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Age-Related Alterations in the Arterial Microvasculature of Skeletal Muscle

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This study investigated the possibility that the aging process results in alterations in the structure and/or functional reactivity of the microvessels that could contribute to increased resistance to blood flow in working skeletal muscle. Initially, latex casts were made of the cremaster muscle microvasculature in adult (12 mo) and senescent (24 mo) male Fischer 344 rats. Although the average diameter was not different between age groups, segmental length (distance between adjacent branches) increased significantly (3rd order) during aging. Additionally, in vivo experiments were performed to determine the response of the vessels to the topical application of norepinephrine and adenosine. There was no increase in vasoconstriction produced by norepinephrine; however, the vasodilation in response to adenosine declined dramatically (1st and 2nd order) with advancing age. It can be concluded that the increase in skeletal muscle vascular resistance during contraction in aged male rats could be explained by morphological changes and/or the diminished vasodilation elicited by adenosine.

IT is well recognized that there is a diminished work capacity in elderly persons. The decrease in skeletal muscle performance could be due to alterations in cardiac function, the structure or function of the peripheral vasculature, or the muscle tissue and its respiratory enzymes. Although many classic exercise physiology studies have examined the response of the heart to exercise, peripheral factors that could be involved in alterations in oxygen delivery have only recently been widely investigated.

It has been demonstrated that a large portion of the age-associated decline in $\dot{V}O_2$max in nonendurance-trained elderly individuals is correlated to a loss of muscle mass (Fleg and Lakatta, 1988). However, it is also possible that a decline in the capacity of the vascular system to divert blood flow to a given mass of exercising muscle contributes to diminished performance during senescence. Previous work in our laboratory indicates a reduced ability of the microvasculature in skeletal muscle of aged male rats to decrease vascular resistance (Irion et al., 1987). In these experiments, skeletal muscle blood flow was determined after 4 minutes of intermittent tetanic contractions of the ankle plantar flexor muscle group, elicited by stimulation of the sciatic nerve. As compared to adult (12 mo) rats, there was a significant reduction in the ability of the aged (24 mo) male rats to sustain contractile force, which was associated with a decreased skeletal muscle blood flow.

Additionally, the senescent male rats demonstrated a 30% lower skeletal muscle blood flow in response to the infusion of a maximal dose (15 mg/100 g) of a nonspecific vasodilator (diazoxide). Conversely, aged female rats did not experience a decline in the ability to reduce skeletal muscle vascular resistance in response to muscle contraction (Irion et al., 1988).

The phenomenon observed in the aged male rats could be explained by structural and/or functional changes in the resistance vessels of skeletal muscle. We hypothesized that age-associated alterations in microvascular morphology and/or in the reactivity of vascular smooth muscle would contribute to increased resistance to blood flow in working skeletal muscle.

METHODS

Animal selection. — Male Fischer 344 rats were evaluated for age-related changes in skeletal muscle morphology and their reactivity to topical application of various vasoactive agents. Two groups of rats were studied; one group representing adult animals (12 mo) and the second group representing senescent animals (24 mo). Fischer 344 rats were identified as being the most appropriate animal model to use in this study because of the apparent resistance of this strain to age-related vascular lesions (Coleman et al., 1977).

Microvascular Morphology

Latex casts. — According to a modification of the procedures described by Dusseau and Hutchins (1979), latex casts were made of the cremaster vasculature. Prior to the infusion of the latex, the vessels were cleared by perfusion with mammalian Ringer's solution. This was followed by a supramaximal dose of sodium nitroprusside to assure maximal dilation and the opening of all arteriolar vessels. Latex was then infused caudally through the abdominal aorta with a perfusion pressure equal to the mean arterial pressure of the animal; the right and left femoral veins were snipped to provide a low resistance outflow. Uniform pressure was maintained until casts were fully hardened and all casts from both age groups were treated identically. The latex-filled cremaster muscle was removed, spread, secured on a paraplast mold, and allowed to air dry. The tissues were then

submerged in 90% alcohol followed by immersion in methyl salicylate. Finally, the muscle was blotted dry and embedded in Canada Balsam on a 7.5 × 5 cm glass slide and covered with an 18 mm cover slip for microscopic viewing. Evaluation of the microvascular morphology of these casts was performed following the same time interval between cast preparation and measurements in both age groups.

Analysis of casts. — Standard procedures for optical measurements used for both cast analysis and the in vivo studies are those routinely used in our laboratory (Lindbom et al., 1982; Mayrovitz and Roy, 1983). The tissues were transilluminated with a Xenon light source through a substage condensor of a Leitz Ortholux microscope; neutral density filters (0.7 and 1.0) were used to enhance images of vessel walls. Measurements were made through the microscope with a calibrated eyepiece micrometer at a magnification of 100× and 200× for the larger (1st and 2nd order) and smaller (3rd and 4th order) vessels, respectively. Birefringence error is minimal in this system and is especially small when compared to the measurements being made.

The primary supply arteriole (1st order) was analyzed as well as three randomly selected vessels of each of the remaining branching orders of arterioles (2nd, 3rd, and 4th order). Internal diameters were taken along the entire length of each vessel immediately proximal and distal to each branch originating from that vessel. Branch diameter (at origin) and segmental length (distance between adjacent branches) were also measured.

Tortuosity determination. — During in vivo analysis of this vascular bed (to be described in the following section), arterioles were randomly selected, recorded on videotape, and the images of these vessels were digitized. Computer analysis provided the following information: linear distance between start and end of vessel (L), actual length of vessel (A), and tortuosity index (A/L).

In Vivo Studies

Experimental system.— The purpose of the experimental setup was to maintain a viable muscle preparation with reactive arterial vessels under normal skeletal muscle environmental conditions. In order to closely approximate the in vivo composition and temperature of the interstitial fluid surrounding the cremaster muscle, a closed chamber was utilized.

Throughout the duration of the experiment, the muscle was superfused with a Krebs-Henseleit solution (KH_2PO_4, 1.19 mM; $NaHCO_3$, 24.99 mM; NaCl, 118.39 mM; KCl 4.75 mM; $CaCl_2$ $6H_2O$, 2.5 mM; & Mg SO_4, 1.19 mM), and the temperature of the buffer in the chamber was held at 34 °C. In addition, the reservoir of buffer was bubbled with a gas mixture of 95% N_2 and 5% CO_2. The gas flow rate was regulated to maintain pO_2 at ≤ 30 mmHg and to provide for the constant maintenance of a pH of 7.4 and a pCO_2 of 40 mmHg in the superfusion solution. Samples of the chamber effluent were analyzed periodically for pO_2, pCO_2, and pH (Radiometer-ABL 330, Copenhagen). It has been previously reported that average cremaster muscle pO_2 is between 10 and 17 mmHg, and it has been demonstrated in this muscle that when tissue pO_2 is increased to greater than 30 mmHg by increasing pO_2 of the superfusion solution, arteriolar diameter decreases significantly (Gorczynski and Duling, 1978). An identical parallel system was constructed for the vasoactive agents that would be tested.

Surgical preparation. — Prior to the initiation of the surgical procedures, animals were weighed to the nearest gram and anesthetized with an intraperitoneal injection of sodium pentobarbital (60 mg/kg). The trachea was then intubated to facilitate spontaneous breathing. The right jugular vein and right carotid artery were cannulated with PE50 tubing for the infusion of supplemental anesthesia and the continuous monitoring of arterial blood pressure. A slow continuous infusion of pentobarbital was used to provide a stable plane of anesthesia. Blood samples analyzed from each age group indicated that blood levels of this drug were not significantly different between groups.

The open preparation of the cremaster muscle for microscopic viewing was adapted from Baez (1973). A longitudinal incision of skin and fascia was made in the midline over the ventral aspect of the scrotum. Continuous superfusion of the exposed tissue with warm buffer solution was begun immediately, and the remaining connective tissue and fascia were carefully dissected away from the muscle. A suture was placed through the tip of the pouch as an anchor and an incision was made in the enveloping cremaster muscle; this opened the muscle along the ventral surface directly opposite the main paired arterial and venous vessels. The vas deferens and the vascular supply to the testis were ligated, and the underlying structures were separated from the cremaster muscle and removed.

When the necessary clearing of the muscle was complete, ligatures were attached around the border of the muscle. The animal was then placed in the prone position and transferred to the board which held the cremaster chamber. The muscle was spread over a preheated pedestal, the free ends of the ligatures were secured, and the chamber was immediately filled with previously warmed and bubbled buffer solution. The muscle was stretched such that there was no folding of the tissue, and overstretching (which would reduce blood flow) was avoided. An equilibration period of one hour (both age groups) was then initiated.

Equilibration period. — The primary purpose of this period was to allow the arterial microvessels to stabilize after experiencing vasodilation as a result of the release of vasoactive mediators such as prostaglandins during surgical preparation. During this period, a map was drawn of the branching pattern of the microvasculature architecture, and the sites for measurement of each arteriolar vessel order (1st–4th) were selected and specifically indicated on the map. The primary arterial vessel supplying each cremaster muscle was considered the first order vessel, and second, third, and fourth order arteriolar vessels represented successive branching orders from this parent artery. Monitoring of mean arterial pressure and body temperature was also started at this time. Throughout the experimental protocol, neither mean arterial

pressure nor pulse pressure varied between age groups.

Near the end of the equilibration period the viability of the preparation was assessed. The tissue was examined for red blood cell extravasation, leukocyte margination, and edema. Responsiveness of randomly selected arteriolar microvessels to 10^{-3} acetylcholine was evaluated. A usable preparation lacked the above-mentioned signs of excessive tissue trauma and demonstrated a minimum of 20% (2nd order) increase in diameter to the topical application of acetylcholine.

Experimental protocol. — Vasodilation in response to adenosine and vasoconstriction elicited by norepinephrine were measured in adult and aged male rats. Once the viability of the muscle preparation was verified, the exposure of the tissue to the vasoactive agents was initiated. Stock solutions of each substance to be tested were prepared fresh daily, and final dilutions were mixed in the buffer solution just prior to use. Immediately preceding its addition to the chamber, the agent was placed in a warm bath and bubbled (95% N_2/5% CO_2) so that the appropriate temperature, gas tensions, and pH had been established. During this time, baseline internal diameter measurements were recorded for each arteriolar vessel order. Following this period, the system was switched from the irrigation of the muscle with buffer to the superfusion with the selected experimental agent. In order to avoid possible photoinactivation of norepinephrine, the reservoir and the entire system were wrapped in aluminum foil during these exposures.

Internal diameter measurements (Leitz Ortholux microscope, 100–200×) of each vessel order were made with a calibrated eyepiece graticule at approximately one-minute intervals. Each exposure was continued until the peak response had been achieved as designated by no further change in diameter over several successive measurements. The system was then switched back to the superfusion of the chamber with the buffer solution, and the recovery period was begun. Diameter measurements were taken periodically until the baseline value had been reached. The muscle was then allowed an additional 10–15 minute equilibration prior to the following exposure. Along with the continuous monitoring of mean arterial pressure via right carotid artery using a Statham pressure transducer and core temperature, arterial blood samples were analyzed for pO_2, pCO_2, and pH to determine that the animal was in a stable physiological condition during the experimental procedures. The animals were sacrificed by an overdose of pentobarbital at the end of the experiment. Percent body fat was calculated based on the lean body mass (Tuma et al. 1985). Briefly, body density of the animals was determined by volume displacement, and the lean body mass was then estimated by the regression equation of Rathbun and Pace (1945).

Statistical analysis. — All in vivo diameter changes were analyzed with nonrepeated measures analyses of variance followed by Tukey HSD post hoc analysis when appropriate; a separate test was run for each experimental agent. Other data were analyzed by unpaired *t*-tests.

Table 1. General Characteristics of Adult and Senescent Fischer 344 Male Rats, Mean ± *SD*

	12 month	24 month
Body weight (grams)	419 ± 32.5 *n* = 26	435 ± 32.5 *n* = 24
Mean arterial pressure (mm Hg)	122 ± 25 *n* = 15	119 ± 15 *n* = 14
Percent body fat	49.6 ± 5.3 *n* = 5	45.4 ± 3.4 *n* = 9
Cremaster weight, dry (milligrams)	129 ± 16 *n* = 24	142 ± 16* *n* = 21

*$p < .05$.

Table 2. Effect of Age on Microvascular Morphology, Mean ± *SEM*

Vessel Order	Age (in months)	Vessel Diameter[a]	Segmental Length	Branch Diameter[a]
1	12	159 ± 12.5	1998 ± 160	79 ± 6
1	24	157 ± 8.9	2428 ± 283	82 ± 5
2	12	76 ± 8.0	1104 ± 105	41 ± 3
2	24	80 ± 9.4	1411 ± 152	43 ± 2
3	12	32 ± 3.6	338 ± 30	21 ± 1
3	24	39 ± 5.8	451 ± 26*	23 ± 2
4	12	22 ± 1.8		15 ± 1
4	24	24 ± 1.3		15 ± 1

Note. $n = 5$; values are expressed in microns.
[a]maximally dilated.
*$p < .05$.

RESULTS

General physical and physiological characteristics of adult (12 month) and senescent (24 month) male Fischer 344 rats are presented in Table 1. It is apparent that the two age groups are similar in these parameters.

Morphological data obtained from measurements on maximally dilated latex casts are presented in Table 2. Vessel

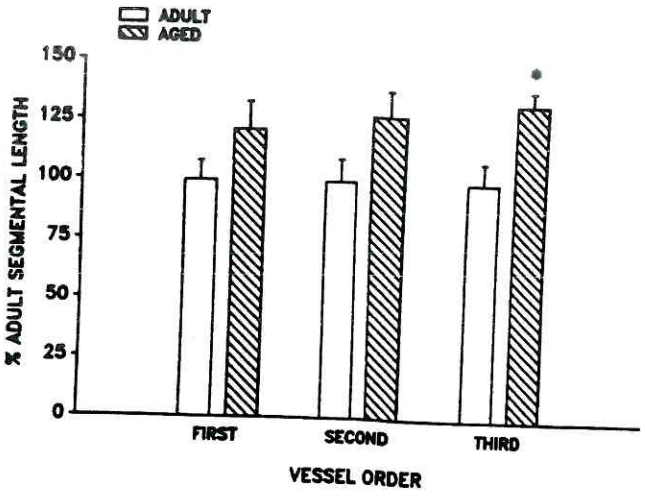

Figure 1. Segmental length (distance between adjacent branches) of 1st, 2nd, and 3rd order arterioles measured from maximally dilated latex casts of the cremaster muscle microvasculature of adult (12 mo) and senescent (24 mo) male rats. Casts were analyzed from 5 animals of each age group; the one primary supply vessel and 3 randomly selected 2nd and 3rd order vessels were examined from each rat. Values represent percent of adult segmental length (mean ± *SE*); *significantly > 12 mo, $p < .05$.

diameter measurements were taken at the origin of the vessel and along the entire length of the vessel and were averaged for each vessel, each animal, and, finally, for each age group. When these grouped results were statistically analyzed, no differences were found between age groups in vessel diameter. However, there was a trend for increased segmental length in the older animals in the first and second order vessels and a statistically significant difference in the third order arterioles. This age-related alteration in segmental length is illustrated in Figure 1. Finally, the tortuosity index (actual length/linear length) of third order arterioles in the rat cremaster muscle was not found to differ between 12 (1.197 ± 0.05, $n = 7$) and 24 (1.173 ± 0.06, $n = 9$) months of age.

Before testing the in vivo diameter changes of arteriolar vessels to the experimental agents, preliminary experiments were conducted to compare the baseline diameters of each age group and to determine their potential for vasodilation and vasoconstriction. Following a 1 hour equilibration period, in vivo vessel diameters were not significantly different between the ages in any of the four vessel orders measured (Table 3). Table 3 also includes diameters of maximally dilated latex casts (separate group of experimental animals) taken at a similar location along the vessel as was examined during the in vivo experiments. A comparison of baseline diameters and maximal diameters confirms that all vessel orders (as defined in Methods) in both age groups had the potential for similar diameter changes. That is, the baseline and maximal diameters were not different between age groups, but the baseline and maximal diameters were significantly different within each age group for each vessel order. The topical application of gradually increasing concentrations of norepinephrine established that all vessel orders in both age groups could be constricted to the point of vessel closure. The exposure of the cremaster microvasculature to potent concentrations of acetylcholine (10^{-3}M) confirmed that both age groups of rats had reestablished vascular tone after the surgery and could demonstrate a similar increase in diameter over baseline.

Table 3. Baseline and Maximal Arteriolar Diameters

	12 month		24 month	
	Baseline	Maximal	Baseline	Maximal
1st order	135 ± 18[a]	174 ± 25	146 ± 20	174 ± 6
2nd order	78 ± 20	94 ± 12	84 ± 25	109 ± 6
3rd order	32 ± 12	51 ± 7	33 ± 8	63 ± 8
4th order	15 ± 3	31 ± 5	18 ± 5	30 ± 6

Note. $n = 14$ (baseline, in vivo); $n = 5$ (maximal, latex casts). Baseline diameters were measured on the in vivo preparations following a 1 hr equilibration period and were not significantly different between the ages in any of the 4 vessel orders. Maximal diameters were measured on maximally dilated latex casts at the same location as was used for baseline measurements. All baseline diameters were significantly less than the corresponding maximal diameter.

[a]mean ± *SD* expressed in microns.

Table 4. Vasodilation in Response to Adenosine (10^{-3}M)

	12 month	24 month
1st order	19.4 ± 16.5[a]	4.0 ± 4.0*
2nd order	16.5 ± 13.2	5.3 ± 2.9**
3rd order	8.8 ± 5.0	6.7 ± 5.8
4th order	4.8 ± 2.4	5.7 ± 3.3

[a]$n = 14$; mean ± *SD* expressed in microns.
*$p < .02$.; **$p < .01$.

The values presented in Table 4 (increase in vessel diameter in microns) demonstrate that adenosine (10^{-3}M) produced a significantly greater dilation in the adult than in the aged rats in first and second order arteriolar vessels. However, the response of the smaller arterioles (3rd and 4th order) was not different between the age groups.

Values which represent the percent decrease in diameter from baseline elicited by norepinephrine are given in Table 5. These results indicate that the reactivity of skeletal muscle arteriolar microvessels to high concentrations of norepinephrine (10^{-5}M and 10^{-4}M) is not altered during the aging process. However, it appears that the arterioles of the senescent animals may, if anything, be less sensitive to the lowest concentration tested (10^{-6}M), although this could not be demonstrated statistically in this study.

Discussion

Although the effect of the aging process on large blood vessels has been frequently studied, the microvasculature has received very limited attention. In addition, the animals previously examined have often not truly represented the senescent population of that species. For example, differences between young (1–3 mo) and adult (12–14 mo) rats have been reported as aging effects when, in reality, they represent developmental changes (Altura and Altura, 1980; Hruza and Zweifach, 1967). Furthermore, earlier literature regarding vascular aging commonly presents results obtained from strains of the rat species which are prone to age-related vascular pathologies. Therefore, the purpose of the present study was to examine the skeletal muscle arterial

Table 5. Vasoconstriction in Response to Norepinephrine

Vessel Order	10^{-6}M		10^{-5}M		10^{-4}M	
	12 mo	24 mo	12 mo	24 mo	12 mo	24 mo
1	32.7 ± 6.3	19.7 ± 12.1	65.2 ± 4.4	66.4 ± 4.5	66.4 ± 6.9	71.4 ± 2.7
2	40.9 ± 7.9	33.2 ± 16.1	54.7 ± 17.6	68.0 ± 12.5	62.1 ± 10.6	72.2 ± 3.1
3	50.3 ± 14.8	39.2 ± 15.5	50.7 ± 11.2	81.7 ± 21.3	85.7 ± 24.8	80.0 ± 17.3
4	59.5 ± 36.6	40.4 ± 9.4	82.2 ± 35.7	100.0 ± 0.0	83.3 ± 28.9	83.3 ± 28.9

Four adult (12 mo) and six aged (24 mo) male rats were evaluated for their vascular responsiveness to norepinephrine. Values represent percent decrease in diameter from baseline; mean ± *SD*.

microvasculature in truly aged animals (24-month-old Fischer 344 rats) which have been reported to be free of vascular disease (Coleman et al., 1977).

The cremaster muscle was selected because it can be prepared with minimal surgical trauma, and its thickness (< 400 μm) allows for successful transillumination. When compared to various thigh muscles, the microvessels of the cremaster muscle were found to respond similarly to touch, exposure, local and body heating, and vasoactive agents (Grant, 1964), and histologically the cremaster muscle was reported to have the same structure and innervation as limb muscle (Grant, 1966). However, the cremaster muscle is not a locomotor muscle, and changes observed in it may not be precisely reflected in muscles of locomotion. In spite of this the cremaster muscle is commonly used to study various aspects of the skeletal muscle microcirculation (Harris et al., 1975; Bohlen et al., 1977; Mayrovitz and Roy, 1983; Faber, 1988).

Morphology. — We hypothesized that the aging process would result in structural alterations in the microvascular architecture that could contribute to an increase in skeletal muscle vascular resistance. Although we considered the possibility of a decrease in arteriolar maximal diameter with increasing age as a factor mediating increased resistance, our results demonstrated that the average maximal diameter of first through fourth order arterioles was not different between the age groups.

A tendency for increased segmental length in first and second order arterioles and a significantly longer segmental length in third order vessels was found in the senescent rats in this study. This implies that any given length of parent vessel has fewer branches originating from it, in the aged animals. One method by which vascular resistance is decreased in a tissue experiencing increased metabolism, such as exercise, is an opening of parallel circuits. However, since the aged rats have a reduced availability of vessels which could be opened during exercise, this might contribute to the higher skeletal muscle vascular resistance which was reported in the aged male rats during contraction (Irion et al., 1987).

The implication of a diminished number of small arterioles with increasing age is that there are fewer vessels available to distribute oxygen and nutrients to a given amount of tissue. Therefore, potential age-related changes in tissue mass must be considered. From the results of this study, it appears that cremaster muscle weight increases. It is unlikely that this is actual tissue growth, but it could be due to the infiltration of fat (Borkan et al., 1983) or connective tissue (Pettigrew and Gardiner, 1987). In addition, the change in muscle mass from adult to aged is very slight (9%) and is probably statistically different because of the large number of animals, but physiologically it is insignificant. Since this muscle obviously does not atrophy, a reduced number of arterial branches for any given length of parent vessel represents a rarefaction of distributing vessels.

It is possible that other changes in the microvascular architecture that compensate for the rarefaction occur with age. One consideration is that the arteriolar vessels become more tortuous during the aging process and, therefore, result in a greater length of vessel for any given area of tissue. This could mean that there is no decline in the number of arteriolar branches to supply an area of tissue, despite an increased segmental length. However, third order arterioles, which had significantly greater segmental length in the older animals, showed no age-related alteration in tortuosity. The finding of a relative rarefaction of skeletal muscle resistance vessels, and the finding that the arterioles do not increase in tortuosity, suggest that there are fewer distributing vessels to supply blood to any given amount of skeletal muscle in senescent male rats.

Reactivity. — Adenosine, which is liberated when ATP is utilized in cellular metabolism, has a variety of well-known regulatory effects on the cardiovascular system. In addition to its influences on coronary blood flow and cardiac function, adenosine causes vasodilation in skeletal muscle. Therefore, it has been suggested as a mediator of the increase in skeletal muscle blood flow associated with muscular activity (Dobson et al., 1971; Proctor and Duling, 1982). Results of the present investigation demonstrate that skeletal muscle microvascular responsiveness to adenosine decreases dramatically as a function of increasing age (Table 4). This suggests that the reduced ability of skeletal muscle arterioles to vasodilate in response to increased levels of extracellular adenosine could contribute to the increased vascular resistance previously observed in working skeletal muscle in aged rats (Irion et al., 1987). This reduction in muscle blood flow in the aged animals was associated with a diminished work capacity.

Although the specific mechanism involved in this age-related alteration cannot be elucidated from these results, it is interesting to consider the similarities between the β-adrenergic receptor and the adenosine receptors. At least several of the purinergic receptors are coupled to their intracellular events through the adenylate cyclase enzyme system, as in the β-receptor. Although the β-receptor has not been studied in the microcirculation in relation to aging, β-receptor function has been shown to decline with increasing age in many tissues, including the heart (Lakatta, 1987) and large blood vessels (Pan et al., 1986; Hyland et al., 1987; Hynes and Duckles, 1987). Perhaps the age-related alteration observed in the vascular response to adenosine in the present study is produced by a similar mechanism.

Reports of the effect of the aging process on the vascular response to adenosine are basically lacking in the literature. However, relaxations caused by adenosine in coronary arteries removed from beagles of various ages were examined by Toda et al. (1987). They found that the median effective concentration of adenosine did not differ between adult and senescent animals. Although these findings are inconsistent with those of the present investigation, they are not necessarily contradictory, as the vessels examined were from a different segment of the arterial tree and from a different species. Alterations in vascular responsiveness to adenosine, relative to the aging process, have not been examined in the microcirculation prior to the present study.

We hypothesized that a second mechanism contributing to the decreased ability of aged male rats to reduce local vascular resistance during muscle contraction could be an

increased vascular sensitivity to norepinephrine (NE). It has been previously demonstrated that arteriolar microvessels of the gastric submucosa in senescent (25 mo) rats are more sensitive to topically applied NE than are the same vessels in adult (10 mo) rats (Ballard et al., 1983). The NE experiments in the present investigation, therefore, were conducted to determine if skeletal muscle arterioles undergo similar age-related changes. However, the results indicate that this aging phenomenon does not occur in skeletal muscle (Table 5). That is, there was no difference between the adult and aged rats in the response of the parent artery feeding the cremaster muscle and three subsequent branching orders of arterioles to the two highest concentrations (10^{-4}M and 10^{-5}M) of NE. In addition, although statistical significance could not be demonstrated, the vasoconstriction of all four of these vessel orders elicited by the lowest concentration (10^{-6}M) of NE appears to decline with advancing age. Although a diminished sensitivity to a near threshold concentration of NE cannot be definitively reported, it can be concluded that an increased arteriolar sensitivity to NE with increasing age does not occur in skeletal muscle. Therefore, this is not a factor which influences the age-related increase in vascular resistance in working skeletal muscle.

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