Low-flow vascular remodeling in the metabolic syndrome X

David W. Stepp, David M. Pollock, and Jefferson C. Frisbee

Vascular Biology Center and Department of Physiology, Medical College of Georgia, Augusta, Georgia 30912; and Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226

Submitted 2 September 2003; accepted in final form 10 November 2003

Low-flow vascular remodeling in the metabolic syndrome X. Stepp, David W., David M. Pollock, and Jefferson C. Frisbee. Am J Physiol Heart Circ Physiol 286: H964–H970, 2004.—Peripheral microvascular dysfunction is a common affliction in patients with the metabolic syndrome X. Previous studies have described a number of vascular impairments in vasomotor control in both human patients and animal models of syndrome X, but the net effect of these impairments on microvascular structure has not been examined. The goal of the current study was to test the hypothesis that syndrome X reduces muscle perfusion and induces vascular remodeling. The obese Zucker rat was used as a model of syndrome X, and the microcirculation of the hindlimb and brain were examined. Obese Zucker rats were obese, hyperlipidemic, hyperinsulinemic, and hyperglycemic. Blood flow to the hindlimb was reduced by 59% in obese rats relative to lean rats. Skeletal muscle resistance arteries of the hindlimb microcirculation of obese rats had thinner walls, smaller lumens, and reduced distensibility. Hindlimb microvessels from obese rats also demonstrated reduced expression of vascular smooth muscle cell markers. Each of these traits is consistent with low-flow remodeling. In contrast, the cerebral microcirculation, where flow is vigorously autoregulated, showed no vascular remodeling nor were there changes in microvascular smooth muscle marker expression. Neither physical activity nor muscle mass were significantly different between lean and obese rats. Taken together, these findings suggest that syndrome X, by reducing hindlimb blood flow, induces a marked remodeling of microcirculation to favor smaller, less distensible vessels. This remodeling may result in an architectural limitation of maximum perfusion capacity and may be an important maladaptation in the progression of peripheral microvascular disease.

MATERIALS AND METHODS

Animals. All experiments used 13- to 15-wk-old male lean (LZR) and obese Zucker (OZR) rats (Harlan) fed standard rat chow and tap water ad libitum. Rats were housed in the animal care facility at either the Medical College of Georgia or the Medical College of Wisconsin, both of which are approved by the American Association for the Accreditation of Laboratory Animal Care, and the respective Institutional Animal Care and Use Committees.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

The Metabolic Syndrome X is an emerging epidemic in Western cultures and consists of the combined presentation of multiple cardiovascular risk factors (17). These factors, including hypertension, insulin resistance, and obesity, directly contribute to the higher incidence of cardiovascular diseases, including peripheral vascular disease, coronary artery disease, and renal disease found in patients with syndrome X (3, 15). The underlying mechanisms of this elevated incidence are unresolved, but microvascular dysfunction has been implicated as a contributing factor. The effects of syndrome X on microvascular structure and function are poorly understood. Recently, we have used the obese Zucker rat as a model of syndrome X to examine the effects of this affliction on vasomotor control in the skeletal muscle microcirculation of the hindlimb. The results of these studies show reduced vasodilation to nitric oxide-dependent stimuli (12) and hypoxia (9) and augmented constriction to α-adrenergic (23) and myogenic (11) stimulation. These findings demonstrate that the hindlimb microcirculation of a model of syndrome X may be predisposed to chronic reductions in blood flow secondary to the loss of vasomotor control. Accordingly, we hypothesized that the hindlimb blood flow would be reduced in a model of syndrome X and that the structure of the microcirculation may remodel to reflect chronic reductions in blood flow.

The effects of chronic reductions in perfusion on vascular structure have been the subject of recent study in several groups (5, 16, 18, 25). Chronic flow reduction via surgical manipulation results in a reduction in both lumen diameter and cross-sectional wall area. Dedifferentiation of the smooth muscle component of the vessel wall is also observed via downregulation of the smooth muscle markers calponin and caldesmon (5). As a result of this remodeling, the maximum perfusion capacity of the affected vessel is reduced. However, the demonstration of low-flow remodeling in a disease model has been lacking.

The objective of the current study was to test the hypothesis that the previously observed loss of vasomotor control results in reduced hindlimb blood flow and low flow remodeling in syndrome X. Vascular structural parameters and mechanics were assessed in the isolated pressurized gracilis artery as a representative resistance artery using videomicroscopy. Smooth muscle cell (SMC) markers calponin, caldesmon, and α-actin were used to assess SMC dedifferentiation via protein expression assay. Hindlimb blood flow was assessed by ultrasonic flowmetry. Basic hemodynamic and physical activity parameters were assessed by whole animal telemetry. Data from these experiments show that syndrome X results in a remodeling of the hindlimb microcirculation consistent with chronic flow reduction. Wall thickness and lumen are reduced, and compliance of the vessel wall is lost. Muscle blood flow is reduced, and the expression of SMC-specific markers calponin and 128K caldesmon is decreased. In the cerebral circulation, where flow is aggressively autoregulated, no remodeling was observed and SMC markers were unchanged. Neither a reduction in physical activity nor muscle mass explains the reduced perfusion. Taken together, these studies provide the first documentation of low-flow remodeling in a model of vascular disease.

THE METABOLIC SYNDROME X is an emerging epidemic in Western cultures and consists of the combined presentation of multiple cardiovascular risk factors (17). These factors, including hypertension, insulin resistance, and obesity, directly contribute to the higher incidence of cardiovascular diseases, including peripheral vascular disease, coronary artery disease, and renal disease found in patients with syndrome X (3, 15). The underlying mechanisms of this elevated incidence are unresolved, but microvascular dysfunction has been implicated as a contributing factor. The effects of syndrome X on microvascular structure and function are poorly understood.

Recently, we have used the obese Zucker rat as a model of syndrome X to examine the effects of this affliction on vasomotor control in the skeletal muscle microcirculation of the hindlimb. The results of these studies show reduced vasodilation to nitric oxide-dependent stimuli (12) and hypoxia (9) and augmented constriction to α-adrenergic (23) and myogenic (11) stimulation. These findings demonstrate that the hindlimb microcirculation of a model of syndrome X may be predisposed to chronic reductions in blood flow secondary to the loss of vasomotor control. Accordingly, we hypothesized that the hindlimb blood flow would be reduced in a model of syndrome X and that the structure of the microcirculation may remodel to reflect chronic reductions in blood flow.

The effects of chronic reductions in perfusion on vascular structure have been the subject of recent study in several groups (5, 16, 18, 25). Chronic flow reduction via surgical manipulation results in a reduction in both lumen diameter and cross-sectional wall area. Dedifferentiation of the smooth muscle component of the vessel wall is also observed via downregulation of the smooth muscle markers calponin and caldesmon (5). As a result of this remodeling, the maximum perfusion capacity of the affected vessel is reduced. However, the demonstration of low-flow remodeling in a disease model has been lacking.

The objective of the current study was to test the hypothesis that the previously observed loss of vasomotor control results in reduced hindlimb blood flow and low flow remodeling in syndrome X. Vascular structural parameters and mechanics were assessed in the isolated pressurized gracilis artery as a representative resistance artery using videomicroscopy. Smooth muscle cell (SMC) markers calponin, caldesmon, and α-actin were used to assess SMC dedifferentiation via protein expression assay. Hindlimb blood flow was assessed by ultrasonic flowmetry. Basic hemodynamic and physical activity parameters were assessed by whole animal telemetry. Data from these experiments show that syndrome X results in a remodeling of the hindlimb microcirculation consistent with chronic flow reduction. Wall thickness and lumen are reduced, and compliance of the vessel wall is lost. Muscle blood flow is reduced, and the expression of SMC-specific markers calponin and 128K caldesmon is decreased. In the cerebral circulation, where flow is aggressively autoregulated, no remodeling was observed and SMC markers were unchanged. Neither a reduction in physical activity nor muscle mass explains the reduced perfusion. Taken together, these studies provide the first documentation of low-flow remodeling in a model of vascular disease.

MATERIALS AND METHODS

Animals. All experiments used 13- to 15-wk-old male lean (LZR) and obese Zucker (OZR) rats (Harlan) fed standard rat chow and tap water ad libitum. Rats were housed in the animal care facility at either the Medical College of Georgia or the Medical College of Wisconsin, both of which are approved by the American Association for the Accreditation of Laboratory Animal Care, and the respective Instituti-
tional Animal Care and Use Committees approved all protocols. All rats were anesthetized with an injection of pentobarbital sodium (60 mg/kg ip). Rats received a tracheal intubation for the maintenance of a patent airway and a carotid arterial cannula for the determination of arterial blood pressure.

Measurement of hindlimb blood flow. A microrheology flow probe (Transonic) was placed around the femoral artery, immediately distal to its origin from the iliac artery, to continuously monitor the volume flow of blood to the hindlimb.

Telemetry. Telemetry transmitters (Data Sciences; St. Paul, MN) were implanted according as described previously (21) under pentobarbital sodium anesthesia (65 mg/kg ip; Abbott, North Chicago, IL). A midline incision was used to expose the abdominal aorta, which was briefly occluded to allow insertion of the transmitter catheter. The catheter was secured in place with tissue glue. The transmitter body was then sutured to the abdominal wall along the incision line as the incision was closed. Rats were allowed to recover from surgery and returned to individual housing for at least 1 wk before data acquisition was initiated. Aortic pressure, heart rate, and physical activity were continuously monitored for a period of 7 days between 13 and 14 wk of age.

Assessment of physical activity. To determine whether levels of physical activity were comparable between lean and OZR at 13–14 wk of age, two assessments were performed. First, physical activity counts were assessed by radio telemetry as described above. These counts reflect the frequency of movement of the animal across a grid, and each count reflects one movement of the animal. Second, because inactivity causes muscle atrophy, the mass of key muscles in the hindlimb was measured by dissection of these muscles and obtaining wet weights in grams.

Measurements of carotid blood flow. Cerebral blood flow was estimated using measurements of internal carotid artery blood flow. In these protocols, five LZR and five OZR were maintained under free-breathing isoflurane anesthesia (2–3%) and subjected to surgical resection of the carotid circulation to occlude the left common carotid and right external carotid arteries. In this configuration, common carotid blood flow reflects internal carotid artery flow. The internal carotid services only the brain. Right carotid artery blood flow in these animals was measured by ultrasonic flowmetry.

Determination of maximum resistance. To determine maximum perfusion capacity, the resistance of the hindlimb to fixed levels of flow was determined. In five LZR and five OZR, the aorta was cannulated above the iliac bifurcation and below the renal and mesenteric branches. Vessels were quickly dissected free and snap frozen in liquid nitrogen. Frozen samples were pulverized with a alloy steel sample holder and stored at −80 °C until assayed. Before the experimental procedures were started, the perfusate and superfusate PSS were replaced with a Ca²⁺-free PSS. Vessels were then challenged with 10⁻⁷ M norepinephrine until all vascular reactivity was eliminated and active tone was lost. At this time, the intraluminal pressure was cycled between 0 and 160 mmHg. To ensure that a negative intraluminal pressure was not exerted on the vessel, 5 mmHg was used as the “0 mmHg” intraluminal pressure point; all other values of intraluminal pressure were multiples of 20 mmHg up to 160 mmHg (skeletal muscle vessels) or 140 (cerebral vessels). Specific pressure values were randomized to prevent the occurrence of ordering effects. After 10 min at each value of intraluminal pressure, the inner and outer diameter of the passive arteriole was determined.

All calculations of passive arteriolar wall mechanics are similar to those used previously by Baumbach and Hadju (1). Vessel wall thickness was calculated as

\[
WT = \frac{(OD - ID)}{2}
\]

where WT represents wall thickness (in μm) and OD and ID represent arteriolar outer and inner diameter, respectively (in μm).

Arteriolar cross-sectional wall area (CSWA; μm²), assuming the arteriole is round, was calculated as

\[
CSWA = \left(\pi \left(\frac{OD}{2}\right)^2\right) - \left(\pi \left(\frac{ID}{2}\right)^2\right)
\]

Incremental arteriolar distensibility (Dist inc; percent change in arteriolar diameter/mmHg) was calculated as

\[
Dist_{inc} = \left(\frac{\Delta OD}{\pi (ID)^2}\right) \times 100
\]

where \(\Delta OD\) represents the change in internal arteriolar diameter for each incremental change in arteriolar pressure (\(\Delta P_{in}\)).

For the calculation of circumferential stress, intraluminal pressure was converted from mmHg to N/m², where 1 mmHg = 1.334 × 10⁻² N/m². Circumferential stress (σ) was then calculated as

\[
\sigma = \frac{(P_l - ID)}{(2WT)}
\]

Circumferential strain (ε) was calculated as

\[
\varepsilon = \frac{(ID - ID_5)}{ID_5}
\]

where ID₅ represents the internal arteriolar diameter at the lowest intraluminal pressure (i.e., 5 mmHg). Each stress-strain relationship was fitted with the equation

\[
Y = \alpha \cdot e^{\beta X}
\]

where \(Y\) is circumferential stress, \(X\) is circumferential strain, \(\alpha\) is the intercept, and \(\beta\) is the “slope” of the exponential fit. The \(\beta\)-coefficient is used as a relative measure of vascular stiffness.

Western analysis. Expression of smooth muscle markers was examined by the immunoblotting of total protein isolated from the hindlimb (distal femoral and attending branches) or the ventral surface of the brain (circle of Willis, cerebral arteries, and attending branches). Vessels were quickly dissected free and snap frozen in liquid nitrogen. Frozen samples were pulverized with a alloy steel pestle and mortar. The cell extract was prepared in a lysis buffer containing the following components: 50 mM Tris-HCl, 0.1 mM EDTA, 0.1 mM EGTA, 10% SDS, 10% deoxycholic acid, 0.27 mg/ml 4-(2-aminoethyl)-benzenesulfonylfluoride hydrochloride, 300 mM NaCl, 1% Nonidet P-40, and 0.5% sodium deoxycholate. The extracts were clarified by centrifugation, and the protein concentrations were determined using a Bradford method.
Table 1. Summary data for lean and obese Zucker rats

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>372±31</td>
<td>665±5*</td>
</tr>
<tr>
<td>Plasma glucose, mg/dl</td>
<td>143±8</td>
<td>224±7*</td>
</tr>
<tr>
<td>Plasma sodium, mmol/l</td>
<td>156±4</td>
<td>155±2</td>
</tr>
<tr>
<td>Plasma potassium, mmol/l</td>
<td>4.0±0.5</td>
<td>4.1±1.0</td>
</tr>
<tr>
<td>Plasma triglyceride, mg/dl</td>
<td>54.0±4.0</td>
<td>443.0±80.0*</td>
</tr>
<tr>
<td>Plasma total cholesterol, mg/dl</td>
<td>51.0±5.0</td>
<td>95.0±10.0*</td>
</tr>
<tr>
<td>Plasma thyroid hormone, μg/dl</td>
<td>4.6±1.2</td>
<td>3.6±1.3</td>
</tr>
<tr>
<td>Plasma cortisol, μg/dl</td>
<td>1.2±0.2</td>
<td>1.4±0.5</td>
</tr>
<tr>
<td>Plasma insulin, μU/ml</td>
<td>57±5</td>
<td>218±15*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10 rats. *P < 0.05.

Table 2. Hemodynamic and muscle mass data

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>96±2</td>
<td>106±3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>397±7</td>
<td>365±6</td>
</tr>
<tr>
<td>Muscle mass, g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gracilis</td>
<td>1.22±0.5</td>
<td>1.22±0.4</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>2.27±0.7</td>
<td>2.25±0.4</td>
</tr>
<tr>
<td>Semiten</td>
<td>1.64±0.6</td>
<td>1.66±0.6</td>
</tr>
<tr>
<td>Seminem</td>
<td>1.85±0.6</td>
<td>1.78±0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10 rats.
significant (NS)). Brain mass was also similar between LZR and OZR (1.97 ± 0.04 vs. 1.94 ± 0.03 g, n = 5, P = NS).

Wall dimensions. A representative hemotoxylin and eosin stain of gracilis arteries from perfusion-fixed Zucker rats is shown in Fig. 2, and the relationship between pressure and internal diameter and wall thickness of the gracilis artery (assayed by video microscopy) are shown in Fig. 3. Arteries from OZR had smaller lumens (Fig. 3A) and thinner walls (Fig. 3B) than those of LZR. At maximal pressure, internal diameter was reduced 31% (238 ± 11 vs. 165 ± 5 μm, P < 0.001), and wall thickness was reduced 29% (41 ± 3 vs. 30 ± 2 μm, P < 0.01). Wall dimension data for the middle cerebral artery are shown in Fig. 4. No significant differences were observed in the lumen diameter (Fig. 4A) or wall thickness (Fig. 4B) in the middle cerebral artery between LZR and OZR. Parallel experiments in the posterior cerebral artery or the circle of Willis also produced no difference in wall dimensions (data not shown). The summary data for wall dimensions at maximal pressure are shown in Table 3.

Wall mechanics. The compliance of the gracilis artery vascular wall as a function of intraluminal pressure is shown in Fig. 5. Arteries from OZR demonstrated reductions in distensibility (Fig. 5A) over the range of intraluminal pressures, notably in the range of 40–80 mmHg. Reductions in compliance are also demonstrated by a leftward shift in the stress-strain relation (Fig. 5B). Data from the middle cerebral artery are shown in Fig. 6. Neither distensibility (Fig. 6A) nor the stress-strain relation (Fig. 6B) were significantly different between vessels from LZR and OZR.

Vascular SMC dedifferentiation. To further substantiate that the changes in vessel structure reflected low-flow remodeling, the expression of smooth muscle markers was assayed. The results are shown in Fig. 7. Representative Western blots are shown in Fig. 7A, and summary data from four experiments are shown in Fig. 7B. High-molecular-mass caldesmon (128 K) and SMC calponin were reduced by 75% and 56%, respectively, when normalized to HSP90 expression. The expression of α-actin was not significantly different between vessels from LZR and OZR. Figure 8 illustrates the expression of smooth muscle markers in cerebral vessels from LZR and OZR. Figure 8A shows a representative Western blot, and Fig. 8B provides summary data. No significance differences were observed between any smooth muscle markers in the cerebral circulation from either LZR or OZR.

Hindlimb vascular resistance. To determine whether the above changes correlate with a change in maximum hindlimb vascular resistance, resistance to flow in the maximally dilated
vasculature was determined. The data are shown in Fig. 9. Calculated resistance at high levels of flow was significantly greater in OZR relative to LZR, consistent with remodeling to reduced lumen diameter in the resistance circulation.

**DISCUSSION**

The objective of the current study was to determine the effects of the combined presentation of obesity, Type II diabetes, and dyslipidemia on vascular structure and mechanics in the peripheral circulation. The key findings of these experiments are that vascular remodeling occurs in the hindlimb, that this remodeling occurs in parallel with reduced blood flow and increased maximum resistance in the hindlimb, and that this remodeling does not correlate with reduced physical activity.

Remodeling of the microcirculation is considered a hallmark of established vascular disease. The best known form of vascular remodeling occurs in hypertension, in which there is often hypertrophy of the vascular wall and a reduction in lumen size (14). The remodeling observed in hypertension is thought to reflect, in part, a response to the physical pressure against the vascular wall and an effort to normalize wall tension by increasing wall thickness. Another major determinant of blood vessel structure is flow. Surgical shunts produce increases in lumen size and wall thick-

---

**Table 3. Summary data for wall dimensions at maximal pressure**

<table>
<thead>
<tr>
<th></th>
<th>Gracilis Artery</th>
<th>Middle Cerebral Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inner diameter,</strong> μm</td>
<td>Lean: 238 ± 10</td>
<td>Obese: 165 ± 5*</td>
</tr>
<tr>
<td></td>
<td>Lean: 320 ± 7</td>
<td>Obese: 224 ± 7*</td>
</tr>
<tr>
<td><strong>Outer diameter,</strong> μm</td>
<td>Lean: 41 ± 3</td>
<td>Obese: 30 ± 2*</td>
</tr>
<tr>
<td></td>
<td>Lean: 23 ± 1</td>
<td>Obese: 20 ± 2</td>
</tr>
<tr>
<td><strong>CSWA, μm²</strong></td>
<td>Lean: 35,438 ± 2,392</td>
<td>Obese: 18,291 ± 5,144*</td>
</tr>
<tr>
<td><strong>Wall-to-lumen ratio</strong></td>
<td>Lean: 0.04 ± 0.01</td>
<td>Obese: 0.04 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>Lean: 0.0017</td>
<td>Obese: 0.016 ± 0.01</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10 rats. CSWA, cross-sectional wall area. *P < 0.05, obese vs. lean.

---

Fig. 5. Microvascular compliance in gracilis arteries from lean and obese Zucker rats. A: relationship between intraluminal pressure and incremental distensibility. B: relationship between circumferential wall stress and circumferential wall strain. Data are means ± SE from n = 11 vessels, one from each animal, for each group. *P < 0.05.

Fig. 6. Microvascular compliance in middle cerebral arteries from lean and obese Zucker rats. A: relationship between intraluminal pressure and incremental distensibility. B: relationship between circumferential wall stress and circumferential wall strain. Data are means ± SE from n = 9 vessels, one from each animal, for each group.
ness in high flow pathways and decreases in these variables in low flow pathways (5, 13, 24). Whereas considerable insight has been gleaned from these interventions, evidence of low flow remodeling in the setting of vascular dysfunction has not been identified.

In the current study, we observe remodeling in a disease model, the OZR, which we attribute to reduced perfusion. In the peripheral circulation, where muscle flow is low, the arterial wall is reduced in thickness and cross-sectional area, the maximum lumen is smaller, and smooth muscle markers indicate dedifferentiation of vascular smooth muscle. As illustrated by Buus and coworkers (5), these are all indicators of low-flow remodeling. In the cerebral circulation, where flow is known to vary very little (4), vascular structure, distensibility, and the expression of vascular SMC markers are unchanged. These findings lend additional credence to the argument that the changes observed in the peripheral circulation are due to reduced blood flow because the cerebral circulation would be exposed to the same blood chemistry profile as the peripheral vessels. Taken together, these data provide the first evidence that reduction in hindlimb blood flow, in parallel with the vascular pathologies of syndrome X, are sufficient to induce vascular remodeling.

Similar changes in vascular structure have been observed with the hindlimb unweighting model. This model, in which the rats lower limbs are immobilized and perfusion is reduced (7), was used in an elegant study by Delp et al. (8) to identify microvascular effects of chronic unweighting. Parallel to reduced perfusion, skeletal muscle arterioles demonstrated reduced wall thickness in feed arteries and 1A arterioles from rats, which had been suspended relative to controls. Interestingly, the degree of wall thickness was reduced ~20–40% with complete immobilization of the hindlimbs, whereas our study found a ~30% reduction.
while the animals were still active and free moving. The potent remodeling and reduced perfusion in the OZR therefore most likely reflects the less dilated, more constricted state of the vasculature, rather than low flow due to inactivity.

Another common cause of reduced blood flow to skeletal muscle is atrophy of skeletal muscle, resulting in reduced oxygen demand and thus reduced perfusion (26). To determine whether low flow remodeling was due to a loss of muscle mass in the OZR, several key muscles of the hindlimb were removed and weighed. As shown in Table 2, all muscles preserved their mass, consistent with the relatively normal daily physical activity shown in Fig. 1. These findings rule out a simple lack of activity and muscle loss as the underlying basis for reduced blood flow in the hindlimb of the OZR.

An additional finding in these studies is that the compliance of the arterial wall is significantly reduced in arterioles from the peripheral vasculature of the OZR. This is evidenced by a reduction in the incremental distensibility and a leftward shift in the stress-strain curve. The basis for this observation is unclear. Whereas it is tempting to speculate that low flow remodeling has effects on vascular mechanics, it must be emphasized that the OZR is also afflicted with a borderline hypertension as shown in our studies and similar work using radiotelemetry (6, 20). Hyperpertension has been shown to cause reductions in microvascular distensibility (2, 10), although the hypertensive effect is concomitant with vascular hypertrophy (19), whereas the current remodeling is associated with vascular wall reduction. Although beyond the scope of the current work, additional studies are warranted to explore the effects of chronic reductions in flow on microvascular distensibility.

In conclusion, we report here for the first time evidence of microvascular low-flow remodeling in an animal model of disease. This remodeling is characterized by reduced lumen size, atrophy of the vascular wall, and dedifferentiation of the vascular smooth muscle comprising the wall. In beds where flow is preserved, no remodeling is observed. Neither a loss of muscle mass nor a reduction in physical activity explain the remodeling observed in these animals. These data suggest that previously described losses in vasomotor control are sufficient to induce perturbations in vascular structure. The specific pathways and functional impact of these changes remain to be determined. We suggest that these alterations in vascular structure secondary to reduced perfusion may be an important step in the progression of diabetic peripheral vascular disease.

ACKNOWLEDGMENTS

The authors thank Deron W. Jones, Francis A. Sylvester, Hiram Ocasio, Julie R. Campbell, and James D. Mintz for the valuable assistance in these experiments.

GRANTS

We acknowledge support from National Heart, Lung, and Blood Institute Grant HL-37303 (to D. W. Stepp) and the American Heart Association (Scientist Development Grant to D. W. Stepp and J. C. Frisbee) in completion of this work.

REFERENCES