Forearm Resistance Vessel Abnormalities and Insulin Resistance in Obese Adolescents

Albert P. Rocchini, Catherine Moorehead, Victor Katch, Jane Key, and Kathleen M. Finta

To determine if structural changes in forearm resistance vessels are associated with insulin resistance, we evaluated the relation between minimum forearm vascular resistance and insulin resistance in 95 obese adolescents before and after weight loss. Insulin resistance was assessed by fasting insulin levels and sum of insulin values after an oral glucose tolerance test in all 95 subjects and whole body glucose uptake during euglycemic hyperinsulinemia in 35 of 95 subjects. Structural changes in forearm vessels were assessed by measurement of minimum forearm vascular resistance during 10 minutes of ischemic exercise. As compared with our normal values, obese adolescents had a significantly (p<0.01) decreased maximal forearm blood flow (41.6±1.4 versus 67.1±2.4 ml/min/100 ml) and increased minimum forearm vascular resistance (2.9±0.4 versus 1.6±0.7 mm Hg/ml/min/100 ml). There was a significant relation (p<0.01) between minimum forearm vascular resistance and fasting insulin, sum of insulins, and whole body glucose uptake. After a 20-week weight-loss program, minimum forearm vascular resistance decreased (3.0±0.3 versus 2.0±0.2, p<0.01), maximal forearm blood flow increased (41±2.3 versus 57±3.9, p<0.01), and forearm volume remained unchanged. We also observed a significant (p<0.01) relation between the decrease in minimum forearm vascular resistance and the decrease in fasting insulin (r=0.29), decrease in sum of insulins (r=0.42), and increase in whole body glucose uptake (r=0.63). In summary, obese adolescents not only appear to have structural changes in forearm vessels, but these changes also correlate with the degree of insulin resistance. (Hypertension 1992;19:615-620)

KEY WORDS • plethysmography • obesity • insulin • norepinephrine • weight loss • vascular resistance

Although numerous epidemiological studies have suggested that there may be a relation between insulin resistance and hypertension, it has not been unequivocally demonstrated that insulin resistance can cause hypertension. One of the physiological and tissue-specific consequences of selective insulin resistance that may modulate the development of hypertension is abnormal vascular regulation. Because insulin and insulin-like growth factors are mitogens, capable of stimulating smooth muscle proliferation,1-4 chronic hyperinsulinemia could result in vascular smooth muscle hypertrophy and narrowing of the lumen of resistance vessels, ultimately leading to the development of hypertension.5 In addition, both Natali et al6 and Laakso et al7 have reported that obese subjects with insulin resistance have attenuated limb vasodilator responses to hyperinsulinemia. Because we have previously demonstrated that obese adolescents appear to have structural changes in their forearm resistance vessels,8 the current study was designed to determine if structural changes in the forearm resistance vessels of obese adolescents are associated with insulin resistance.

Methods

A total of 95 obese adolescents (39 boys and 56 girls) and 40 nonobese adolescents (13 boys and 27 girls) were studied. Fifteen of the obese adolescents9,10 and seven of the nonobese adolescents11 were included in previous reports. None of the subjects was taking any medications or had any medical illness, including renal, liver, endocrinologic, or cardiovascular disease. Obesity was defined as weight-for-height above the 75th percentile for age and sex and triceps and subscapular skin-fold thicknesses above the 80th percentile for age and sex.8 For the study of the effect of weight loss, all the obese subjects entered a 20-week weight-loss program consisting of diet and behavior modification.12 The 87 adolescents who completed this program underwent repeat testing. The study protocol was approved by the Institutional Review Board, and the parents of all the subjects gave informed consent before the study began.

Experimental Protocol

The adolescents were studied as outpatients at the Clinical Research Center. After an overnight fast, all adolescents reported at 7:30 AM, a heparin lock was inserted in an antecubital vein, and arterial pressure and heart rate were measured every 5 minutes for 60 minutes by means of an Air-Shields automated blood pressure monitor (Healthdyne Co., Hatboro, Pa.) and...
an appropriately sized cuff. At 9 AM, all adolescents had
blood drawn for levels of fasting insulin, fasting glucose,
norepinephrine, and serum electrolytes. In all adoles-
cents, forearm blood flow was measured in the right arm
with a mercury-in-Silastic strain-gauge plethysmograph
and venous occlusion. During measurements of forearm
blood flow, circulation to the hand was arrested by
inflation of a cuff around the wrist to the point of
suprasystolic pressure. Four blood flows were recorded
every 10 seconds, and an average value was calculated
while blood pressure was measured in the left arm.
Forearm vascular resistance was calculated by dividing
mean arterial pressure by forearm blood flow. Minimum
forearm vascular resistance was assessed by inflation of
the cuff on the upper right arm to above systolic
pressure for 10 minutes to occlude arterial flow while
the adolescents squeezed a rubber ball 10 times. After
release of the arterial occlusion, forearm blood flow was
measured after 5 seconds and every 10 seconds there-
after for 3 minutes. The peak blood flow recorded after
release of arterial occlusion was used to calculate the
minimum forearm vascular resistance. At 10 AM, an oral
glucose tolerance test was performed in 95 of 155 obese
and 40 of 58 nonobese adolescents. The oral glucose
tolerance test consisted of 1.75 g/kg (maximum, 75 g)
oral glucose. Blood was sampled for glucose and insulin
levels at 15, 30, 45, 60, 90, and 120 minutes after the
glucose load. The sum of the insulin values at these time
points was used as an estimate of insulin resistance.
After lunch, all adolescents had body composition mea-
sured by hydrostatic weighing as described by Katch et
al.13
On a separate day, 35 of the obese adolescents
returned for a euglycemic insulin clamp.11 These obese
adolescents did not significantly differ in any measured
variable from the other 60 adolescents. With the ado-
clescents in a semisupine position, polyethylene cannulas
were inserted into an antecubital vein in one arm and
into a warmed dorsal hand vein in the other arm. After
a 30-minute control period, a primed, constant infusion
of insulin was administered that started at a dose of 800
milliunits/m², was exponentially decreased over 10 min-
utes, and was followed by a constant dose of 40 milli-
units/m²/min. Concomitantly with the insulin, an intrave-
nous infusion of 20% glucose was administered by a
variable-infusion syringe pump (Harvard Apparatus,
Mills, Mass.). Blood samples were obtained at 5-minute
intervals for determination of blood glucose concentra-
tion. The glucose infusion rate was varied every 5
minutes to hold glucose concentration constant at base-
line. The amount of glucose required to maintain eugly-
cemia was used as an estimate of whole-body glucose
disposal.

**Laboratory Procedures**

Plasma glucose was assayed by the glucose oxidase
method (Beckman glucose analyzer, Beckman Instru-
ments, Inc., Fullerton, Calif.). Plasma insulin was mea-
sured by radioimmunoassay. Plasma norepinephrine
was measured by high performance liquid chromatog-
raphy with electrochemical detection.14 Cardiac output
was estimated using standard two-dimensional Doppler
ultrasonographic techniques.

**Statistical Analysis**

All values reported are mean±SEM. Analysis of
variance was used to compare differences between
obese and nonobese adolescents. Comparisons before
and after weight loss were made using a repeated-
measures analysis of variance. The relations between
forearm blood flow and resistance and fasting insulin,
sum of the insulin values after an oral glucose tolerance
test, and whole body glucose uptake were assessed using
product-moment correlations, partial correlations, and
regression models.

**Results**

We observed that, when compared with the nonobese
adolescents, the obese adolescents have significantly
higher systolic, diastolic, and mean blood pressures;
cardiac output; heart rate; plasma norepinephrine lev-
els; fasting insulin levels; and sum of the insulins after
an oral glucose tolerance test (Table 1). Although we
have not performed euglycemic insulin clamps on
nonobese adolescents, we have performed insulin
clamps on 24 nonobese young adults aged 18–24 years
(mean, 22.3 years).12,13 Compared with these nonobese
young adults, the obese adolescents had significantly
reduced whole body glucose uptake (8.7±0.6 versus
4.4±0.2 mg of glucose/kg/min, p<0.001). The obese
adolescents also had increased resting forearm blood
flow and decreased resting forearm vascular resistance
(Table 1). However, after maximal ischemic dilation,
the obese adolescents had significantly decreased post-
ischemic maximal forearm blood flows and increased
posts ischemic minimum forearm vascular resistances. As
compared with the obese adolescents, ischemic vasodi-
lation resulted in a significantly larger increase in for-
arm blood flow in the nonobese adolescents (60.6±4.3
ml/min/100 ml increase in forearm blood flow [non-
obese] versus 27.1±1.2 ml/min/100 ml increase in for-
arm blood flow [obese], p<0.001). The increase in
forearm blood flow from rest to posts ischemia correlated
with the degree of insulin resistance (Figure 1). Table 2
summarizes the simple and partial correlations of is-
chemia-induced maximal forearm blood flow and mini-

![Figure 1](Figure showing scatterplot)
were all measured, stepwise multiple regression analysis revealed that the sum of insulins, and whole body glucose uptake were all measured, stepwise multiple regression analysis revealed that whole body glucose uptake was the only step entered into the relation for minimum forearm vascular resistance ($F=53.2$).

The 87 adolescents who were studied before and after weight loss were separated into two groups: those who lost more than 1 kg of body weight during the 20 weeks (weight-loss group) and those who lost less than 1 kg (no-weight-loss group) (Table 3). Weight loss was associated with a significant decrease in arterial pressure, heart rate, cardiac output, fasting insulin, sum of insulins, and increase in whole body glucose uptake. Weight loss also resulted in a decrease in body weight, resting forearm blood flow, and minimum forearm vascular resistance and an increase in resting forearm vascular resistance and maximal postischemic forearm blood flow. There was a significant relation between the decrease in resting forearm blood flow and the decrease in both fasting insulin ($r=0.22, p<0.04$) and the sum of insulins after a glucose tolerance test ($r=0.41, p<0.001$) and in the increase in whole body glucose uptake $r=0.55, p<0.001)$. There was also a significant relation between both the increase in maximal postischemic forearm blood flow and the decrease in minimum forearm vascular resistance and the decrease in both fasting insulin ($r=0.21, p<0.05; r=0.29, p<0.02$) and the sum of insulins ($r=0.39, p<0.001; r=0.42, p<0.001$) and the increase in whole body glucose uptake ($r=0.56, p<0.001; r=0.63, p<0.001$) (Figure 2). In the 30 obese adolescents in whom body composition, norepinephrine, fasting insulin, sum of insulins, and whole body glucose uptake were all measured both before and after weight loss, stepwise multiple regression analysis revealed that the change in whole body glucose uptake was the only step entered into the relation for both the change in minimum forearm vascular resistance ($F=49.2$) and the change in postischemic maximal forearm blood flow ($F=40.3$).

Because changes in forearm blood flow after weight loss could be related to changes in forearm size, forearm circumference was measured in all subjects 10 cm below the olecranon, and forearm volume was measured in 40 subjects by water displacement. Weight loss was not associated with a significant change in either forearm circumference (Table 3) or forearm volume (1,745±35 versus 1,709±39 ml).

**Discussion**

Structural changes in resistance vessels of the forearm can be assessed physiologically by measurement of vascular resistance during ischemia-induced maximal

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**TABLE 1.** Age, Weight, Body Composition, Blood Pressure, Hormonal Measurements, and Resting and Postischemic Forearm Blood Flow and Vascular Resistance in Obese and Nonobese Adolescents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonobese</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>13.8±0.5</td>
<td>13.7±0.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>48.4±3.6</td>
<td>79.1±2.7*</td>
</tr>
<tr>
<td>%Fat</td>
<td>20.9±1.1</td>
<td>41.2±0.8*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173±15.1</td>
<td>174±14</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>105±3</td>
<td>124±1*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>60±2</td>
<td>76±1*</td>
</tr>
<tr>
<td>Fasting insulin (mcg/ml)</td>
<td>9±2</td>
<td>24±1*</td>
</tr>
<tr>
<td>Sum of insulins (mcg/ml)</td>
<td>245±26</td>
<td>619±26</td>
</tr>
<tr>
<td>M (mg glucose/kg/min)</td>
<td>...</td>
<td>4.4±0.2</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>195±45</td>
<td>350±32*</td>
</tr>
<tr>
<td>FBF (ml/min/100 ml)</td>
<td>5.9±0.7</td>
<td>13.5±0.8*</td>
</tr>
<tr>
<td>FVR (mm Hg/ml/min/100 ml)</td>
<td>13.4±1.1</td>
<td>7.9±1*</td>
</tr>
<tr>
<td>Max FBF (ml/min/100 ml)</td>
<td>67.1±2.4</td>
<td>41.6±1.4*</td>
</tr>
<tr>
<td>MFVR (mm Hg/ml/min/100 ml)</td>
<td>1.6±0.7</td>
<td>2.9±0.4*</td>
</tr>
<tr>
<td>ΔFVR (ml/min/100 ml)</td>
<td>60.6±4.3</td>
<td>27.1±1.2*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72±2</td>
<td>81±1*</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>7.8±0.5</td>
<td>10.8±0.4*</td>
</tr>
</tbody>
</table>

%Fat, percentage of body weight due to fat; B, blood pressure; M, whole body glucose uptake; FBF, forearm blood flow; FVR, forearm vascular resistance; Max FBF, maximal postischemic FBF; MFVR, minimum postischemic FVR; ΔFVR, change in FBF from rest to postischemia; bpm, beats per minute. *p<0.01, obese vs. nonobese.

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**TABLE 2.** Simple and Partial Correlations Between Maximal Postischemic Forearm Blood Flow and Minimum Forearm Vascular Resistance and Variables in Obese Adolescents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Max FBF</th>
<th>MFVR</th>
<th>Max FBF</th>
<th>MFVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Fat</td>
<td>0.22 (p&lt;0.05)</td>
<td>0.29 (p&lt;0.03)</td>
<td>0.07 (NS)</td>
<td>0.1 (NS)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.24 (p&lt;0.04)</td>
<td>0.21 (p&lt;0.04)</td>
<td>0.13 (NS)</td>
<td>0.12 (NS)</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>0.28 (p&lt;0.004)</td>
<td>0.33 (p&lt;0.004)</td>
<td>0.05 (NS)</td>
<td>0.01 (NS)</td>
</tr>
<tr>
<td>Sum of insulins</td>
<td>0.56 (p&lt;0.001)</td>
<td>0.5 (p&lt;0.001)</td>
<td>0.52 (p&lt;0.001)</td>
<td>0.51 (p&lt;0.001)</td>
</tr>
<tr>
<td>M</td>
<td>0.63 (p&lt;0.001)</td>
<td>0.65 (p&lt;0.001)</td>
<td>0.61 (p&lt;0.001)</td>
<td>0.59 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Max FBF, maximal postischemic forearm blood flow; MFVR, minimum postischemic forearm vascular resistance; % Fat, percentage of body weight due to fat; M, whole body glucose uptake.

*Partial correlations were calculated for sum of insulins, %fat, and norepinephrine using n=95 did not take into account the effect M had on relations, because only 35 subjects had the M measure. Partial correlation for M took into account all other variables.
TABLE 3. Effect of Weight Loss on Weight, Body Composition, Blood Pressure, Hormonal Measurements, and Forearm Flows and Resistances in Obese Adolescents After 20-Week Weight-Loss Program

<table>
<thead>
<tr>
<th>Variable</th>
<th>Weight-loss group (n=57)</th>
<th>No-weight-loss group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before weight loss</td>
<td>After weight loss</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.6±3.9</td>
<td>65.4±3.7†</td>
</tr>
<tr>
<td>%Fat</td>
<td>41.3±1.1</td>
<td>34.9±1.7†</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>125±2</td>
<td>112±2*†</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75±2</td>
<td>68±2*†</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>82±2</td>
<td>72±4*†</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>10.7±0.4</td>
<td>8.9±0.3</td>
</tr>
<tr>
<td>Fasting insulin (microunits/ml)</td>
<td>23.1±1.9</td>
<td>14.2±1.9†</td>
</tr>
<tr>
<td>Sum of insulins (microunits/ml)</td>
<td>644±64</td>
<td>275±45†</td>
</tr>
<tr>
<td>M (mg glucose/kg/min)</td>
<td>4.4±0.4</td>
<td>5.8±0.2†</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>372±54</td>
<td>207±61†</td>
</tr>
<tr>
<td>FBF (ml/min/100 ml)</td>
<td>13.7±1.1</td>
<td>9.9±1.5†</td>
</tr>
<tr>
<td>FVR (mm Hg/ml/min/100 ml)</td>
<td>8.1±0.6</td>
<td>9.4±0.9†</td>
</tr>
<tr>
<td>Max FBF (ml/min/100 ml)</td>
<td>41±2.3</td>
<td>57.4±3.9†</td>
</tr>
<tr>
<td>MFVR (mm Hg/ml/min/100 ml)</td>
<td>3.0±0.3</td>
<td>2.0±0.2†</td>
</tr>
<tr>
<td>Right arm circumference (cm)</td>
<td>27.6±2.1</td>
<td>27.1±1.9</td>
</tr>
</tbody>
</table>

%Fat, percentage of body weight due to fat; BP, blood pressure; bpm, beats per minute; M, whole body glucose uptake; FBF, forearm blood flow; FVR, forearm vascular resistance; Max FBF, maximal postischemic FBF; MFVR, minimum postischemic FVR.

*p<0.01, weight-loss vs. no-weight-loss group; †p<0.01, before vs. after weight loss.

Several studies have documented that the minimal vascular resistance measured at peak reactive hyperemia can be used as an index of the structural component of vascular resistance. Using venous occlusion plethysmography, investigators have demonstrated in both children and adults that structural changes in the resistance vessels appear to occur with hypertension. As can be seen in Tables 1 and 2, the current study demonstrates that obese adolescents not only appear to have structural changes in forearm vessels but also that these changes correlate with the degree of insulin resistance. In particular, we demonstrated a significant relation between minimum forearm vascular resistance and three estimates of insulin resistance: fasting insulin concentration, sum of the insulins after an oral glucose tolerance test, and insulin-mediated whole body glucose uptake. Because minimum forearm vascular resistance is a calculated value, it is important to realize that both of the components (mean arterial pressure and maximal forearm blood flow) used in its calculation were significantly different in the obese adolescents as compared with the nonobese adolescents. We observed that, although obese adolescents had significantly elevated resting forearm blood flows, ischemic exercise only resulted in a tripling of forearm blood flow in the obese adolescents, whereas the nonobese adolescents experienced nearly an 11-fold increase in forearm blood flow. The reduced vasodilator response observed in the obese adolescents correlated with the degree of insulin resistance (Figure 1). Our observation of obese adolescents having an attenuated limb vasodilator response to ischemia is consistent with the findings of Natali et al and Laakso et al, both of whom have reported that obese subjects with insulin resistance have attenuated limb vasodilator responses to hyperinsulinemia.
The exact nature of the forearm vascular changes are unknown but may involve vascular smooth hypertrophy, with increased wall-to-lumen ratio, decreased number of resistance vessels, or decreased size of the vessels without hypertrophy. 5,16 Egan and Julius18 demonstrated in adults with essential hypertension that minimal forearm vascular resistance correlated with increased sympathetic drive as assessed by plasma norepinephrine levels, and they speculated that chronic sympathetic stimulation may have increased minimum forearm vascular resistance by producing vascular smooth muscle hypertrophy. In the current study, although the obese adolescents had significantly higher plasma norepinephrine levels than those observed in the nonobese adolescents, we observed only a weak correlation between plasma norepinephrine level and both ischemia-induced maximal forearm blood flow and minimum forearm vascular resistance. In addition, the relation between norepinephrine level and minimum forearm vascular resistance lost statistical significance when the degree of insulin resistance was taken into account. In contrast to plasma norepinephrine level, we observed a significant relation between insulin resistance and both ischemia-induced maximal forearm blood flow and minimum forearm vascular resistance. In addition, we also demonstrated that with weight loss, there was a significant relation between the decrease in minimum forearm vascular resistance and the improvement in insulin resistance.

The major limitation of the current study is that, although we have demonstrated a relation between insulin resistance and structural changes in the resistance vessels of obese adolescents, we have not proved that this relation is causal. There are at least three ways of explaining the observed association between insulin resistance and elevated minimum forearm vascular resistance: 1) insulin resistance and elevated minimum forearm vascular resistance are two abnormalities that coexist in many obese adolescents but are not mechanistically related, 2) abnormalities of skeletal muscle vascular structure are the cause and not the result of insulin resistance, and 3) insulin resistance is directly related to the development of vascular changes.

Because weight loss was not associated with a significant change in either forearm circumference or forearm volume, it does not appear that the increase in ischemia-induced maximal forearm blood flow and the decrease in minimum forearm vascular resistance associated with weight loss are solely due to changes in forearm size. In addition, because we observed a significant relation between the improvement in insulin resistance and the improvement in minimum forearm vascular resistance after weight loss independent of changes in adiposity, we believe that our data support the hypothesis that insulin resistance could be either responsible for or the result of structural changes in the forearm resistance vessels observed in obese adolescents.

The mechanism whereby insulin resistance could cause an elevation in minimum forearm vascular resistance was not examined directly in the current study. However, other researchers have suggested that insulin and insulin-like growth factors are mitogens capable of stimulating smooth muscle proliferation and vascular hypertrophy.21-22 Insulin has been documented to stimulate the activity of the sodium-proton exchanger in skeletal muscle and adipocytes.21,22 Enhanced sodium-proton exchange could lead to intracellular calcium accumulation,23 which would be expected to enhance the sensitivity of the vascular smooth muscle to the pressor effects of norepinephrine and angiotensin.24-25 Increased sodium-proton exchange also would lead to intracellular alkalosis,6,26 a known stimulator of protein synthesis and cell proliferation,28 and thus could lead to the changes in minimum forearm vascular resistance observed in obese adolescents.

In summary, the current study has demonstrated that obese adolescents not only appear to have structural changes in forearm resistance vessels but also that these changes correlate with the degree of insulin resistance. Further studies will be necessary to determine if these vascular changes are the cause or the result of insulin resistance.

References


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