Impaired Microvascular Function in Obesity
Implications for Obesity-Associated Microangiopathy, Hypertension, and Insulin Resistance

Renate T. de Jongh, MD; Erik H. Serné, MD, PhD; Richard G. IJzerman, MD; Greetje de Vries; Coen D.A. Stehouwer, MD, PhD

Background—Obesity is associated with an increased risk of developing microangiopathy, hypertension, and insulin resistance. We hypothesized that obesity is a primary cause of microvascular dysfunction, which may contribute to the development of these obesity-related disorders.

Methods and Results—We examined microvascular function in 16 lean (body mass index <24 kg/m²) and 12 obese (body mass index >30 kg/m²) healthy women (mean age, 38.9±6.7 years) in the basal state and during physiological systemic hyperinsulinemia. We determined skin capillary recruitment after arterial occlusion with capillaroscopy and skin endothelium-independant vasodilation by iontophoresis of acetylcholine and sodium nitroprusside. Obese women, compared with lean women, had higher systolic blood pressure (P<0.05), impaired insulin sensitivity (P<0.01), impaired capillary recruitment in the basal state (P<0.05) and during hyperinsulinemia (P<0.05), and impaired acetylcholine-mediated vasodilation in the basal state (P<0.05) and during hyperinsulinemia (P<0.01). Sodium nitroprusside-mediated vasodilation was similar in lean and obese women. Capillary recruitment and acetylcholine-mediated vasodilation were positively correlated with insulin sensitivity (r=0.58, P<0.01 and r=0.55, P<0.01, respectively) and negatively with blood pressure (r=−0.64, P<0.001 and r=−0.42, P<0.05, respectively) in both lean and obese women.

Conclusions—Obesity is characterized by impaired microvascular function in the basal state and during hyperinsulinemia and, in both lean and obese women, microvascular dysfunction is associated with increased blood pressure and decreased insulin sensitivity. These findings are consistent with a contribution of impaired microvascular function to the development of obesity-related microangiopathy, hypertension, and insulin resistance. (Circulation. 2004;109:2529-2535.)

Key Words: microcirculation, obesity, insulin

The current obesity epidemic implies that obesity is becoming an increasingly important risk factor for cardiovascular disease.1-2 This is the case not only for large-artery disease, such as myocardial infarction and stroke,3,4 but also for disease entities that are caused wholly or in part by microangiopathy, notably retinopathy, nephropathy, and heart failure.5-7

How obesity causes large-artery disease and microangiopathy is poorly understood. In part, these may be the consequences of obesity-associated hypertension, insulin resistance, and dyslipidemia, but these risk factors cannot entirely explain the association of obesity with large-artery disease and microangiopathy.5,6

We hypothesized that obesity may be a primary cause of microvascular dysfunction and that this has several pathophysiological consequences. First, it may constitute a pathway through which obesity increases blood pressure and decreases insulin sensitivity. In addition, it may directly contribute to obesity-associated microangiopathy. Indeed, there is some evidence that measures of obesity in healthy individuals are associated with impaired microvascular function.8 In addition, microvascular dysfunction has been shown to increase peripheral vascular resistance and antedate the development of hypertension, indicating a role for microvascular dysfunction in the development of hypertension.9-11

Finally, microvascular dysfunction in the basal state and during hyperinsulinemia has been proposed to partially explain defects in the ability of insulin to increase glucose uptake in insulin-resistant states such as hypertension and obesity,12,13 because impaired recruitment of nutritive capillaries in muscle during physiological hyperinsulinemia may impair glucose delivery and uptake.14

In view of these considerations, we hypothesized that obesity is characterized by impaired microvascular function in the basal state and during physiological hyperinsulinemia and that such impairments may contribute to the development of obesity-associated microangiopathy, hypertension, and
insulin resistance. To investigate this, we examined microvascular function in the basal state and during physiological hyperinsulinemia in lean and obese women.

Methods

Subjects
We included 16 lean (body mass index <24 kg/m²) and 12 obese (body mass index ≥30 kg/m²) women. Volunteers were recruited through advertisements in newspapers. Participants were healthy as judged by medical history, nondiabetic, normotensive (<140/90 mm Hg) as determined by triplicate office blood pressure measurement, nonsmokers, and they did not use any medication except oral contraceptives. All participants gave informed consent for participation in the study. The study was undertaken with approval of the local ethics committee and performed in accordance with the Declaration of Helsinki.

Study Design
All individuals underwent the study protocol as shown in Figure 1. All measurements were conducted in a fasting state on an outpatient basis in a quiet, temperature-controlled room (23.4 ± 0.5°C) and after 30 minutes of acclimatization. The 0.65% saline infusion served as a control for a study of the effects of a lipid infusion on microvascular function; these results are not reported in the present article.

Hyperinsulinemic, Euglycemic Clamp
Insulin sensitivity was determined with the hyperinsulinemic, euglycemic clamp method as described previously, with an insulin infusion rate of 40 μU · m⁻² · min⁻¹. The M-value is defined as the glucose infusion rate during the second hour of the clamp expressed per kilogram of body weight. The M/I value is the M-value expressed per unit of plasma insulin concentration. A time- and volume-control study was performed in an identical manner at a later date.

Skin Microvascular Measurements
Nailfold capillaries in finger skin were recorded before and after 4 minutes of arterial occlusion with a digital cuff. This procedure was performed twice, and the mean of both measurements was used for analyses. We estimated baseline capillary density by counting the number of continuously erythrocyte-perfused capillaries during a 15-second period. Other capillaries can be seen to be intermittently perfused, and these may represent an important functional reserve. We used postocclusive reactive hyperemia to estimate this functional reserve. Postocclusive capillary recruitment was calculated by dividing the number of continuously erythrocyte-perfused capillaries during a 15-second period by the baseline density. The day-to-day coefficient of variation of postocclusive capillary recruitment was 15.9 ± 8.0%, as determined in 10 individuals on 2 separate days.

Microvascular endothelium-(in)dependent vasodilation was evaluated with laser Doppler flowmetry together with iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP) as described previously. The day-to-day coefficient of variation was 12.2 ± 9.7% for ACh-mediated vasodilation and 16.4 ± 8.1% for SNP-mediated vasodilation, as determined in 10 individuals on 2 separate days. To exclude possible nonspecific microvascular reactivity, we studied the effects of hyperinsulinemia on vehicle responses of ACh (mannitol 3%) and SNP (water for injection).

Blood Pressure
Ambulatory 24-hour blood pressure monitoring (Spacelabs 90207) was performed as described previously. One of the obese women did not complete the measurement because of intolerance to the continuous presence of the cuff around the arm. During study days, blood pressure measurements were determined as depicted in Figure 1 (Colin Press-Mate BP-8800). The average of 3 measurements during each period was used for further analyses.

Statistical Analyses
Data are expressed as mean ± SD or median (interquartile range) as appropriate. To examine differences in microvascular function between lean and obese women, we used the mean of 2 microvascular measurements, ie, the first 2 measurements on the insulin study day (Figure 1). (The use of the mean of the first 2 microvascular measurements on the saline study day gave similar results.) For analysis of associations, we used the mean of 4 microvascular measurements, ie, the first 2 measurements on both the insulin and saline study days (Figure 1).

The distribution of variables was tested for normality. A nonpaired Student’s t test was used to compare lean with obese women and a paired Student’s t test to compare insulin with saline infusion. The Wilcoxon signed-rank test for 2 related samples was used to examine insulin-mediated effects on vehicle responses. Multiple regression analysis was used to investigate confounding by systolic blood pressure, blood lipid concentrations, oral contraceptive use, or menstrual phases and to study associations with adjustment for age. Interaction analysis was performed to study whether associations were different between lean and obese women. A 2-tailed probability value of P < 0.05 was considered significant.

Results

Characteristics of Lean and Obese Women
Obese women had lower HDL cholesterol and higher triglyceride, free fatty acid, insulin, and glucose concentrations and were more insulin resistant than lean women (Table 1). Although all individuals were normotensive, systolic blood pressure was higher in obese women.

Metabolic and Hemodynamic Variables Before and During Insulin and Saline Infusion in Lean and Obese Women
Compared with saline infusion, blood glucose concentrations increased during insulin infusion in lean women, because glucose concentrations were clamped at 5 mmol/L (0.6 ± 0.6 versus −0.1 ± 0.9 mmol/L, P < 0.05) (Table 2).
sive capillary recruitment was diminished in obese women

density between lean and obese women (Table 3). Postocclu-
Compared With Lean Women
Microvascular Function Is Impaired in Obese

TABLE 1. Characteristics of Both Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Lean Women</th>
<th>Obese Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=16)</td>
<td>(n=12)</td>
</tr>
<tr>
<td>Age, y</td>
<td>39.0±6.7</td>
<td>38.8±7.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.1±8.3</td>
<td>111.2±19.6†</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.3±1.9</td>
<td>38.5±6.6‡</td>
</tr>
<tr>
<td>WHR</td>
<td>0.78±0.06</td>
<td>0.92±0.07†</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>5.1±0.5</td>
<td>5.1±0.8</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>2.8±0.4</td>
<td>2.9±0.7</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>2.0±0.6</td>
<td>1.5±0.3*</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>0.8±0.3</td>
<td>1.4±0.8†</td>
</tr>
<tr>
<td>Plasma FFAs, μmol/L</td>
<td>0.44±0.08</td>
<td>0.65±0.12†</td>
</tr>
<tr>
<td>Plasma insulin, pmol/L</td>
<td>30±8</td>
<td>82±30†</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>4.3±0.4</td>
<td>4.8±0.4†</td>
</tr>
<tr>
<td>M/I value (mg · kg⁻¹ · min⁻¹ · pmol · L⁻¹) x 100</td>
<td>2.1±1.0</td>
<td>0.5±0.3‡</td>
</tr>
<tr>
<td>24-Hour systolic blood pressure, mm Hg</td>
<td>115±8</td>
<td>123.7±*</td>
</tr>
<tr>
<td>24-Hour diastolic blood pressure, mm Hg</td>
<td>72±7</td>
<td>70±6</td>
</tr>
<tr>
<td>24-Hour heart rate, bpm</td>
<td>79±11</td>
<td>82±8</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; WHR, waist-to-hip ratio; M/I value, glucose infu-
sion rate during the second hour of the hyperinsulinemic clamp expressed per kilo-
gram body weight and per unit of plasma insulin concentration.

*P<0.05, †P<0.01.

Microvascular Function Is Impaired in Obese Compared With Lean Women

There were no differences in baseline perfused capillary density between lean and obese women (Table 3). Postocclu-
sive capillary recruitment was diminished in obese women (P<0.05) (Table 3; Figure 2). Iontophoresis of ACh induced a lower relative increase in perfusion in obese than in lean women (P<0.05). SNP-mediated vasodilation was not different between the 2 groups (P=0.7).

Compared with lean women, obese women had dyslipidemia and increased systolic blood pressure (Table 1). Multiple regres-
sion analysis demonstrated that adjustment for free fatty acids (FFAs) did not materially affect the association of obesity with either impaired capillary recruitment (β=−16.2 versus −16.3 percentage points) or ACh-mediated vasodilation (β=−147.2 versus −144.6 percentage points). Adjustment for HDL cholesterol or triglyceride concentrations also gave similar results (data not shown). Adjustment for systolic blood pressure did not change the association between obesity and impaired capillary recruitment (β=−16.8 versus −16.3 percentage points) but reduced the association between obesity and impaired ACh-mediated vasodilation by 38% (β=−89.4 versus −144.6 percentage points). The associations did not change materially if the use of oral contraceptives or phase of the menstrual cycle (follicular or luteal) was added to the model (data not shown).

Microvascular Function Is Associated With Blood Pressure and Insulin Sensitivity in Lean and Obese Women

Figure 3 shows that decreased capillary recruitment and ACh-mediated vasodilation were associated with both increased 24-hour systolic blood pressure and decreased insulin sensitivity in lean and obese women. Interaction analysis indicated that these associations were not significantly influ-
cenced by the presence of obesity (data not shown). The use of the M/I value instead of the M/I value did not lead to different conclusions (data not shown).

Insulin-Induced Changes in Microvascular Function Are Impaired in Obese Compared With Lean Women

Compared with saline infusion, insulin infusion did not change baseline perfused capillary density but increased postocclusive capillary recruitment in lean (15.4±13.4 versus −0.4±8.7 percentage points, P<0.001) and obese women (17.4±12.2 versus 2.3±6.1 percentage points, P<0.01) (Ta-

TABLE 2. Metabolic and Hemodynamic Variables Before and During Infusions of Insulin and Saline

<table>
<thead>
<tr>
<th></th>
<th>Before Infusion</th>
<th>During Infusion</th>
<th>Before Infusion</th>
<th>During Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>4.2±0.4</td>
<td>4.9±0.4†‡</td>
<td>4.3±0.3</td>
<td>4.2±0.5</td>
</tr>
<tr>
<td>Plasma insulin, pmol/L</td>
<td>25±10</td>
<td>378±1021§</td>
<td>24±8</td>
<td>19±8†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118±14</td>
<td>117±12</td>
<td>119±9</td>
<td>120±15</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>65±9</td>
<td>63±7</td>
<td>64±9</td>
<td>67±9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67±11</td>
<td>68±21</td>
<td>66±12</td>
<td>70±14†</td>
</tr>
<tr>
<td>Obese women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>4.7±0.6</td>
<td>5.0±0.2</td>
<td>4.8±0.5</td>
<td>4.7±0.6</td>
</tr>
<tr>
<td>Plasma insulin, pmol/L</td>
<td>79±30</td>
<td>483±187†§</td>
<td>84±31</td>
<td>63±28†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128±8</td>
<td>135±8§</td>
<td>130±10</td>
<td>135±11†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70±9</td>
<td>74±9</td>
<td>70±7</td>
<td>75±6†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±6</td>
<td>80±6†</td>
<td>72±6</td>
<td>76±6†</td>
</tr>
</tbody>
</table>

* P<0.05, †P<0.01 during vs before infusion; ‡P=0.05, §P<0.01 change during insulin vs saline infusion; ||P<0.05 change in obese vs lean women.
different (P=0.8), postocclusive capillary recruitment during insulin infusion was lower in obese than lean women (54.8±15.4 versus 72.4±25.1%, P<0.05).

Compared with saline infusion, insulin infusion did not influence baseline skin perfusion. Insulin infusion augmented ACh-mediated vasodilation in lean (162±116 versus −55±154 percentage points, P<0.01) but not in obese women (−43±212 versus −23±207 percentage points, P=1.0). The change in obese women was different from that in lean women (P<0.01). Insulin or saline infusion did not affect SNP-mediated vasodilation in either lean or obese women. Insulin infusion did not affect the responses to ACh vehicle (median [interquartile range] before versus during insulin infusion, 67% [25%–174%] versus 95% [34%–163%], P=0.8; tested in 3 obese and 11 lean women) or SNP vehicle (40% [−16% to 139%] versus 67% [16%–171%], P=1.0; tested in 6 obese and 10 lean women).

Similar results were obtained if absolute increases in capillary density and perfusion during iontophoresis of ACh, SNP, and vehicles of both substances were used instead of relative increases (data not shown).

Skin temperature and insulin-mediated changes in skin temperature during microvascular measurements did not differ between lean and obese women (data not shown).

**Discussion**

The central new finding of this study is that obese, compared with lean, women are characterized by impaired skin microvascular function in the basal state and during physiological hyperinsulinemia. Specifically, we show that in obese women, postocclusive capillary recruitment and microvascular endothelium–dependent vasodilation are decreased; that the insulin-induced increase of microvascular endothelium–dependent vasodilation is abolished; and that, although the insulin-induced increase in postocclusive capillary recruitment is preserved, net postocclusive capillary recruitment during hyperinsulinemia is impaired. In addition, we found that impaired microvascular function is associated with decreased insulin sensitivity and increased blood pressure in both lean and obese women. These findings are consistent with a role for microvascular dysfunction in the development of obesity-related microangiopathy, hypertension, and insulin resistance.
Our finding of an inverse relationship between microvascular function and blood pressure in both obese and lean women is consistent with a role for microvascular dysfunction in the development of hypertension in obesity and extends previous findings in patients with borderline hypertension, in normotensive and hypertensive lean individuals, and in individuals with a familial predisposition to hypertension. Our study was cross-sectional, and we therefore cannot exclude the possibility that microvascular dysfunction was the result of small increases in blood pressure. However, the fact that differences in blood pressure could explain at most a small part of the differences in microvascular function between lean and obese women strongly suggests that presence of obesity is a more important predictor of microvascular dysfunction than blood pressure per se.

We are the first to demonstrate that obesity is associated with microvascular dysfunction both in the basal state and during hyperinsulinemia and that this microvascular dysfunction is related to insulin resistance. These results are consistent with but do not prove a causal link between microvascular dysfunction and impairment of insulin-mediated glucose uptake. Our findings are in agreement with previous studies in resistance vessels. However, these studies measured changes in total limb blood flow, whereas recent studies in rats and humans have demonstrated the importance of the microvascular distribution pattern rather than total blood flow. According to this concept, insulin redirects blood flow from nonnutritive vessels to nutritive capillary beds, thereby increasing access of glucose and insulin to muscle cells, independently of changes in total blood flow. Indeed, in rat muscle, infusion of Intralipid or tumor necrosis factor-α (TNF-α) impairs both insulin-induced capillary recruitment and glucose uptake. In addition, obese Zucker rats are characterized by both impaired insulin-induced glucose uptake and impaired capillary perfusion in the basal state.
and during hyperinsulinemia. We now show that this concomitant impairment in insulin sensitivity and microvascular function in the basal state and during hyperinsulinemia is also present in obese women. We also show that microvascular dysfunction in the basal state was significantly associated with reduced insulin-induced glucose uptake in lean and obese women. The latter finding extends previous observations in normotensive and hypertensive individuals. Taken together, these data are consistent with a role for microvascular dysfunction in the development of insulin resistance in obesity.

In obese women, the insulin-induced increase of microvascular endothelium-dependent vasodilation was abolished, but the insulin-induced increase in postocclusive capillary recruitment was preserved (Figure 2). The explanation for this discrepancy is not entirely clear. The stimulus used in postocclusive capillary recruitment (ie, increased flow) differs from that used in microvascular endothelium-dependent vasodilation (ie, ACh), and insulin-induced changes in the responses to these stimuli may be differentially sensitive to obesity. In addition, capillary perfusion is thought to be regulated not only by precapillary arteriolar tone and arteriolar vasoemotion but also by the characteristics of the capillary network itself.

The pathophysiological mechanism behind the relationship between obesity and microvascular dysfunction is probably multifactorial. Adipose tissue secretes substances, such as FFAs, TNF-α, and adiponectin, that can influence microvascular function. An increase in FFAs impairs vascular function in resistance vessels in humans and in microvasculature in rats. Fasting FFA levels were not associated with microvascular function in the present study, but this does not exclude a role for FFA dynamics in modulating microvascular function. In addition, in rats, acute TNF-α elevation impairs insulin-induced capillary recruitment and glucose uptake, and in humans, it concomitantly impairs insulin-induced endothelium-dependent vasodilation in resistance vessels and glucose uptake. Adiponectin levels are reduced in obesity, and adiponectin has a vasoprotective effect, as demonstrated by associations between hypoadiponectinemia and impaired endothelial function in resistance vessels. At this point, it should be emphasized that the cross-sectional design of our study does not exclude the possibility that there are as yet unmeasured variables that (in part) explain the association between obesity and microvascular dysfunction, such as physical fitness or diet. These possibilities require further studies.

Figure 3. Correlations between capillary recruitment, ACh-mediated vasodilation, 24-hour systolic blood pressure, and insulin sensitivity in lean (open circles) and obese (closed circles) women. Correlation coefficients are adjusted for age.
Although muscle is the main peripheral site of insulin-mediated glucose uptake and vascular resistance, we studied skin and not muscle microvascular function because, in skin, functional capillary recruitment can be directly visualized and measured in vivo. Comparable insulin-mediated metabolic and microvascular effects can be demonstrated in skin and muscle.\(^2^7\)\(^2^9\) In addition, skin microvascular function is associated with blood pressure,\(^8\)\(^1^3\) and hypertension is characterized by defects in both muscle and skin microvascular function.\(^1^3\)\(^3^0\) Thus, the study of skin microvascular function seems a reasonable model of muscle microvascular function.

Caution should be taken in extrapolating the present findings in women to men, although previous data have shown that the association between waist-to-hip ratio and skin microvascular function is similar in men and women (Erik H. Sern, MD, PhD, et al, unpublished data, 2002). We studied women to minimize effects of sex differences. Previous studies have shown sex differences in skin blood flow responses to provocative maneuvers\(^3^1\) and in endothelial NO production in skin microvasculature.\(^3^2\) In addition, extrapolation to other populations of women should be performed with caution because of possible selection bias. However, if anything, one would expect that the present results underestimated the effects of obesity in general, because we studied a group of healthy, nonhypertensive, and non-diabetic obese women. Finally, the small number of participants may have concealed an interaction of obesity in the relationship between microvascular function and insulin-mediated glucose uptake.

In summary, we are the first to report that obesity is associated with impaired skin microvascular function, measured as postocclusive capillary recruitment and endothelial-dependent vasodilation, in the basal state and during physiological hyperinsulinemia. In addition, we demonstrated that impaired microvascular function is associated with increased blood pressure and impaired insulin sensitivity in lean and obese women. The obesity-related impairment in microvascular function may contribute to the increased risk of developing microangiopathy, hypertension, and insulin resistance. Further studies are necessary to elucidate the mechanisms that link obesity and impairment of microvascular function. Such studies are an important step to develop strategies in the prevention of obesity-associated microangiopathy, hypertension, and insulin resistance.

Acknowledgments

This work was supported by grants from the Dutch Diabetes Research Foundation (DFN 98.102) and from The Netherlands Organization for Health Research and Development (ZonMw 940.37.025).

References

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_Circulation_. 2004;109:2529-2535; originally published online May 10, 2004;
doi: 10.1161/01.CIR.0000129772.26647.6F
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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