Intestinal Microvascular Growth During Maturation in Diabetic Juvenile Rats

Joseph L. Unthank and H. Glenn Bohlen

To determine if intestinal microvascular growth is impaired in diabetic juvenile animals, a segment of the terminal ileum was marked and the microvasculature of this segment observed at the age of 5 weeks and again at the age of 10–11 weeks in normal and diabetic Sprague Dawley rats. Diabetes was induced by streptozotocin after the first observation period and the plasma glucose concentration exceeded 500 mg% by the age of 10–11 weeks. Microvascular growth was quantitated by measurements of the number, length, and maximally dilated inner diameters of specific arterioles and by intercapillary distances in the marked intestinal region at both ages. Although intestinal enlargement was much greater in diabetics, there was no change in the number of arterioles during maturation and intercapillary distances were equivalent in diabetic and normal rats. In normal and diabetic animals, the arteriolar length increased to match bowel elongation, however, increases in bowel and arteriolar lengths in diabetic animals were about twice that of normal rats. During juvenile maturation, the maximally dilated inner diameters of the small arterioles in diabetic animals were increased compared with their normal counterparts. Thus, arteriolar growth during maturation is characterized by changes in the length but not in the number of vessels in intestine of both normal and diabetic rats. The perfusion of about 90% more tissue by mass for each arteriole in diabetic rats is facilitated by arteriolar dilation. The maintenance of normal intercapillary distances in the intestinal muscle of diabetic rats, despite the much greater than normal bowel growth, requires the accelerated formation of new capillaries. (Circulation Research 1988;63:429–436)

Microangiopathy associated with the diabetic state has been shown to compromise both the anatomy and the physiological regulation of the microvasculature. Abnormalities in vessel wall characteristics and vascular density develop very rapidly in severely diabetic animals. Consequently, the development of diabetes in juvenile animals is of particular concern because of possible interference with the process of microvascular growth during maturation. Studies in normal juvenile rats during their rapid growth phase after weaning indicate that individual smooth muscle cells hypertrophy and existing vessels elongate but few, if any, new microvessels are formed. Therefore, the normal growth of the vasculature seems to follow a course of existing cell and vessel hypertrophy rather than hyperplasia. The situation in diabetic juvenile animals could be distinctly different if normal microvascular growth by hypertrophy is compromised by the diabetic state or if existing microvessels are sufficiently damaged to become nonfunctional and to atrophy. Indications of a loss of microvessels during diabetes has included both decreased arteriolar density and increased intercapillary distances in skeletal muscle and intestine of diabetic rats and mice.

Our hypothesis is that growth of the microvasculature is impaired in diabetic juvenile animals such that by adult life, the microvasculature is underdeveloped in the context of vascular density and maximum diameter of arterioles. To determine if the process of microvascular growth is altered in juvenile animals by the onset of diabetes, a newly developed technique was used to evaluate both tissue and microvascular growth by comparison of the same area of intestine at two time points during an animal’s life. With this technique, it is possible to determine if changes in arteriolar density and intercapillary distances are due to alterations in the number of microvessels or are the result of changes in tissue dimensions associated with growth.
Materials and Methods

Chemicals
The following chemicals were used in this study: Sodium pentobarbital, isoproterenol HCl, adenosine, and FITC-albumin (bovine) (Sigma Chemical, St. Louis, Missouri); sodium thiopental and Normasol-R, a physiological Ringer’s solution (Abbott Laboratories, North Chicago, Illinois); atropine sulfate (Elkins-Sinn, Cherry Hill, New Jersey); and tetracycline HCl (American Cyanamid, Wayne, New Jersey).

Arteriolar Classification
The arterioles of the intestinal microvasculature were classified by branching order in accordance with a previously reported scheme. In brief, the large arterioles, such as those numbered in Figure 1, which arise from the small intestinal arteries at the mesenteric border of the bowel and traverse the radial axis of the bowel through the submucosa are termed the first-order arterioles (1A’s). The intermediate-sized arterioles that interconnect adjacent first-order arterioles, as seen in Figure 1, are identified as second-order arterioles (2A’s). The small arterioles designated as 3A’s branch from the 2A’s but cannot be seen in Figure 1. The terminal arterioles of the intestinal muscle and mucosal layers originate from these 3A’s.

Animal Groups and Preparation
Three shipments of 10–12 male Sprague-Dawley rats were obtained from Harlan Sprague-Dawley (Indianapolis, Indiana) at 4 weeks of age. Each shipment was randomly divided into three groups. Two of the groups, which are designated as chronically studied normal and diabetic rats, were subjected to the protocol for marking a segment of the terminal ileum and repeated observation of the microvasculature of this marked segment as previously reported and as briefly detailed below. The remaining rats composed the group of control diabetic rats, which were used to determine if the

FIGURE 1. Photomicrographs of the marked ileal segment at both times of observation for chronically studied normal and diabetic rats. Age of animal at time of photography is indicated above each photomicrograph. All photomicrographs are at the same magnification. Bar beneath bottom panels represents 1.0 mm. Specific first-order arterioles, which traverse the bowel from mesenteric to antimesenteric borders, are identified by numbers beneath each panel. Within each animal, the same arterioles present at first observation are also present at second observation.
surgery and manipulation of the intestine altered intestinal or microvascular growth of the chronically studied diabetic rats. A prior study had indicated that similar chronic studies of the small intestine of 4–9-week-old rats did not influence vascular, intestinal, or physical growth. The intestinal marking and initial observation of the microvasculature of the chronically studied diabetic and normal rats were performed when the rats were approximately 5 weeks old. This initial time of observation is referred to as T1. One week later the rats of the chronically studied diabetic and control diabetic groups were made diabetic by the injection of streptozotocin (45 mg/kg) into the tail vein. At the age of 10–11 weeks, the marked segments of the chronically studied normal and diabetic rats were observed for the final time, designated as T2. The experiments with the diabetic control rats were also performed at the age of 10–11 weeks. The average duration of diabetes was 32.0 ± 1.8 days in the chronically studied diabetic rats and 35.0 ± 3.4 days in the control diabetics.

All rats were fasted for 18–24 hours prior to laparotomy to allow for clearing of the intestine. Chronically studied normal and diabetic rats were anesthetized with sodium pentobarbital (40 mg/kg, 10 mg/ml i.p.) at age 5–6 weeks. At the age of 10–11 weeks (T2), rats of all groups were anesthetized with sodium thiopental (100 mg/kg, 100 mg/ml i.p.) and were tracheotomized. All rats were placed upon a heating pad to maintain body temperature at 37°C when locomotive function was lost.

**Experimental Protocol**

**Chronically studied rats: First observation.** At approximately 5 weeks of age (T1), a segment of the terminal ileum of the rats in the chronically studied normal and diabetic groups was exteriorized through a midline abdominal incision into a semicircular viewing chamber attached to the animal with surgical adhesive drape (Steri-Drape, Surgical Products Division/3M, St. Paul, Minnesota). A section of the exposed ileal loop with an easily identifiable branching pattern of the large arterioles in the bowel wall or arteries in the mesentery was marked with dots of India ink released from a micropipette inserted into the bowel wall. The marked ileal segment was then photographed at low magnification with a 35-mm camera on an Olympus SZH dissecting microscope (New Hyde Park, New York). The resulting photographs were used to determine the number of 1A’s and 2A’s in the marked intestinal segment and to measure the radial and longitudinal dimensions of the marked segment. A micrograph of a stage micrometer was taken during each experiment and used to determine the magnification of the photographs.

Following the photography, the preparation was moved to an Olympus BHMJ microscope with an Olympus fluorescent attachment and 0.2 ml/kg of 5% FITC-albumin was administered to the rat via the tail vein. A video tape recording was made of the fluorescing microvessels with a closed-circuit video system that consisted of a SIT Model 66 video camera (Dage-MTI, Michigan City, Indiana), a Model PM17ITTIC Ikegami monochrome monitor (Ikegami Tsushinki, Tokyo, Japan), and a Mitsubishi HS329UR four-head VHS videocassette recorder (Cypress, California). From this recording, measurements were made of the number of 3A’s, maximally dilated inner arteriolar diameters, and intercapillary distances. All photography and video tape recordings of the arterioles and capillaries were done with the intestinal vasculature maximally dilated by topical 10–7 M adenosine and intestinal motility was suppressed with 5 × 10–7 M isoproterenol. A × 20 Nikon water immersion objective (n.a. = 0.33) was used during video tape recording and produced a total magnification of ×800 at the video monitor.

After the completion of the video tape recordings, the intestinal loop was returned to the abdominal cavity and the abdominal wound was closed in two layers with 3-0 silk sutures. Until the animals recovered from anesthesia, they were kept under a heat lamp to maintain body temperature. For one day before surgery and three days after surgery, the animals were given 1.1% tetracycline with 1.1% dextrose in their drinking water.

**Chronically studied rats: Second observation.** Approximately 5 weeks after the first observation of the tissue, the same section of the terminal ileum was observed again. Positive identification of the same tissue section was made by the arteriolar branching pattern and remnants of the India ink dots. Photography and video tape recordings of the marked section were repeated while the vessels were maximally dilated with topical application of adenosine (10–4 M). At the end of T2, both ends of the exteriorized loop of the ileum were ligated and immersion fixed by replacing the suffusion solution with fixative (2.5% glutaraldehyde in 0.1 M cacodylate/HCl buffer, pH 7.4) and injecting a small amount of fixative into the intestinal lumen. The fixed loop was excised and used at a later time to obtain measurements of intestinal mass per unit intestinal length and intestinal mass per 1A, 2A, and 3A. In these later measurements, the wet weight of the section of bowel in the area used for in vivo observations was determined and the number of arterioles of each type were counted.

**Control diabetic rats.** At 10–11 weeks of age, the terminal ileum of these rats was prepared for intravital fluorescent microscopy as described above and a video tape recording was made for intercapillary distances. Subsequently, the exteriorized loop was fixed and excised. This tissue would be used to determine the mass of tissue perfused by individual types of arterioles and the mass per unit length of intestine.
Measurements

From the photomicrographs and video tape recordings of chronically studied diabetic and normal rats, it was possible to identify the same arterioles at T1 and T2 and compare the lengths and inner diameters of these vessels. 1A's, 2A's, and 3A's in the defined regions were evaluated to determine if specific vessels had been lost or if new vessels were present at T2. From enlarged photomicrographs, measurements were made of arteriolar segment lengths defined by branch points and the lengths of the longitudinal and radial axis of the marked ileal segment. The photomicrographs were placed over a computer digitizing tablet calibrated with a photomicrograph of a stage micrometer, and the various lengths of interest were then determined by tracing over the blood vessels with the graphics tablet stylus. Maximally dilated inner diameters at identical locations on 1A, 2A, and 3A were evaluated at T1 and T2 from the video tape recordings. Intercapillary distances were also measured from the video tape recordings of the marked tissue region at T1 and T2 for chronically studied normal and diabetic animals. For control diabetic rats, the intercapillary distances were measured near the midpoint between the mesenteric and antimesenteric borders of the bowel, as was typically done for the other two animal groups. The distance between walls of adjacent capillaries was measured by placing a paper strip across the video monitor and marking the location of capillary walls onto the paper. The distance between marks on the paper strip was later measured on a computer digitizing tablet calibrated to the image of a stage micrometer recorded at the same magnification as the capillaries.

Statistics

Differences between groups were evaluated with one-way analysis of variance. A t test was used to compare measurements within a group at T1 and T2 and also to determine if T2/T1 ratios within a group were significantly different from 1.00. All data are presented as the mean ± SEM.

Results

Values for the parameters of body, intestinal, and microvascular growth for the normal and diabetic rats used in this study are presented in Table 1. The plasma glucose concentration of all diabetic rats was greater than 350 mg/100 ml within 1 week after the induction of diabetes by streptozotocin and averaged over 500 mg/100 ml at 10-11 weeks of age. At T2, none of the indexes of physical, intestinal, or microvascular growth for chronically studied diabetic rats were significantly different (p<0.05) from those of the control diabetic animals. This indicated that the physical, intestinal, and microvascular growth of the chronically studied diabetic rats was not altered by the laparotomy, marking, and observation of the bowel wall at T1. Although the body mass of the chronically studied diabetics was approximately 25% less than the chronically studied normal animals, the radial growth and thickening of the intestinal wall, as indicated by the mass of intestine

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal</th>
<th>Diabetic</th>
<th>Control diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (days)</td>
<td>39 ± 1.0 (8)</td>
<td>34 ± 0.5 (15)</td>
<td>NA</td>
</tr>
<tr>
<td>T2 (days)</td>
<td>76 ± 1.1 (6)</td>
<td>73 ± 1.5 (8)</td>
<td>76 ± 3.1 (5)</td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (grams)</td>
<td>137 ± 6.9 (8)</td>
<td>108 ± 2.0 (15)</td>
<td>NA</td>
</tr>
<tr>
<td>T2 (grams)</td>
<td>329 ± 9.0 (6)</td>
<td>250 ± 6.9* (7)</td>
<td>286 ± 23.4 (5)</td>
</tr>
<tr>
<td>Blood glucose at T2 (mg/100ml)</td>
<td>106 ± 2.3 (6)</td>
<td>528 ± 13.5* (10)</td>
<td>501 ± 55.3 (5)</td>
</tr>
<tr>
<td>Intestinal mass per unit length at T2 (mg/mm)</td>
<td>8.52 ± 0.76 (5)</td>
<td>13.97 ± 1.06* (7)</td>
<td>11.81 ± 0.58 (5)</td>
</tr>
<tr>
<td>Intestinal mass per arteriole at T2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/1A</td>
<td>11.49 ± 0.48 (10)</td>
<td>21.87 ± 1.25* (7)</td>
<td>22.53 ± 1.73 (4)</td>
</tr>
<tr>
<td>mg/2A</td>
<td>0.47 ± 0.04 (9)</td>
<td>0.758 ± 0.020* (6)</td>
<td>0.729 ± 0.51 (4)</td>
</tr>
<tr>
<td>mg/3A</td>
<td>0.095 ± 0.22 (4)</td>
<td>0.169 ± 0.024 (6)</td>
<td>0.158 ± 0.029 (4)</td>
</tr>
<tr>
<td>Intercapillary distances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 longitudinal</td>
<td>59 ± 4.0 (5)</td>
<td>55 ± 4.8 (5)</td>
<td>NA</td>
</tr>
<tr>
<td>T2 longitudinal</td>
<td>61 ± 5.7 (5)</td>
<td>65 ± 3.4 (5)</td>
<td>66 ± 1.8 (3)</td>
</tr>
<tr>
<td>T1 radial</td>
<td>91 ± 9.1 (5)</td>
<td>97 ± 3.0 (5)</td>
<td>NA</td>
</tr>
<tr>
<td>T2 radial</td>
<td>78 ± 6.8 (5)</td>
<td>75 ± 5.4 (5)</td>
<td>76 ± 2.3 (3)</td>
</tr>
</tbody>
</table>

Intercapillary distances in the longitudinal bowel axis are measurements of the distance between walls of adjacent capillaries of the inner muscle layer and intercapillary distances in the radial bowel axis are for capillaries of the outer muscle layer. T1 is the first observation and T2 is the second observation of the same tissue region.

* Dotted diabetic ≠ dotted normal; p<0.01.
† Intercapillary distance T2 ≠ T1; p<0.05.
per unit of intestinal length, was over 60% greater for diabetic than normal animals (Table 1). Photomicrographs (Figure 1) of the marked ileal segment of a chronically studied normal and diabetic rat illustrate the enlargement of the intestine from T1 to T2. The enhanced degree of intestinal enlargement in the diabetic rat is very obvious.

From the combination of photomicrographs and video tape recordings of the intestinal segments, it was possible to determine if specific arterioles present at T1 had been lost during the interval between observations or if new arterioles were present at T2. The numbers beneath each photomicrograph in Figure 1 identify individual 1A that arise from intestinal arteries of the mesentery and traverse the bowel wall. 2A's branch from each 1A. It is apparent in Figure 1 that within the marked ileal segment of both the chronically studied normal and diabetic rats, the numbers of 1A's and the branching patterns formed by these arterioles are identical at T1 and T2. This was a consistent finding in every animal examined, whether diabetic or normal. The data in Table 2 demonstrate that the addition or loss of a 1A, 2A, or 3A is a rare event. Not a single 1A or 2A was lost from or added to the marked intestinal segments of the chronically studied diabetic and normal rats. A small number of 3A's (less than 5% of the total number) were found to be either lost or added at T2 in both normal and diabetic rats.

As a consequence of the increased intestinal growth in the diabetic rats without an appreciable change in the number of arterioles, the intestinal mass per arteriole is greater in the chronically studied diabetics than the normal rats (Table 1). The arterioles of the diabetic rats also undergo a greater degree of elongation than normal rats during juvenile maturation as shown by the plot of T2/T1 ratios of 1A and 2A lengths in Figure 2. The increase in lengths of 1A and 2A segments was 28% and 17% in normal rats and 47% and 50% in diabetic rats. Comparisons of inner diameters of specific individual arterioles when all vascular tone was abolished (10^-4 M adenosine and 5 x 10^-7 M isoproterenol) at T1 and T2 revealed that the maximum diameters of 1A remained unchanged in both diabetic and normal animals over a 5-6-week period. However, the T2/T1 ratios for maximally dilated inner diameters of 2A's and 3A's are significantly larger in the diabetic rats than the normals as shown in Figure 3.

As is apparent in Figure 1, the bowel of normal and diabetic animals expanded in the radial and longitudinal axes during the 4-5-week study period. The effect of intestinal growth upon intercapillary distances was one of the concerns of this study. Figure 4 illustrates relative changes in both bowel axis length and intercapillary distances from T1 to T2 in chronically studied normal and diabetic rats. The longitudinal bowel axis of diabetic rats and the radial bowel axis of both normal and diabetic rats...
were significantly increased from T1 to T2. The increase in the radial bowel axis in diabetic rats was much greater than normal rats. The T2/T1 ratios of intercapillary distances in the longitudinal bowel axis (capillaries of the inner muscle layer) are not significantly different from 1.0 or the T2/T1 ratio for bowel axis. However, intercapillary distances in the radial bowel axis (capillaries of the outer muscle layer) are significantly decreased from T1 to T2 for both normal and diabetic rats in spite of the enlargement of this bowel axis. Furthermore, the intercapillary distances in the radial bowel axis of diabetic rats are less than in normal rats even though there was more enlargement of the bowel of diabetics compared with normals in the radial axis. The results expressed in Figure 4 suggest that the number of capillaries in the inner muscle layer remained constant from T1 to T2 whereas new capillaries were added during the elongation of the outer muscle layer.

**Discussion**

The technique recently described in this journal for the evaluation of microvascular growth has been used in this study to compare intestinal microvascular growth during juvenile maturation in diabetic and normal rats. The results of this study demonstrated that the bowel hypertrophy in uncontrolled diabetes without a concomitant increase in numbers of arterioles (Table 2) causes about a 90% increase in the mass of intestinal tissue perfused by a single arteriole (Table 1). Expression of arteriolar density as number of vessels per mass of tissue would have indicated that the intestinal vascularity of the diabetic animals is 40–50% less than normal animals. It is important to emphasize that these decreases in arteriolar density were not the result of arteriolar rarefaction. In fact, the number of large, intermediate, and small arterioles does not change during intestinal enlargement in either normal or diabetic rats (Table 2). The existing arterioles simply elongate to match the growth of the intestine in normal and diabetic rats (Figures 1 and 2). However, the intestines of the diabetic rats of this study demonstrated considerably more enlargement than was observed in the normal rats and therefore greater arteriolar elongation was required in diabetic than normal rats (Figures 1 and 4). The enhanced enlargement of the bowel is common in the diabetic animal and was not influenced by the technique used in the current study as bowel mass per unit length is identical in chronically studied diabetics and control age and colony matched diabetic rats (Table 1).

Earlier studies have demonstrated that arteriolar diameters in diabetic animals may either be increased, decreased, or remain the same. The differences are probably due in part to the time in the progression of the disease when diabetic animals are studied. In general, short term diabetes is associated with vasodilation, whereas vasoconstriction or an anatomical decrease in vessel diameter can occur in prolonged diabetes. In this study as shown in Figure 3, the maximally dilated inner diameters of the individual large arterioles, the 1A's, and the small arterioles, the 3A's, in normal rats did not change appreciably from the age of 5 weeks to the age of 10–11 weeks. The intermediate diameter arterioles, the 2A's, decreased in maximally dilated diameter in normal animals. Comparison of the same arterioles at two time points indicated that relative to normal vessels, the individual 2A's and 3A's of diabetic rats increased their maximally dilated inner diameters, particularly the arterioles in the 3A classification. This dilation may represent a possible mechanism by which the metabolic requirements of an increased amount of tissue is provided by the same number of arterioles in diabetic animals. These observations of arteriolar dilation in diabetic rats are consistent with recent studies in adult rats after 4 weeks of streptozotocin-induced diabetes which reported that intestinal blood flow per mass of tissue is increased and precapillary resistance is decreased.
During the span of time from 5 weeks to 10–11 weeks of age, the surface area of the intestinal muscle layer increased by 40 ± 10.3% in normal rats and by 145 ± 18.5% in diabetic rats. This change in surface area is based on the relative changes in the longitudinal and radial bowel axes as shown in Figure 4. Had no new capillaries been formed in the muscle layers of either normal or diabetic animals, intercapillary distances in each bowel axis would have been expected to increase by the same proportion as elongation of that bowel axis. However, as supported by the data in Table 1 and Figure 4, intercapillary distances in the longitudinal bowel axis (inner muscle layer) did not increase as much as axis length and decreased for the radial bowel axis (outer muscle layer). In fact, the actual intercapillary distances were only marginally increased for the longitudinal axis and substantially decreased for the radial axis in normal and diabetic rats at T2. The only way that these observations can be explained is no loss of capillaries in the longitudinal axis (inner muscle layer capillaries) and a net gain of capillaries in the radial axis (outer muscle layer capillaries). For diabetic animals, the 71% increase in intestinal radial axis length and 23% reduction in intercapillary distance by T2 predicted approximately a 100% increase in the number of capillaries. In comparison, in the radial bowel axis of normal rats there was at most a 40–50% increase in number of capillaries. For the intestinal longitudinal axis of normal and diabetic animals, a similar analysis indicates very little change in the number of capillaries as previously reported for this bowel axis in juvenile Wistar rats. In previous studies of adult rats made diabetic with streptozotocin, an increase in muscle layer intercapillary distances was found in the intestine, and similar results are available for the skeletal muscle vasculature of both diabetic juvenile and adult mice. These previous observations of diabetic animals would indicate at best no gain of capillaries in the bowel as it expands during diabetes in adult rats and a loss of capillaries in skeletal muscle as the muscle tissue decreases in mass. The most important interpretation of the current results is that in diabetic juvenile animals, at least the visceral smooth muscle vasculature of the longitudinal muscle layer (radial axis in Figure 4) can substantially increase the number of capillaries available for tissue perfusion even during severe diabetes.

The reason the number of capillaries in the outer muscle layer of diabetic rats increased more than in the inner muscle layer is not known. The muscle layers share a common arteriolar supply from the 3A's but do have separate terminal arterioles to perfuse their respective capillaries. In normal 5-week-old Sprague Dawley rats, the average intercapillary distance in the outer muscle (radial bowel axis) is approximately 50% greater than in the inner muscle (longitudinal bowel axis). By the age of 10–11 weeks, the intercapillary spacing of outer muscle layer is only about 25% greater than in the inner muscle layer. By adult life (age>20 weeks), prior studies of normal Sprague Dawley rats indicated no appreciable difference in the intercapillary distances of the two muscle layers. These various observations are interpreted to indicate that although the two muscle layers have different capillary densities early in life, the greater addition of capillaries in the outer than inner muscle layer during maturation gradually produces approximately equivalent intercapillary spacing by adult life. This same process could be present in the diabetic juvenile animals. However, the greater linear growth of the bowel axes requires a greater than normal formation of new capillaries in order to maintain a near-normal capillary spacing (Table 1 and Figure 4).

In conclusion, the results of this study indicate that the intestinal microvasculature of juvenile animals during the early phase of diabetes has a well-developed ability to support microvascular
growth in terms of elongation of arterioles, enlargement or maintenance of their maximally dilated diameters and formation of new capillaries in the muscle layer. However, in both normal and diabetic animals, there was no attempt to increase the number of arterioles despite substantial hypertrophy of the tissue, particularly in diabetic animals. These collective observations support the hypothesis that formation of new arterioles to support tissue hypertrophy in juvenile normal and diabetic animals up to the age of 10–11 weeks is unlikely. Therefore, increased vascular density at the capillary level and enlargement of existing arterioles may be the only compensatory mechanism available to match microvascular perfusion to the growth of the tissue in the early stages of juvenile maturation.

References


KEY WORDS • diabetes • juvenile • microcirculation • growth
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Circ Res. 1988;63:429-436
doi: 10.1161/01.RES.63.2.429
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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