Microvascular flow and tissue $\text{PO}_2$ in skeletal muscle of chronic reduced renal mass hypertensive rats

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Received 4 February 2000; accepted in final form 20 June 2000

Lombard, Julian H., Jefferson C. Frisbee, Andrew S. Greene, Antal G. Hudetz, Richard J. Roman, and Peter J. Tonellato. Microvascular flow and tissue $\text{PO}_2$ in skeletal muscle of chronic reduced renal mass hypertensive rats. Am J Physiol Heart Circ Physiol 279: H2295–H2302, 2000.—This study determined whether arteriolar blood flow, capillary red blood cell (RBC) velocity, capillary hematocrit ($\text{Hct}_{\text{cap}}$), and tissue $\text{PO}_2$ are altered in cremaster muscles of rats with chronic reduced renal mass hypertension (RRM-HT) relative to normotensive rats on high- or low-salt (NT-HS vs. NT-LS) diet. The blood flow in first- through third-order arterioles was not different between NT and HT rats, either at rest or during maximal relaxation of the vessels with $10^{-4}$ M adenosine. Capillary RBC velocity was similar between the groups at rest but was elevated in RRM-HT and NT-HS rats during adenosine superfusion. $\text{Hct}_{\text{cap}}$ was reduced at rest in RRM-HT and NT-HS rats compared with NT-LS and was reduced in RRM-HT rats during adenosine-induced dilation. Tissue $\text{PO}_2$ was reduced in RRM-HT and NT-HS rats compared with NT-LS rats during control conditions and was lower in RRM-HT than in NT-LS rats during adenosine-induced dilation. These results indicate that both RRM-HT and chronic exposure of normotensive rats to a high-salt diet lead to reduced tissue oxygenation, despite the maintenance of normal arteriolar blood flow.

removal of local blood flow and tissue PO$_2$ may be reduced during hypertension because of a variety of factors, e.g., active constriction or structural narrowing of resistance vessels leading to a decreased flow and reduced oxygen delivery in the microcirculation, an increased diffusion distance for oxygen resulting from a reduced microvessel density (rarefaction) (21), or changes in microvessel hematocrit. Any reduction in tissue PO$_2$ under these conditions could have adverse effects that impair tissue function, as recently suggested by studies demonstrating an enhanced rate of skeletal muscle fatigue in rats with reduced renal mass hypertension (36). Finally, it is possible that tissue perfusion could remain elevated to some extent in the chronic stage of volume-expanded hypertension, leading to a maintained elevation in arteriolar blood flow and tissue PO$_2$.

Despite the potential importance of local blood flow and tissue oxygenation in regulating vascular resistance, there have been no direct studies assessing key
variables associated with these processes in the face of chronic volume-expanded hypertension. The goal of the present study was to determine arteriolar blood flow, capillary erythrocyte velocity, capillary hematocrit (Hct\textsubscript{cap}), and tissue Po\textsubscript{2} in the cremaster muscle of rats with chronic reduced renal mass (RRM) hypertension and in normotensive control rats on high- and low-salt diet to test the hypothesis that these variables are maintained at normal levels during the established stage of volume-expanded hypertension.

**MATERIALS AND METHODS**

**Animal groups.** Chronic reduced renal mass hypertension was produced in male Sprague-Dawley rats by surgically reducing kidney mass by 75% and placing the rats on a high-salt diet of 4% NaCl (no. 113756, Dyets, Bethlehem, PA) and AIN-76A (Dyets) for 4–6 wk, as previously described (32, 34). Two groups of normotensive sham-operated controls were also prepared and maintained on either high-salt or low-salt diet (0.4% NaCl; no. 113755 AIN-76A, Dyets) for an equivalent time. All protocols and procedures used in this study were approved by the Animal Care Committee of the Medical College of Wisconsin.

**Experimental procedure and data analyses.** On the day of the experiment, rats were anesthetized with pentobarbital sodium (45–50 mg/kg ip). The trachea was cannulated to ensure a patent airway, and a carotid artery and femoral vein were cannulated for measurement of arterial pressure and for the administration of supplemental anesthesia, respectively. In some experiments, an arterial blood sample (200 μl) was obtained from the carotid artery cannula to measure arterial Po\textsubscript{2} with a blood gas analyzer (model 168, Corning). After the initial surgery was complete, the right cremaster muscle was prepared for television microscopy, taking care not to interrupt the deferential feed vessels (26).

The rat was placed on the stage of a Leitz Laborlux microscope, and the cremaster muscle was continuously superfused at 35°C with physiological salt solution (PSS) equilibrated with a 5% CO\textsubscript{2}–95% N\textsubscript{2} gas mixture, to ensure that perfused at 35°C with physiological salt solution (PSS) equilibrated with a 5% CO\textsubscript{2}–95% N\textsubscript{2} gas mixture, to ensure that oxygen delivery to the cremaster muscle was from the microcirculation and not from the superfusion solution. The PSS used in these experiments had the following ionic composition (in mM): 130 NaCl, 4.7 KCl, 1.6 CaCl\textsubscript{2}, 1.18 NaH\textsubscript{2}PO\textsubscript{4}, 1.17 MgSO\textsubscript{4}, 14.9 NaHCO\textsubscript{3}, and 0.026 disodium EDTA. Succinylcholine chloride (0.1 mM) was also added to the superfusion solution to prevent spontaneous contractions of the muscle.

Internal diameters of first- through third-order arterioles were measured by television microscopy (34) with the use of a video micrometer (model IV-550, For-A Instruments, Tokyo, Japan). Centerline flow velocity in individual arterioles was measured with an optical Doppler velocimeter (Texas A&M Instruments, College Station, TX). Volume flow within individual arterioles was calculated according to the following equation (35)

\[
F = (v/1.6) \cdot \pi r^2 \cdot 0.001
\]

where \(F\) is volume flow (nl/s), \(v\) is the centerline velocity (mm/s\textsuperscript{-1}), 1.6 is a conversion factor to obtain average cross-sectional velocity, and \(r\) is the radius of the arteriolar lumen. For capillary red blood cell (RBC) velocity measurements, videotapes were made utilizing a 436-nm band-pass filter to enhance the contrast between RBC and the background. RBC velocities were measured from the videotapes by cross-correlation in the frequency domain by using the dual window technique, as previously described (14). Each measurement of RBC velocity in an individual capillary was the mean of five 17-s sampling intervals.

Hct\textsubscript{cap} was determined by counting the number of erythrocytes within a measured capillary segment from still frames of the video record. Final Hct\textsubscript{cap} measures represent the mean of multiple determinations made during these periods. The calculation of Hct\textsubscript{cap} was performed by using the following equation (11) and published values for mean corpuscular volume (MCV) and capillary diameter (D) in the rat cremaster muscle (27)

\[
H_{\text{CAP}} = (n \cdot \text{MCV} \cdot 100)/\left(\pi \cdot (D/2)^2 \cdot L\right)
\]

where \(n\) represents the number of erythrocytes in a given length of capillary (L), MCV = 72 μm\textsuperscript{3}, and \(D = 6.7\) μm, respectively.

Tissue Po\textsubscript{2} was measured with recessed tip microelectrodes (2–6 μm tip diameter) fabricated by the Linsenmeier and Yancey method (31). The electrodes were polarized at −0.7 V, and tissue Po\textsubscript{2} was determined amperometrically utilizing a picoammeter equipped with a polarizing circuit (Stanley Stumpf, Indianapolis, IN). Tissue Po\textsubscript{2} measurements were obtained by placing the electrode on the surface of the cremaster muscle, slightly indenting the tissue. The electrodes were calibrated in saline equilibrated with 0% O\textsubscript{2} and 21% O\textsubscript{2} at 35°C immediately before and after each measurement. Tissue Po\textsubscript{2} was determined by using a linear regression equation based on the calibration currents measured in 0% O\textsubscript{2} and 21% O\textsubscript{2}, and measurements were discarded if any significant change occurred in the calibration currents. Tissue Po\textsubscript{2} was measured between capillaries to provide an estimate of Po\textsubscript{2} in the least oxygenated parts of the tissue (33).

After an initial equilibration period of 30–60 min, variables were measured during resting conditions and during maximal relaxation of the arterioles produced by superfusing the cremaster muscle with PSS containing 10−4 M adenosine. Arteriolar diameter and volume flow measurements were obtained in one group of rats, capillary RBC velocity and Hct\textsubscript{cap} measurements in another, and tissue Po\textsubscript{2} measurements in a third group of rats. All rat groups were prepared and maintained in an identical fashion to ensure uniformity between groups.

**Statistical analyses.** All data are presented as means ± SE. Differences between groups were determined with the use of ANOVA, followed by Tukey’s test, post hoc. Differences within groups (i.e., control versus maximal dilation) were determined by using Student’s \(t\)-test. A probability value of \(P < 0.05\) was considered to be statistically significant.

**RESULTS**

In these experiments, mean arterial pressure in RRM-hypertensive rats (150 ± 4 mmHg, \(n = 13\)) was significantly higher than that in sham-operated rats on a high-salt diet (128 ± 5 mmHg, \(n = 15\)) or a low-salt diet (125 ± 3 mmHg, \(n = 14\)). Arterial pressure in the sham-operated control groups was not different. Arterial Po\textsubscript{2} was not different in any of the groups and averaged 77 ± 4 mmHg in the low-salt rats, 83 ± 3 mmHg in the high-salt shams, and 79 ± 5 mmHg in the RRM-hypertensive rats.

The diameter of first- through third-order arterioles of the cremaster muscle during control conditions and during superfusion of the preparation with 10−4 M adenosine in the three animal groups is presented in
Fig. 1. Within a vascular segment, there were no differences in the control diameter of arterioles between normotensive rats on low- and high-salt diet and RRM-hypertensive rats, with the exception of second-order arterioles, where arteriolar diameter in the hypertensive rats was significantly less than that in normotensive rats on the low-salt diet. Adenosine superfusion caused significant increases in arteriolar diameter in all the groups. When the arterioles were relaxed with adenosine, there was no difference in the diameter of any arteriolar segment in the three rat groups, with the exception of third-order arterioles of RRM-hypertensive rats, where arteriolar diameter was significantly greater than that in normotensive rats on the low-salt diet.

Volume flows in first- through third-order arterioles of RRM-hypertensive rats and sham-operated controls on low- or high-salt diets are summarized in Fig. 2. Maximal relaxation of the vessels with adenosine caused significant increases in blood flow in all arteriolar branching orders of the RRM-hypertensive rats, and in third-order arterioles of both normotensive control groups. There were no significant differences in volume flow in comparable orders of arterioles between RRM-hypertensive rats, low-salt shams, or high-salt shams during control conditions or adenosine-induced dilation.

Figure 3 compares capillary erythrocyte velocities in RRM-hypertensive rats and both normotensive control groups. There were no significant differences in capillary red cell velocity in any of the groups during resting conditions. During maximal dilation with adenosine, capillary RBC velocity was significantly higher in RRM-hypertensive rats and in normotensive rats on a high-salt diet than in normotensive rats on a low-salt diet.

The data describing the Hct_cap in the three groups under control conditions and during superfusion of the muscle with 10^{-4} M adenosine are summarized in Fig. 4. Under normal PSS superfusion, Hct_cap was significantly reduced in normotensive rats on the high-salt diet and in RRM-hypertensive rats, compared with values calculated for normotensive rats on the low-salt diet. During superfusion with PSS containing 10^{-4} M adenosine, Hct_cap was reduced in RRM-hypertensive rats compared with either normotensive rat group. Hct_cap was not different between the two normotensive rat groups during adenosine superfusion.

Tissue Po2 values in cremaster muscles of RRM-hypertensive rats and their normotensive controls are summarized in Fig. 5. Tissue Po2 in RRM-hypertensive rats was significantly lower than that in rats given a low-salt diet, both at rest and during maximal relaxation of the vessels with adenosine. Tissue Po2 in normotensive rats on the high-salt diet was signific-
sificantly lower than that in rats on the low-salt diet during control conditions and also tended to be lower during adenosine superfusion, although the latter difference was not significant.

DISCUSSION

Potential role of acute and long-term autoregulatory mechanisms in regulating local blood flow, tissue Po2, and vascular resistance in volume-expanded hypertension. Under physiological conditions, local autoregulatory mechanisms maintain normal levels of tissue perfusion by dilating resistance vessels when blood flow is decreased and constricting them when blood flow is increased in excess of the metabolic needs of the tissue.
Tissue Po₂ is a critical variable in local autoregulatory responses, and increased oxygen availability leads to arteriolar vasoconstriction in many different vascular beds.

In volume-expanded forms of hypertension, the initial increase in arterial pressure is associated with an elevated cardiac output, which returns toward normal values as peripheral vascular resistance increases (6, 7). Several investigators have proposed that this elevation of total peripheral resistance in volume-expanded hypertension occurs because flow-dependent autoregulatory mechanisms increase local vascular resistance in response to overperfusion of peripheral vascular beds (4, 6, 7). In the chronic phase of volume-expanded hypertension, long-term autoregulatory mechanisms mediated via structural changes in the vasculature (e.g., microvessel rarefaction or structural narrowing of vessels) have been proposed to maintain normal levels of tissue blood flow in the absence of active arteriolar vasoconstriction (6, 8).

Arteriolar blood flow. To date, the effect of volume-expanded hypertension on blood flow in individual microvessels has not been determined, and it is unknown whether arteriolar blood flow is maintained at normal values during hypertension. Classical theory predicts that arteriolar blood flow will be normal in the established phase of hypertension after local autoregulatory mechanisms have responded to the initial overperfusion of the vascular bed. However, if neural or humoral vasoconstrictor mechanisms or structural alterations of blood vessels increase resistance independent of metabolic needs, microvascular blood flow may be reduced in peripheral vascular beds during hypertension (6).

In an earlier study, Roy and Mayrovitz (38) reported that resting blood flow was reduced in the cremasteric microcirculation of spontaneously hypertensive rats relative to normotensive controls, suggesting that active vasoconstriction can override local autoregulatory mechanisms in some forms of hypertension. However, in the present study, arteriolar blood flow at rest and during adenosine-induced dilation were not different in RRM-hypertensive rats and normotensive controls on high- or low-salt diet. The latter finding is consistent with previous studies of RRM-hypertensive dogs (30) and rats (39), indicating that blood flow is normal in most vascular beds during established RRM hypertension.

The observations of similar regional blood flows (30, 39) and similar flows in individual arterioles (present study) are consistent with the hypothesis that acute or long-term autoregulatory mechanisms lead to an elevation of local vascular resistance to maintain a constant tissue perfusion, despite the substantial elevation of arterial pressure in this classic form of volume-expanded hypertension. A possible contribution of long-term autoregulatory mechanisms, or “structural autoregulation” of blood flow (6, 8) to the elevated vascular resistance in RRM-hypertension is suggested by the similar flows in arterioles of hypertensive and normotensive rats during maximal relaxation of the vessels with adenosine. Under these conditions, structural narrowing of arterioles or anatomic rarefaction of microvessels in chronic hypertension would increase vascular resistance in hypertensive rats to prevent overperfusion of tissues without requiring active constriction of precapillary resistance vessels.

Capillary RBC velocity. Capillary RBC velocity is a critical variable determining tissue Po₂ under normal physiological conditions, and changes in capillary RBC velocity due to elevated vascular tone or structural changes in the vasculature could affect oxygen supply to the tissue in hypertension. In the present study, capillary RBC velocities during control conditions were not different in the RRM-hypertensive rats and normotensive rats on high- and low-salt diets. However, when the cremasteric microcirculation was dilated with adenosine, capillary RBC velocities in RRM-hypertensive rats and in normotensive rats on a high-salt diet were significantly higher than those in rats on a low-salt diet. These observations are consistent with previous reports of similar (24) or elevated (25) capillary RBC velocities in microcirculation of hypertensive rats relative to normotensive controls and provide further evidence that constriction of resistance vessels and structural alterations in the vasculature do not lead to a reduction in tissue blood flow in this form of hypertension. However, a normal or elevated capillary RBC velocity is not characteristic of all forms of hypertension, because Wolf et al. (42) reported a reduced capillary flow velocity in the retinal microcirculation of human essential hypertensives with an established history of elevated blood pressure.

Hctcap. To our knowledge, the present results represent the first observations addressing the effects of chronic high-salt diet and volume-expanded hypertension on skeletal muscle Hctcap. The range of values for Hctcap in the present study corresponds well with those reported in previous studies of the rat cremaster muscle (27) and hamster cremaster muscle (11, 29), from...
which methods employed for determining Hct_{cap} in the present study were taken. The results of our experiments clearly demonstrate that cremaster muscle Hct_{cap} is reduced under control conditions with chronic RRM hypertension and during chronic exposure of normotensive rats to a high-salt diet. When microvessels are maximally dilated, Hct_{cap} is still reduced in rats with RRM hypertension, but it is no longer different in normotensive rats on low- or high-salt diet.

Previous studies suggest a possible mechanism through which Hct_{cap} is reduced. Hansen-Smith et al. (23) demonstrated that microvessel density decreases in RRM hypertension and during exposure to high-salt diet in normotensive rats. With the use of a mathematical model of the hamster cheek pouch microcirculation, Greene et al. (20) determined that microvessel rarefaction increases blood flow heterogeneity within microvascular networks. This increased flow heterogeneity at microvessel bifurcations could reduce mean capillary tube hematocrit as a result of an enhanced manifestation of the network Fahraeus effect (3, 37).

Under conditions of maximal dilation, Hct_{cap} was not different between normotensive rats on low- and high-salt diet, but was reduced in RRM-hypertensive rats. If the speculation forwarded in the preceding paragraph regarding the effects of microvessel density on Hct_{cap} is accurate, these observations suggest that high-salt diet alone may cause the development of primarily functional rarefaction, where some microvessels are unperfused yet are physically present under control conditions. In contrast, with RRM hypertension, more extensive anatomic rarefaction of microvessels may be present, in which more of the arterioles and capillaries are physically lost. This speculation is supported by our earlier observations indicating that, whereas both RRM-hypertensive rats and normotensive rats on a high-salt diet exhibit microvessel rarefaction relative to normotensive rats on a low-salt diet, the extent of microvessel rarefaction is more extensive in the hypertensive rats (19).

It is also possible that a reduction in systemic hematocrit could lead to the decrease in microvascular hematocrit in the sham-operated rats on a high-salt diet and in the RRM-hypertensive rats, although the extent to which a reduction in systemic hematocrit would be reflected in the microcirculation is unclear. Although some studies indicate that increases in dietary salt intake do not cause any changes in systemic hematocrit (12), other studies (22) have indicated that a carefully controlled elevation in sodium intake (employing a salt-free liquid food regimen in conjunction with water and sodium chloride infusion) can lead to a reduction of systemic hematocrit in Sprague-Dawley rats, as well as in Dahl salt-sensitive and salt-resistant rats. Some studies of RRM-hypertension (e.g., 10, 30) indicate that an initial reduction of systemic hematocrit also occurs in this experimental model of volume-expanded hypertension. However, most studies of the response of RRM animals to elevated salt intake, and that of Greene et al. (22), who investigated the response of normotensive Sprague-Dawley rats and Dahl rats to elevated salt intake, have been conducted over relatively short time periods. Many studies of the early stages of RRM hypertension (e.g., 5, 10, 30) have employed saline infusion to produce volume expansion, rather than an increase in dietary salt intake. Under those conditions, the degree of volume expansion and hemodilution that would occur should be greater than it would be after prolonged exposure to an elevated salt intake. However, it is also possible that decreased erythropoietin levels resulting from the renal mass reduction could contribute to a reduction in systemic hematocrit in the hypertensive rats.

Tissue oxygenation. A major question addressed in the present study concerns the effect of RRM hypertension on tissue P_{O2}. Measurements of tissue P_{O2} are important in determining whether tissue oxygenation is rigidly maintained at normotensive control levels during volume-expanded hypertension, whether tissue P_{O2} is elevated because of continued overperfusion of the vascular bed, or whether tissue O_{2} supply may be impaired in hypertension due to structural and functional alterations in the vasculature, e.g., vasoconstriction (38), microvascular rarefaction (23), higher levels of O_{2} consumption (40), or impaired vascular control mechanisms (15, 16).

The present experiments demonstrate that tissue P_{O2} in the cremaster muscle of RRM-hypertensive rats is significantly lower than that in normotensive rats on low-salt diet during control conditions and during adenosine-induced dilation of the microcirculation. This finding suggests that tissue P_{O2} in this vascular bed is not maintained at normotensive control levels during the established stage of volume-expanded hypertension. By extension, the observation of a lower tissue P_{O2} in the microcirculation of the hypertensive rats suggests that regulation of tissue P_{O2} is not the sole factor responsible for the maintenance of normal blood flows in the skeletal muscle microcirculation of these rats during the established stage of hypertension. However, the observation of a reduced P_{O2} in the microcirculation of the hypertensive rats does not imply that the microvasculature is incapable of regulating tissue P_{O2} or that oxygen availability is not a regulated variable. For example, it is conceivable that tissue P_{O2} may be regulated more precisely in the absence of anesthesia and neuromuscular blockade, which would lower oxygen demand. More importantly, previous studies (34) have demonstrated that skeletal muscle arterioles of RRM-hypertensive rats exhibit changes in active tone in response to altered oxygen availability. In that study, cremasteric arterioles of rats in both the early and the established stages of RRM hypertension constricted in response to elevated superfusion solution P_{O2}, and oxygen-induced constriction of arterioles of the hypertensive rats was actually enhanced compared with that of normotensive controls (34). Therefore, it is conceivable that, in the absence of oxygen-dependent autoregulatory mechanisms, structural changes in upstream vessels and microvessel rarefaction would cause tissue P_{O2} to be even lower in hypertensive rats. However, it is also possible that an im-
paired ability of the vessels to dilate in response to reduced PO2 may enable the hypertensive rats to maintain active tone and an elevated vascular resistance despite the reduction of tissue PO2 in these rats. The latter hypothesis is supported by the results of recent studies (32, 41) demonstrating that isolated skeletal muscle resistance arteries of RRM-hypertensive rats, and normotensive rats on a high-salt diet, exhibit an impaired relaxation in response to reduced PO2 relative to those of normotensive controls on a low-salt diet.

Another interesting observation in the present study was that tissue PO2 in the cremaster muscle of normotensive controls on a high-salt diet was significantly lower than that in normotensive rats on a low-salt diet during control conditions and also tended to be lower during adenosine-induced dilation of the microcirculation. The latter observation suggests that elevated salt intake per se can contribute to a reduction of tissue PO2 in some vascular beds. This observation is consistent with recent findings (15, 16, 23) that indicate that high-salt diet alone can lead to significant structural and functional alterations in the vasculature independent of an elevation in arterial blood pressure. In this regard, one functional alteration that may be especially important in allowing rats on a high-salt diet to maintain active tone in the face of a reduced tissue PO2 is an impaired relaxation in response to reduced PO2 and prostacyclin, a probable mediator of hypoxic relaxation in skeletal muscle resistance arteries (32, 41).

The lower tissue PO2 that we observed in the RRM-hypertensive rats and in normotensive controls on the high-salt diet is not due to a reduction in tissue blood flow, because arteriolar flow and capillary RBC velocity were not reduced in these rats relative to normotensive rats on a low-salt diet. On the basis of theoretical studies (21) and our previous measurements of microvessel density (19, 23), it is likely that a reduced density of arterioles and capillaries and the reduction in Hctcap (2) play an important role in contributing to the lower tissue PO2 in the cremaster muscle of RRM-hypertensive rats and normotensive rats on the high-salt diet relative to controls on the low-salt diet.

Our observation that tissue PO2 is lower in the cremaster microcirculation of RRM-hypertensive rats contrasts with the studies of Boegehold and Bohlen (1), who reported that PO2 in the spinotrapezius muscle of spontaneously hypertensive rats was not different from that in normotensive controls during resting conditions. However, the spinotrapezius muscle exhibits little or no rarefaction (1, 13, 18) in contrast with observations in the cremaster muscle (34). The existence of a lower tissue PO2 in rarefied vascular beds is supported by earlier measurements in our laboratory (21), which indicate that tissue PO2 is reduced in the cremaster muscle of spontaneously hypertensive rats relative to normotensive controls.

Physiological significance. In conclusion, the present study demonstrates that resting flow in arterioles of rats with chronic RRM hypertension is similar to that in normotensive rats on either the high-salt diet or the low-salt diet. These observations are consistent with the hypothesis that local autoregulatory mechanisms and/or structural alterations to the vasculature elevate vascular resistance and normalize tissue blood flow in volume-expanded hypertension. However, tissue PO2 in the cremaster muscle of RRM-hypertensive rats and normotensive rats on high-salt diet is lower than that in rats on low-salt diet. The latter observations suggest that both RRM hypertension and chronic elevations in dietary salt intake in normotensive rats can interfere with the ability of the microcirculation to maintain normal tissue oxygenation, and that the elevation of peripheral vascular resistance during the established stage of hypertension does not occur solely because of the action of local autoregulatory mechanisms to maintain tissue PO2 at normal values during chronic volume-expanded hypertension. Rather, it appears that the hypertensive rats can maintain an elevated vascular resistance despite the reduced PO2 in the skeletal muscle circulation and conceivably in other vascular beds. The ability of the hypertensive rats and the normotensive rats on a high-salt diet to maintain active tone and normal levels of arteriolar blood flow despite the reduction in tissue PO2 is consistent with recent studies demonstrating that both RRM hypertension and high-salt diet in normotensive rats lead to an impaired relaxation of skeletal muscle resistance arteries in response to reduced O2 availability (32, 41). However, the reduction of tissue PO2 in hypertensive rats and in normotensive rats on a high-salt diet may have important functional implications for parenchymal cells during periods of reduced tissue perfusion, reduced oxygen availability, or increased oxygen demand that would be encountered during physiological stresses such as hemorrhage, arterial hypoxemia, or exercise.

We thank Luellen Lougee for skillful assistance in fabricating the oxygen microelectrodes and Victoria Schmitz for technical assistance. We also thank H. Glenn Bohlen, Donald Buerk, Brian R. Duling, and David Damon for advice and assistance in constructing the oxygen electrodes used in these studies.

This work was supported by National Heart, Lung, and Blood Institute Grants HL-29587 and HL-37374.

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