action of insulin on endothelium. Vitamin C completely reversed insulin-induced endothelial dysfunction (Figure 3) without affecting the vascular endothelium-independent response (Figure 4). Since vitamin C exerted no effects on endothelial function in the absence of insulin (study D), we infer that vitamin C specifically stops those mechanisms put in motion by insulin, which abolish flow-mediated vasodilation. Therefore, oxidant stress is a most likely intermediate step in insulin-induced endothelial dysfunction.

Recent evidence shows that in the human microcirculation, insulin activates both the nitrergic and the endothelinergic systems.[35] Endothelin-1 induces NAD(P)H oxidase expression in human endothelial cells, with increased generation of superoxide anion.[36] Exogenous hyperinsulinemia activates NAD(P)H in rat aortic endothelium.[37] Thus, we speculate that insulin may cause endothelial dysfunction through increased ET-1 availability and the latter's downstream effects on NAD(P)H oxidase and superoxide anion production.

Our results may be relevant to a number of human diseases. In most insulin-resistant states, such as obesity, hypertension, impaired glucose regulation, and early type 2 diabetes mellitus, fasting hyperinsulinemia[29] is of the same order of magnitude that in our studies has impaired endothelial function in healthy individuals. In those same conditions, endothelial dysfunction is present[10,18,20–22] and is considered an intermediate phenotype for atherosclerosis as well as a target for therapy.[18] A widespread opinion holds that vascular insulin resistance and/or a pathological imbalance of vascular insulin effects is responsible for an involvement of the insulinergic system in atherogenesis,[9] whereas compensatory (or primary) hyperinsulinemia is little more than a proxy of insulin resistance[38] or plays a role through its effects on lipoprotein metabolism[2,39] and/or the fibrinolytic system.[3,40] Our data may lead to revision of this paradigm and may provide grounds to ascribe a pivotal role also to hyperinsulinemia per se in triggering and sustaining atherogenesis through increased oxidant stress and endothelial dysfunction in large conduit arteries.

In summary, modest hyperinsulinemia of the same degree seen in insulin-resistant patients after an overnight fast causes severe endothelial dysfunction in large conduit arteries, an effect that can be prevented by vitamin C, thereby involving increased oxidant stress as an obligate step in its genesis. These data appear to unveil a new scenario in the relation between insulin resistance/hyperinsulinemia and atherosclerosis in humans.

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