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BY

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Oklahoma City, Oklahoma

1966

LOCAL RESPONSES OF SKELETAL MUSCLE AND SKIN VASCULAR BEDS

IN EXERCISE IN THE DOG HINDLIMB

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LOCAL RESPONSES OF SKELETAL MUSCLE AND SKIN VASCULAR BEDS IN EXERCISE IN THE DOG HINDLIMB

CHAPTER I

INTRODUCTION

Venous Responses in Skeletal Muscle in Exercise

There is considerable data in the literature to show that the onset of exercise is followed by increased arterial pressure and cardiac output (4), (9), (14), (15), (22), (34), (38), a minimal elevation, if any, in central venous pressure (15), (38), (55), and a decrease in total peripheral resistance (38), (53).

Despite negligible changes in central venous pressure, plasma volume has been found to decrease in exercise. Holmgren (38), demonstrated that the fluid shift from the vascular compartment amounted to 7 to 9% of the total blood volume in a man doing fifteen minutes of heavy exercise. Earlier, Gregersen (29), showed a loss of 470 milliliters of fluid in a ninety second period, in an athlete running at top speed on a treadmill. Similar results have been published by Ebert and Stead (18), who studied human subjects doing strenuous bicycle work. Such data raise the question as to the mechanism of this fluid loss in the capillaries. While the fluid loss may be explained solely by the increased blood flow and precapillary dilitation of exercise, a possible role for the venous vasculature in this mechanism cannot be discounted.

Capillary hydrostatic pressure is a function of the compliance of the capillary wall and volume of blood in the capillary. Volume is regulated, in turn, by the central arterial and venous pressures and the pre- and postcapillary resistances. While the direction and magnitude of the changes in arterial and venous pressures in exercise are known, the direction and magnitude of the change in the pre- to postcapillary resistance ratio is still a matter of considerable speculation.

It is well known that exercise causes an increase in blood flow through active muscles. Grant (25), has demonstrated in humans that this hyperemia is proportional to the intensity of the work. Wood and Bass (57), with a forearm plethysmograph showed large increases in blood flow in the forearms of individuals doing treadmill work. With a similar technique Corcondilas et al. (13), showed that an increase in flow can be detected within a second of single contraction of forearm muscles. This apparent decrease in pre-capillary resistance has been demonstrated also in animals. Gollwitzer-Meier (24), studied the isolated gastronemius muscle of the dog during stimulation and found a gradual reduction in arterial pressure. Hilton (36), showed that a dilitation of the femoral artery occurred following contractions of hindlimb muscles in the cat. This response was confirmed in cats by D'Silva and Fouche (16).

The combined effect of an increase in arterial pressure with the apparent decrease in precapillary resistance in the intact organism, could increase capillary pressure and, as a result, the filtration rate. However, a commensurate decrease in venous resistance could offset

this increase in capillary pressure, since capillary volume, a determinant of pressure, is a function of the ratio of pre- to postcapillary resistance. Furthermore, Pappenheimer and Soto-Rivera (46), have indicated that the filtration - absorption mechanism in the capillary is five to ten times more sensitive to changes in venous resistance than to arterial resistance.

Landis and Hortenstine (42), commented that studies of vasomotor tone indicate that arterioles and venules tend to dilate or constrict together, thereby not changing capillary pressure. While this statement may be an acceptable generalization, there are exceptions to it. There is increasing experimental evidence to indicate that pre- and postcapillary vessels may respond quite differently to original stimuli. Inchley (39), and Haddy (30), showed such an effect in the dog in response to histamine. The latter investigator demonstrated that under special conditions this agent may cause vasodilitation of precapillary, and vasoconstriction of postcapillary vessels. Mellander (44), showed a differential effect over time in the resistance of pre- and postcapillary vessels in the cat. As a result of sympathetic stimulation, the constriction effect, evident in both beds, persisted longer in the postcapillary vessels. The capacitance vessels were also found to be more sensitive to low frequencies of sympathetic stimulation.

There has been some tendency to interpret the dynamics of the peripheral circulation from central venous pressure determinations. Haddy, et al. (31), used a small vein (0.5 mm diam) catheterization technique in the unanesthetized dog to show that small vein pressures

are spontaneously variable over time. Simultaneous determinations of large vein pressures showed negligible changes. They concluded that central venous pressures may indicate little about the status of the peripheral circulation. Holmgren (38), studied the relationship of central venous pressure and peripheral venous pressure in humans doing bicycle work. The central venous pressure was measured in the right atrium and the peripheral venous pressure was measured simultaneously in an arm vein. During prolonged exercise the pressures varied independently of each other. The author points out that only in one of five experiments was the central venous pressure an accurate indicator of the pressure variations in the peripheral veins.

It is apparent from the previous discussion that the postcapillary vessels are capable of playing a vital and independent role in regulating capillary hydrostatic pressure. It is also evidently true, that the role cannot be identified by the dynamic changes in large veins draining the various parallel, vascular beds. Only recently have attempts been made to elucidate the reaction patterns in local postcapillary venous segments of muscle in exercise.

Kjellmer (40), investigated local pressure-flow dynamics in exercise in the calf muscles of the cat. He utilized the plethysmographic technique, described originally by Mellander (44), for measuring changes in volume of the muscle groups. The skin flow through the experimental system was arrested by ligating the saphenous arteries and veins. The popliteal artery and vein were the only vessels running to and from the calf muscles. When the system was isovolumetric (filtration = absorption), as judged by minimal volume changes, the venous pressure was raised abruptly by a known amount and the ensuing rate of

net outward filtration was measured by the volume change in the plethysmograph. The filtration per unit time, per unit change in pressure (capillary filtration coefficient or CFC), was then used to calculate the mean capillary filtration pressure on the assumption that 80% of the change in vein pressure was transmitted to the capillaries. With the arterial, venous and capillary pressures, the precapillary resistance $\frac{(P_A - P_c)}{F}$, and the postcapillary resistance $\frac{(Pc - Pv)}{F}$, were calculated.

Exercise induced by faradic stimulation of the sciatic nerve increased capillary hydrostatic pressure by 17 mmHg in the most intensely stimulated animals. This pressure increased in proportion to the stimulation rate. In these experiments exercise was accompanied by a dilitation of the resistance vessels and of the capacitance vessels. Kjellmer attributes the rise in capillary pressure to a proportionately greater drop in precapillary resistance than in postcapillary resistance. He concluded that precapillary resistance vessels are more markedly affected by the exercise metabolites than are the postcapillary vessels.

Using the dog as the experimental model, Thulesius and Johnson (54), determined capillary hydrostatic pressure in the isolated calf muscle. A variation of the isogravimetric technique of Pappenheimer and Soto-Rivera (46), was used for this purpose. During exercise, elicited by stimulation of the crural nerve at 1-2 impulses per second, blood flow increased from 8 to 24 ml/min/100g and this was paralleled by an increase in the capillary filtration coefficient (rate of filtration per mmHg). However, calculated capillary pressure did not increase significantly and pre- and postcapillary resistance declined equally. These

observations led the investigators to attribute the increase in the capillary filtration coefficient to a filtration over a greater surface area in the capillaries. They believed this was due to the opening of more precapillary sphincters with the increased blood flow of the exercise.

Sharpey-Schafer (50), used a plethysmographic technique to study what he termed "vasomotor tone" in the exercising forearms of humans. In all of some 200 experiments on sixty subjects the tone of the veins of the forearm was conspicuously increased immediately after exercise. The exercise routine used was not specified. The investigator states that the results were the same in normal and sympathectomized patients, as well as those with severe anemia, absent circulatory reflexes, and those in heart failure. Similar exercise of the opposite arm had no effect on the experimental forearm. The author concluded that the constrictor effect was not nerve mediated and represented a local effect. He further stated that the duration of the increased tone was related to the length of exercise and that the veins remained less compliant a shorter time than the arteries remain dilated.

Sharpey-Schafer's experimental technique involved the measurement of the change in pressure in a large anticubital vein, and the measurement of the volume change in the forearm at a cuff pressure which occluded venous outflow from the forearm. The venous tone was defined as the ratio of the pressure change over time $(\frac{\Delta P}{\Delta T})$ to the volume change over time $(\frac{\Delta V}{\Delta T})$. A rise in the ratio indicated increased tone and a fall indicated decreased tone of the capacitance vessels.

Kjellmer (40), criticized the results of Sharpey-Schafer with the argument that comparison of control and exercise vasomotor tone could

not be made with this system, since the starting blood volume in the forearm is different from the rest to the exercise states. According to Kjellmer, it is possible that the resting, initial volume lies on the linear portion of the characteristic pressure-volume curve for veins, whereas an initial volume in exercise may lie on the upper flat portion of the curve. In such an event, identical changes in volume would cause a greater pressure change in exercise than in the control state. This would lead to the erroneous conclusion that venoconstriction occurred in exercise. Kjellmer, on the basis of venous distensibility calculations with his own data suggested that this was the course of events in Sharpey-Schafer's work. More recently Bevegard and Shepherd (6), have criticized Sharpey-Schafer's results on similar grounds. However, the likelihood of a systematic error in his work is questionable. In reactive hyperemia experiments in which blood flows were comparable to those observed in exercise, Sharpey-Schafer (50), saw no change in venous tone, between control and post-occlusion measurements. This would indicate that it is possible for all blood volumes measured to lie on a linear portion of the pressure-volume curve, despite the differences in magnitude.

Whether the data derived from forearm plethysmographic studies truly reflects venous activity of the muscle bed may be questioned on the basis that such measurements of vascular dynamics include changes in the skin as well as the muscle bed. However, Grant and Pearson (26), have shown that the proportions of skin and bone in the muscular forearm are small (muscle forming 85% of its volume), and that a cutaneous hyperemia as active as the flare causes an increase in forearm blood

flow of 1.0 to 2.2 cc per 100 cc of forearm volume. They state that this is a small change, yet greater than that occurring in the skin as a result of exercise. Shepherd (51), has also presented data, based on the oxygen saturation of blood in deep and superficial veins that indicate very small changes in skin flow with exercise.

While Sharpey-Schafer (50), holds to the view that a local constrictor response of the venous vasculature occurs in exercise, Kjellmer (40), and Thulesius and Johnson (54), have suggested a local dilator response. Blair et al. (8), observed venoconstriction of forearm veins in supine leg exercise, with the nerve supply intact. When the sympathetic nerve fibers to the forearm were blocked with bretylium tosylate the constrictor response was no longer observed. Bevegard and Shepherd (5), studied blood volume changes in the human forearm at constant venous pressures with the nerve supply also intact. They observed a venoconstriction in the forearm with leg exercise, that persisted when arm exercise was added to the routine. However, unlike Sharpey-Schafer (50), the venoconstriction could not be demonstrated in the sympathectomized limb. Recently, the same investigators (6), reported they observed no vasomotor activity in forearm veins with exercise of forearm muscles having intact nerve supplies. It should be noted that the critical "exercise" measurements in this work were completed two to three minutes after exercise.

Experimental evidence for a centrally mediated control mechanism for the venous vasculature is supported by anatomical and teleological evidence cited by Alexander (1), and Folkow and Mellander (21), respectively. The former author makes note of the fact that veins are copiously supplied with nerves as compared with precapillary vessels. Folkow

and Mellander make a case for central control of veins based on their capacitance function, in subserving as a unit, the whole cardiovascular system, rather than the local needs of particular tissues. In fulfilling this function, they state that the venous system will demand a centrally integrated control for satisfactory performance and will only minimally tolerate interference by local regulatory mechanism. They view the precapillary resistance vessels as primarily controlled by a local myogenic mechanism and the postcapillary vessels by a central nervous mechanism.

Circulation in the Skin in Exercise

The skin circulation serves two purposes, nutrition and heat regulation. Hertzman (35), states that the circulation is primarily adjusted as part of the regulation of body temperature because the amount of blood flow to satisfy cutaneous respiratory needs is small.

Christensen et al. (11), used a plethysmographic technique on humans to study the arterial inflow to the finger while the venous return was cut off for a few seconds. Greenfield (27), has pointed out that digital flow is frequently equated with skin flow since the fingers and toes are composed largely of skin. At the same time digital flow was measured, Christensen et al. employed skin thermocouples to measure changes in skin circulation while work was carried out on a bicycle ergometer. At the start of work an instantaneous reduction in the finger blood flow occurred. This was transient but persisted for a longer time as the intensity of the exercise increased, delaying the dilitation that occurs due to an increase in body heat. Thermocouple determinations indicated similar though less pronounced responses in the hands, feet and the skin of the trunk. From these results the invest-

igators concluded that the skin vasoconstriction was of regulatory significance in the adjustment of circulation from rest to work. Since the response is instantaneous it was thought to be nerve mediated.

Barger et al. (3), investigated the response of the skin vasculature of the human forearm to treadmill exercise. The criterion of vascular activity was the time for inducing reactive hyperemia on a skin surface. A weighted plastic ring, described by Greenwood (28), was used to occlude vessels. The subjects walked on the treadmill for ten minutes with the exercise graded by a change in the incline of the walking surface. This group found that the time for inducing reactive hyperemia increased with the intensity of the work, suggesting greater vascular constriction with greater intensity of work. As in the previous study cited, the role of the venous vasculature in this response is not identified.

The work of Wallace (56), represents yet another approach to the study of the venous vasculature in exercise. He used catheters to measure pressures in small skin veins of the hand, large forearm veins and the radial artery in humans. Local exercise of the hand markedly dropped arterial pressure, caused little change in small veins and elevated large vein pressure. This suggests that flow did not increase through the skin.

Segments of superficial veins in humans have been temporarily isolated and studied under various stress conditions (17), (45). The blood is stationary in these veins and the only connection with the rest of the body is through the sympathetic nervous system. In such a preparation pressure increases are interpreted as venoconstriction and

pressure drops as dilitation. Exercise, deep inspiration, positive pressure breathing and the Val Salva maneuvers have been found to produce a constriction in the segments of superficial veins (45). Evidence previously cited (51), (25), suggests that this truly indicates cutaneous vascular activity.

Haddy, et al. (31), used small vein catheters (0.2 - 0.5 mm diam.) to study the responses of these vessels in dogs during exercise. Catheters were located in a small subcutaneous vein in the dorsum of the paw and in a large vein, the cephalic or saphenous. In exercise, small and large vein pressures increased but to a greater degree in the small veins. The nerve supply was intact in these experiments. Apparently, no data are available in which only local venous responses of the cutaneous bed were studied in exercise.

The purpose of the present work was to reinvestigate the local muscle venous responses to exercise in the hindlimb of the dog and to gain some insight into local skin vein activity during this muscular exercise.

CHAPTER II

METHODS

In this study the local effects of exercise and for comparative purposes, reactive and mechanical hyperemia were investigated in forty dogs, ranging in weight from fifteen to twenty kilograms. The animals were anesthetized with sodium pentobarbital, 30/mg/kg, and ventilated with a mechanical respirator (Harvard Apparatus Co., Model 607) via an intratracheal tube.

Lying in a supine position on a table, the skin of the right hindlimb was sectioned along a line from the anterior iliac spine to the pubis, then dorsally to the ischial tubercle to the posterior spine of the ilium, then back to the anterior spine. The femoral artery and vein, with small side branches, were dissected free and exposed for a distance of three to four centimeters on the ventral surface of the thigh. All skeletal muscle, with accompanying vessels, originating on the pelvic girdle or lower spine, and inserting on the hindlimb, were then ligated and sectioned as close to their origins on the trunk as possible. Care was taken in this process to isolate the femoral and sciatic nerves which were subsequently sectioned close to the trunk. Only the femoral artery, femoral vein and the attachment of the femor on the pelvis remained intact.

Following an intravenous injection of 4 mg/kg of sodium heparin,

an extracorporeal venous circuit, filled with low molecular weight Dextran, was inserted between the right femoral, and the medial and dorsal saphenous veins of the experimental limb and the left femoral vein (Figure 1). The circuit included two T-tubes, one between the right femoral and the left femoral vein, and another between the medial-dorsal saphenous veins and the left femoral vein. This system allowed independent flow measurements and samplings of muscle venous blood (right femoral vein to left femoral vein) and skin venous blood (saphenous veins to left femoral vein). Blood flows were measured in graduated cylinders by releasing the clamps on the T-tubes and simultaneously occluding the rubber distal to the T-tubes. Venous outflow, collected in graduated cylinders was returned to the animal by means of a catheter placed in the jugular vein.

Polyethylene catheters were inserted into isolated side branches of the femoral artery and femoral vein for measurements of systemic arterial pressure (P_A) and large muscle vein pressure (P_{LMV}) respectively. A small vein (0.2 to 0.5 mm diameter), which appeared to originate in the quadriceps group of muscles was isolated and catheterized in a retrograde direction for measurement of small muscle vein pressure (P_{SMV}). Extreme care was taken to ascertain that this vessel was patent and that adequate collaterals existed to insure measurement of a true lateral pressure. A glass tipped catheter was inserted into a small vein (0.2 to 0.5 mm diameter) in the subcutaneous tissue of the dorsum of the paw for small skin vein pressure (P_{SSV}) determinations. Another catheter was threaded into a branch of the medial saphenous vein upstream to the large catheter shunting skin flow from the medial

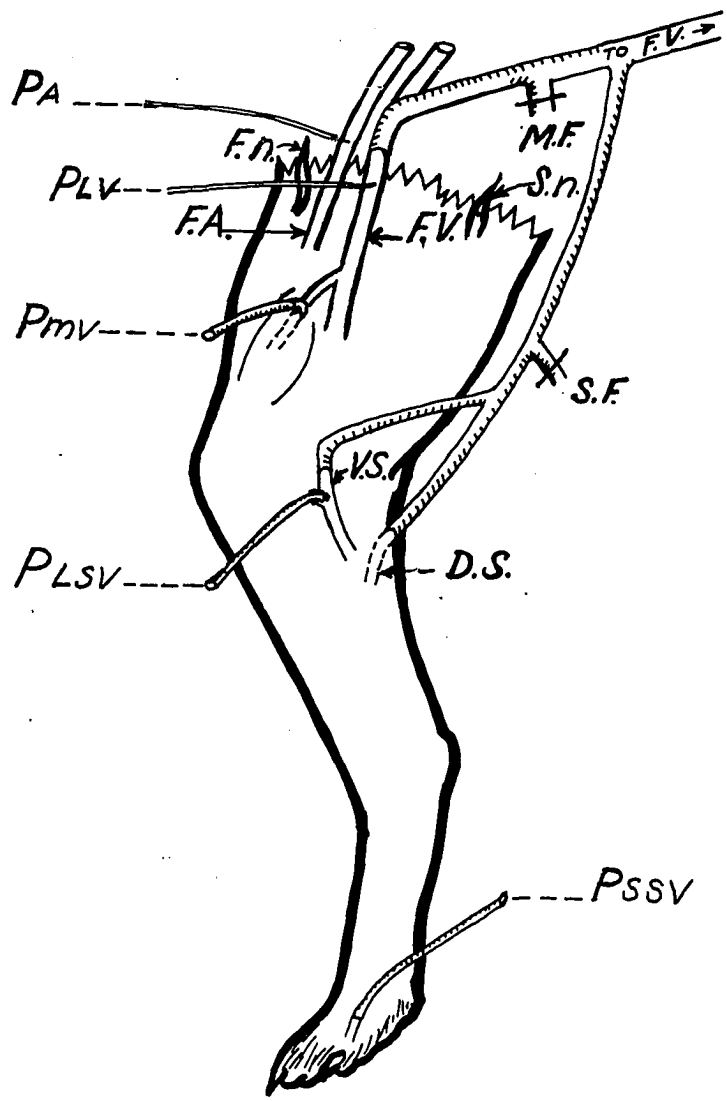

Fig. 1 -Schematic drawing of the extracorporeal circuit. F.N. = femoral nerve, S.N. = sciatic nerve, F.A. = femoral artery, F.V. = femoral vein, M.F. = muscle flow, S.F. = skin flow, V.S. = ventral (medial) saphenous vein, D.S. = dorsal saphenous vein, P_A = femoral artery pressure, P_{LV} = large muscle vein pressure, P_{MV} = small muscle vein pressure, P_{LSV} = large skin vein pressure, P_{SSV} = small skin vein pressure.

saphenous vein to the femoral vein of the opposite limb. Large skin vein pressure (P_{LSV}) was measured at this site. The locations of the catheters used for pressure determinations are indicated in Figure 1.

The arterial, small muscle vein and large muscle vein pressures were monitored continuously on a direct writing oscillograph (Sanborn Co., Waltham, Mass.) by attachment of the catheters to 0 to 75 cm Hg resistance wire pressure transducers. The two skin vein pressures were recorded alternately on one recording channel by means of a multiple stopcock arrangement. A mercury manometer was used to calibrate the recording system before each experiment, and frequent calibration checks were made as the experiments progressed.

The five blood pressure measurements and muscle and skin blood flow determinations were made in control, exercise, immediately post-exercise and post-control states. The blood flows through muscle and skin were measured separately in graduated cylinders for a period of ten seconds and extrapolated to minute volumes. Exercise was simulated by stimulation of the femoral and sciatic nerves with a Grass S-5 square wave stimulator (Grass Instruments, Quincy, Mass.). The attachments to the nerves were made with standard laboratory electrode probes (Harvard Apparatus Co., Dover, Mass.). Exercise measurements were completed when the limb appeared to be in a "steady state" condition, as indicated by minimal variations in the pressures being monitored. During the stimulation of one to two minutes duration, the limb was allowed to move freely in response to musclar activity. Postexercise measurements were taken within three to five seconds after cessation of stimulation and again two to three minutes later (post-control).

Muscle and skin venous resistances were calculated for each period in which pressure and blood flow measurements were made. This was accomplished for the muscle venous bed by subtracting the large muscle vein pressure (P_{LMV}), from the small muscle vein pressure (P_{SMV}) to determine the pressure gradient (ΔP_{MV}), over this segment of the vasculature. Dividing the pressure gradient by the measured muscle blood flow gave the muscle vein resistance (R_{MV}). The skin vein pressure gradient (ΔP_{SV}), was calculated by subtracting the large skin vein pressure (P_{LSV}), from the small skin vein pressure (P_{SSV}). The gradient was then divided by skin flow to give the venous resistance (R_{SV}) through the skin vascular bed. Since the arterial pressure was measured continuously, additional vascular resistance measurements were calculated. These included:

1. Total muscle resistance------$R_{TM} = \frac{P_A - P_{LMV}}{M.F.}$

2. Artery to small muscle vein segment---$R_{ASMV} = \frac{P_A - P_{SMV}}{M.F.}$

3. Total skin resistance--------$R_{TS} = \frac{P_A - P_{LSV}}{S.F.}$

4. Artery to small skin vein segment---- $R_{ASSV} = \frac{P_A - P_{SSV}}{S.F.}$

At the completion of each experiment the skin of the hindlimb was removed and weighed. The remaining limb tissue, muscle and bone, was weighed together. In this study all muscle blood flow determinations are expressed in milliliters per minute, per 100 grams of skinless tissue, and resistance measurements in mm Hg per milliliter per minute per 100 grams of skinless tissue. The skin blood flows are expressed in milliliters per minute, per 100 grams of skin tissue, and

resistance measurements in mm Hg per milliliter per minute per 100 grams of skin tissue. The total blood flow values are expressed in milliliters per minute per 100 grams of limb tissue.

Ten animals were used in the first series of experiments. Mean stimulation parameters for this group were 7.5 volts, 0.5 milliseconds duration and a frequency of 6 per second. The voltage and the frequency of stimulation varied from experiment to experiment, the duration of the stimulus remaining constant. The voltage and frequency, more often the voltage only, were adjusted from 6 volts and 4 per second until adequate contractions of the limb muscles were observed.

Seventeen animals were used in the second exercise series. In this group the mean stimulation parameters were 3.1 volts. 0.2 milliseconds duration and a frequency of 4 per second. The duration of the stimulus and the frequency were held constant in this series as the voltage was increased from one volt to the voltage necessary for the contractions of the limb musculature. Greater care was taken in this series to keep the stimulation parameters at low levels in the hope of eliminating any possibility of stimulating the sympathetic fibers coursing the sciatic and femoral nerve trunks.

In seven exercise experiments blood samples were drawn anaerobically from femoral artery and muscle and skin veins (medial and dorsal saphenous) during control exercise and postexercise states at the time pressures and blood flows were measured. Determinations of oxygen content of the blood were made in duplicate samples with the VanSlyke-Neil blood gas apparatus.

In eleven animals, reactive hyperemia in the hindlimb was studied. Following control determinations of pressures and blood flows, a ligature

was placed around the femoral artery proximal to the site of the catheter for measuring arterial pressure. The constriction of the artery was increased until the pressure was observed to fall to approximately one-half of normal. This state was maintained for two to three minutes during which the pressure and blood flow determinations were made. Within three to five seconds of the release of constriction, pressure and flow measurements were made again. Following a two to three minute period the post-control measurements were made. With these data venous resistance measurements were calculated for the muscle and skin beds as previously described.

In eight animals the venous hematocrits were measured in exercise and reactive hyperemia. Two to three milliliters of the effluent blood of the muscle of the experimental limb were drawn for this purpose. This was done in the time interval in which measurements of pressures and blood flows were made. The blood samples were drawn for hematocrit determinations in control and post-control states, during exercise, immediately postexercise, during partial constriction of the femoral artery and immediately on the release of constriction.

In an attempt to ascertain the presence or absence of increased sympathetic activity during stimulation, a neuromuscular blocking agent, Succinylcholine Chloride (Anectine), was administered. Experiments were carried out on seven dogs using this agent. Following control and exercise measurements of pressures and blood flows, Succinylcholine Chloride was rapidly injected in a concentration of 0.1 mg/cc. The injection was continued until skeletal muscle contractions were abolished. In no case did the quantity of injected Succinylcholine Chloride exceed 1.0 mg.

Within one and one-half to two minutes of the cessation of contractions, while the femoral and sciatic nerves were still being stimulated, measurements of pressures and blood flows were completed. Subsequently, post-exercise measurements were made.

A controlled blood flow maneuver was employed in nine experiments. Venous reactivity to mechanically induced hyperemia, and the responses to exercise with constant blood flow were studied with the preparation.

To control the blood flow rate a finger-type pump (Sigmamotor, Model T6SH, Sigmamotor Inc., Middleport, N.Y.) was used. The blood flow was shunted from the femoral artery of the non-experimental limb, through the pump, and then to the femoral artery of the experimental limb. The systemic arterial pressure was measured with a catheter in the right carotid artery. The perfusion pressure (P_P) was measured at a site proximal to the femoral artery of the experimental limb. This was done by needle puncture of the tubing of the extracorporeal circuit shunting arterial blood from the left to the right femoral artery, the needle, in turn, being attached to a strain gauge. No attempt was made to measure small and large skin vein pressures in these experiments. However, the skin as well as muscle blood flows were measured by means of the venous extracorporeal circuit previously described.

To study the venous responses to mechanical hyperemia the muscle blood flow through the system was increased progressively from a mean flow of 3.6 to 5.9, 8.4, 11.2 and 13.9 ml/min/100 grams skinless tissue. At each flow level the systemic artery pressure (P_A) the perfusion pressure (P_P), and the small and large muscle vein pressure (P_{SMV}) and (P_{LMV}) respectively, were measured, as well as muscle and skin blood

flows. Care was taken to make the measurements when the system had attained a "steady state", as indicated by blood pressure recordings. With these data venous resistance measurements were calculated for the various vascular segments of muscle.

When this maneuver was completed, the muscle blood flow was re-established at an intermediate level, the mean for nine animals being 8.2 ml/min/100 grams skinless tissue. After control measurements of pressures and blood flows were made the femoral and sciatic nerves were stimulated. The mean stimulation parameters were 2.6 volts, a frequency of 4 per second and a duration of 0.2 milliseconds. In this series only the voltage was increased in establishing the level of muscular activity in the limb, the frequency and duration of the stimulus remained constant. During stimulation the measurements of pressures and blood flows were completed and repeated immediately on the cessation of exercise. The experiments were terminated at this point.

The appropriate data in the study were treated with a paired comparison of the observations. The test criterion was "t", and the hypothesis tested was that the mean of the population of differences from the control values, did not differ from zero (52).

CHAPTER III

RESULTS

Local Effects of Exercise on the Vascular Bed of Skeletal Muscle

A typical response of the muscle vasculature in exercise is illustrated in Figure 2. On stimulation the arterial pressure (P_A) decreased slightly, and a small increase occurred in large muscle vein pressure (P_{LV}). The small muscle vein pressure (P_{MV}) rose sharply initially, and this was followed by a slower, progressive increase to a "steady state" value. On cessation of stimulation a sharp drop in pressure was observed, followed by a slower decline to the control pressure level. The sharp increase and decline in muscle vein pressure may reflect the influence of the contracting skeletal muscle on the vasculature. Blood flow through the muscle bed (F), increased during exercise and remained well above the control value immediately post-exercise. The calculated resistance in the muscle vein segment (R_m), increased with exercise and remained above the control value postexercise.

The summarized data for the first series of ten experiments are shown in Table 1. For this group the mean stimulation parameters used were 7.5 volts, a frequency of 6 impulses per second and a stimulus duration of 0.5 milliseconds. Exercise resulted in an average decrease in arterial pressure (P_A) of 10 mm Hg. This fall in perfusion pressure persisted immediately postexercise, and was still slightly below the

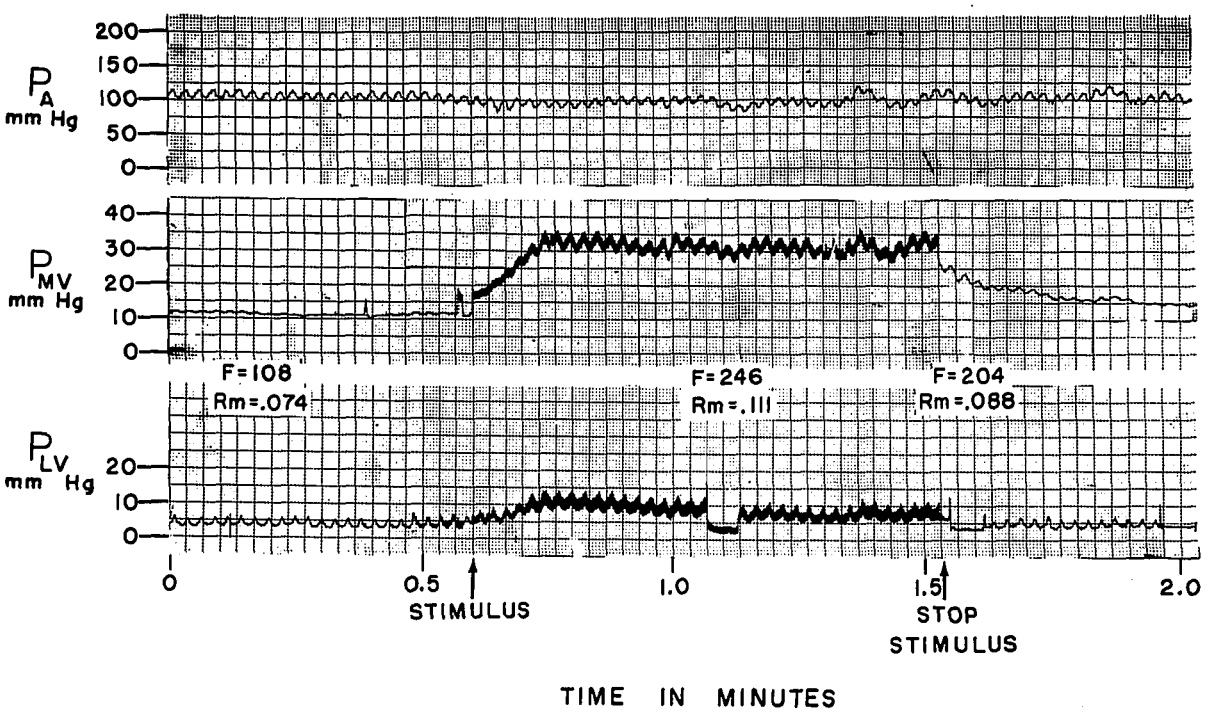

Fig. 2 -Typical pressure responses of the muscle vasculature, with measured blood flow and calculated resistances with exercise. P_A = femoral artery pressure, P_{MV} = small muscle vein pressure, P_{LV} = large muscle vein pressure, F = blood flow, R_M = muscle vein resistance.

TABLE I

LOCAL EFFECTS OF EXERCISE ON THE VASCULATURE OF SKELETAL MUSCLE (n=10)

	P_A mmHg	P_{LMV} mmHg	ΔP_{TM} mmHg	M.F. ml/min /100g S1.T.	R_{TM} mmHg /ml/min /100gS1.T.	ΔP_{ASMV} mmHg	R_{ASMV} mmHg /ml/min /100gS1.T.	P_{SMV} mmHg	ΔP_{MV} mmHg	R_{MV} mmHg /ml/min /100gS1.T.	T.F. ml/min /100g L.T.
CONTROL	100	8	92	9.3	14.43	85	13.35	15	7	0.82	16.3
EXERCISE	90	10	80	20.2	4.88**	51	3.13**	39	29	1.70**	26.9
POSTEXERCISE	92	10	82	20.4	4.89**	57	3.49**	36	26	1.44*	28.2
POST-CONTROL	96	8	88	8.9	11.39	79	10.25*	17	9	1.18	---

* $P < .05$ ** $P < .01$

P_A = femoral artery pressure, P_{LMV} = large muscle vein pressure, ΔP_{TM} = total muscle pressure gradient, M.F. = muscle blood flow in ml/min/100 grams skinless tissue, R_{TM} = total muscle resistance, ΔP_{ASMV} = pressure gradient, artery to small muscle vein segment, R_{ASMV} = resistance, artery to small muscle vein segment, P_{SMV} = pressure small muscle vein, ΔP_{MV} = pressure gradient, muscle vein segment, R_{MV} = resistance, muscle vein segment, T.F. = total limb flow in ml/min/100 grams of limb tissue.

control level two to three minutes after exercise. The large vein pressure (P_{LMV}), rose an average of 2 mm Hg on stimulation, remained steady immediately postexercise, and then returned to the control level. These pressure changes reduced the gradient over the total muscle vascular bed (ΔP_{TM}), at the same time the blood flow increased from 9.3 to 20.2 ml/min/100 grams skinless tissue, and to 20.4 ml/min/100 grams of skinless tissue in the postexercise period. The result was a significant decrease ($P < .01$), in the total muscle resistance (R_{TM}). Resistances calculated over the segment from the femoral artery to the small muscle vein (R_{ASMV}), showed the same pattern of decreases during and immediately postexercise. These changes were significant at the .01 level. In this segment even the post-control resistance was significantly below the control level ($P < .05$). A persisting vasodilitation of this vascular segment is indicated.

The small muscle vein pressure (P_{SMV}), increased from a mean of 15 to 39 mm Hg during exercise. Since the large muscle vein pressure (P_{LMV}) increase was small, the pressure gradient measured over this segment increased. The calculated resistance rose from 0.82 to 1.70 mmHg/ml/min/100 grams of skinless tissue, despite the more than two-fold increase in blood flow. This increase was significant at the .01 level. The postexercise small muscle vein resistance was also significantly elevated above the control value ($P < .05$). This indicated the presence of increased smooth muscle activity in this vascular bed.

These observations suggested the possibility that the vasoactivity in this bed was due to stimulation of sympathetic nerve fibers coursing through the nerve trunks that were stimulated. The study was

continued with another series of seventeen experiments in which the intensity, duration and frequency of stimulation was reduced. In this series the mean stimulation parameters were 3.1 volts, a frequency of 4 impulses per second and a stimulus duration of 0.2 milliseconds. These data are shown in Table 2.

The responses elicited showed a nearly identical pattern to those of the previous series, marked by decreases in mean arterial pressure, total muscle, and artery to small muscle vein resistance. These decreases in resistances were again significant ($P < .01$). The average blood flow increase from control to exercise was slightly greater in this series, and the flow tended to decline immediately postexercise, in contrast to a very small rise postexercise in the previous series (Table 1). Again, a large increase in mean small muscle vein pressure from 13 to 36 mm Hg was observed. This resulted in a significant increase in muscle vein resistance ($P < .01$), despite a nearly three-fold increase in blood flow. As in the previous series, the average resistance in this segment remained elevated postexercise and the difference was significantly above the control level ($P < .05$).

Local Effects of Exercise on the Vascular Bed of the Skin

Tables 3 and 4 show the mean values for pressures, blood flows and resistances for the skin vascular bed in exercise. Table 3 shows the mean responses for eight experiments, when the limb was stimulated at 7.5 volts, a frequency of 6 per second, and an impulse duration of 0.5 milliseconds.

While the arterial pressure decreased by 9 mm Hg on the average, the large skin vein pressure (P_{LSV}) increased an average of 1 mm Hg with

TABLE 2

LOCAL EFFECTS OF EXERCISE ON THE VASCULATURE OF SKELETAL MUSCLE (n=17)

	P_A mmHg	P_{LMV} mmHg	ΔP_{TM} mmHg	M.F. ml/min /100g S1.T.	R_{TM} mmHg /ml/min /100gS1.T.	ΔP_{ASMV} mmHg	R_{ASMV} mmHg /ml/min /100gS1.T.	P_{SMV} mmHg	ΔP_{MV} mmHg	R_{MV} mmHg /ml/min /100gS1.T.	T.F. ml/min /100g L.T.
CONTROL	95	7	88	7.4	15.91	83	15.15	13	6	0.82	10.7
EXERCISE	88	9	79	19.7	4.94**	52	3.65**	36	27	1.63**	21.6
POSTEXERCISE	91	8	83	18.6	5.35**	63	4.13**	28	20	1.26*	20.6
POST-CONTROL	95	7	88	7.9	13.65	80	10.70*	14	7	0.92	11.3

* $P < .05$ ** $P < .01$

P_A = femoral artery pressure, P_{LMV} = large muscle vein pressure, ΔP_{TM} = total muscle pressure gradient, M.F. = muscle blood flow in ml/min/100 grams of skinless tissue, R_{TM} = total muscle resistance, ΔP_{ASMV} = pressure gradient, artery to small muscle vein segment, R_{ASMV} = resistance, artery to small muscle vein segment, P_{SMV} = pressure, small muscle vein, ΔP_{MV} pressure gradient, muscle vein segment, R_{MV} = resistance, muscle vein segment, T.F. = total limb flow in ml/min/100 grams of limb tissue.

exercise. The blood flow through the skin decreased from 36.8 to 33.9 ml/min/100 grams skin tissue and returned nearly to control level post-exercise. The relatively greater decrease in arterial pressure than in skin blood flow resulted in a decrease in total skin resistance (R_{TS}). This decrease was not significant ($P > .05$) but did persist for some minutes after exercise as the table shows. The resistances calculated for the artery to small skin vein segment (R_{ASSV}), followed the same pattern. The mean changes from the control levels were small during, and postexercise, and not significant ($P > .05$).

The small skin vein pressure (P_{SSV}) decreased by an average of two mm Hg in exercise at the same time the small muscle vein pressure (Tables 1 and 2) increased by a factor of approximately 2.5. The slight change in small skin vein pressure coupled with a mean rise of 1 mm Hg in large skin vein pressure reduced the skin vein pressure gradient to a mean of 7 mm Hg. While the blood flow decreased, the gradient decreased proportionately more, so that the mean skin vein resistance (R_{SV}) fell by 0.09 mm Hg/ml/min/100 grams skin tissue. This was not a significant decrease from control ($P > .05$), and the resistance calculated, slightly exceeded the control value postexercise.

In Table 4 the average responses for the skin vascular bed are shown for fifteen experiments, in which the mean stimulation parameters were 3.1 volts, a frequency of 4 per second, and an impulse duration of 0.2 milliseconds.

In this series the large skin vein pressure (P_{LSV}) exhibited no mean change from control. The skin blood flow increased by 3.0 ml/min/100 grams of skin tissue with exercise, in contrast to a mean fall of 2.9 ml/min/100 grams of skin tissue in the previous series (Table 3).

TABLE 3

LOCAL EFFECTS OF EXERCISE ON THE VASCULATURE OF THE SKIN (n=8)

	P_A mmHg	P_{LSV} mmHg	ΔP_{TS} mmHg	S.F. ml/min /100g S.T.	R_{TS} mmHg /ml/min /100gS.T.	ΔP_{ASSV} mmHg	R_{ASSV} mmHg /ml/min /100gS.T.	P_{SSV} mmHg	ΔP_{SV} mmHg	R_{SV} mmHg /ml/min /100gS.T.
CONTROL	97	11	86	36.8	2.68	76	2.19	21	10	0.27
EXERCISE	88	12	76	33.9	2.23	69	2.05	19	7	0.18
POSTEXERCISE	90	11	79	35.9	2.40	70	2.11	20	9	0.29
POST-CONTROL	94	11	83	36.8	2.47	72	2.17	22	11	0.30

*P< .05 ** P < .01

P_A = femoral artery pressure, P_{LSV} = large skin vein pressure, ΔP_{TS} = total skin pressure gradient, S.F. = skin blood flow in ml/min/100 grams of skin tissue, R_{TS} = total skin resistance, ΔP_{ASSV} = pressure gradient, artery to small skin vein segment, R_{ASSV} = resistance, artery to small skin vein segment, P_{SSV} = small skin vein pressure, ΔP_{SV} = pressure gradient, skin vein segment, R_{SV} = resistance, skin vein segment.

TABLE 4

LOCAL EFFECTS OF EXERCISE ON THE VASCULATURE OF THE SKIN (n=15)

	P_A mmHg	P_{LSV} mmHg	ΔP_{TS} mmHg	S.F. ml/min /100g S.T.	R_{TS} mmHg /ml/min /100gS.T.	ΔP_{ASSV} mmHg	R_{ASSV} mmHg /ml/min /100gS.T.	P_{SSV} mmHg	ΔP_{SV} mmHg	R_{SV} mmHg /ml/min /100gS.T.
CONTROL	94	9	85	34.0	3.82	77	3.50	17	8	0.28
EXERCISE	89	9	80	37.0	3.24	74	2.58	15	6	0.19*
POSTEXERCISE	93	9	83	35.6	3.70	75	3.42	17	8	0.28
POST-CONTROL	95	9	86	32.2	3.50	77	3.23	18	9	0.26

* $P < .05$ ** $P < .01$

P_A = femoral artery pressure, P_{LSV} = large skin vein pressure, ΔP_{TS} = total skin pressure gradient, S.F. = skin blood flow in ml/min/100 grams of skin tissue, R_{TS} = total skin resistance, ΔP_{ASSV} = pressure gradient, artery to small skin vein segment, R_{ASSV} = resistance, artery to small skin vein segment, P_{SSV} = small skin vein pressure, ΔP_{SV} = pressure gradient, skin vein segment, R_{SV} = resistance, skin vein segment.

The calculated total skin resistance (R_{TS}), decreased with exercise and remained slightly below the mean control level postexercise and post-control. The artery to small skin vein resistance (R_{ASSV}), followed the same pattern. However, as in the previous series, none of these changes was significant ($P > .05$). The small skin vein average pressure (P_{SSV}), declined by 2 mm Hg with exercise returning to the control value post-exercise. The skin vein resistance (R_{SV}), decreased from a mean of 0.28 to 0.19 mm Hg/ml/min/100 grams of skin tissue, a decrease that was significant at the .05 level. The decrease in skin vein pressure was observed in twelve of fifteen experiments, while in the previous series (Table 3), it occurred in five of eight experiments. The magnitude of the mean change in skin vein resistance (R_{SV}) was nearly identical in both series. This would appear to support the possibility that the decrease in skin venous resistance in exercise (Table 4), represents a true local effect though it did not persist postexercise. The apparent dilitation of the skin venous bed with stimulation appears to be the only significant alteration in responses of the skin vasculature to exercise. There certainly was no indication of an increase in sympathetic nervous activity in the responses of the skin vasculature to stimulation of the femoral and sciatic nerves.

Oxygen Content of Blood in Muscle and Skin Beds in Exercise

Table 5 shows the results of seven experiments in which oxygen contents of muscle and skin blood was determined. On the average, the muscle vein oxygen content decreased by 68% with exercise as the blood flow increased by approximately 260%. The oxygen contents of the skin veins also decreased with exercise, by 10 and 20%, in the dorsal and

TABLE 5

BLOOD FLOWS AND OXYGEN CONTENTS IN MUSCLE AND SKIN EXERCISE

	Control						Exercise				
Exp. No.	M.F. ml/min	S.F. ml/min	Arterial O_2 Cont. vol %	M.Vein O_2 Cont. vol %	M.S.V. O_2 Cont. vol %	D.S.V. O_2 Cont. vol %	M.F. ml/min	S.F. ml/min	M. Vein O_2 Cont. vol %	M.S.V. O_2 Cont. vol %	D.S.V. O_2 Cont. vol %
1.	36	90	8.21	5.83	-	7.74	102	90	0.00	-	5.39
2.	102	120	-	18.50	-	19.98	276	90	5.38	-	18.30
3.	60	36	15.51	10.32	12.45	12.05	240	24	3.04	7.25	12.40
4.	66	90	17.84	13.78	16.83	16.68	174	84	5.46	14.39	15.58
5.	60	63	11.25	7.03	9.39	10.15	105	66	4.68	8.60	9.85
6.	174	48	15.20	13.25	12.30	13.05	336	69	5.39	10.30	12.95
7.	54	54	18.70	12.85	-	16.65	222	39	1.62	-	12.60
Mean	79	72	14.45	11.65	12.74	13.76	208	66	3.65	10.14	12.44

M.F. = Muscle flow in ml/min, S.F. = skin flow in ml/min, M.Vein = muscle vein, M.S.V. = medial saphenous vein, D.S.V. = dorsal saphenous vein.

medial saphenous veins respectively. However, much if not all, of this decline is probably attributable to the 10% decrease in the skin blood flow.

Local Effects of Reactive Hyperemia on the Vascular Beds of Skeletal Muscle and Skin

Reactive hyperemia experiments were performed on eleven animals to study the vascular responses to high blood flows approximating those observed in exercise. Figure 3 shows a typical tracing of the arterial pressure (P_A), small muscle vein pressure (P_{MV}) and the large muscle vein pressure (P_{LV}) in response to partial constriction and release of constriction of the femoral artery. In this experiment muscle blood flow diminished to one-half of the control value with constriction, as the femoral artery pressure decreased from 80 mm Hg to 25 mm Hg, and the large muscle vein pressure remained virtually unchanged. The calculated muscle vein resistance (R_m) remained unchanged with constriction in this experiment. On release of constriction, the muscle blood flow increased to 3.5 times the control value, while the muscle vein pressure gradient ($P_{SMV} - P_{LMV}$) increased proportionately less, resulting in a decrease of 0.013 mm Hg/ml/min in the muscle vein resistance from the control value.

Tables 6 and 7 show the mean values of pressures, blood flows and calculated resistances for skeletal muscle and skin respectively. The mean arterial pressure (P_A) decreased (Table 6) to approximately one-half of the control value during partial constriction. The large muscle vein pressure (P_{LMV}) showed minimal change, 1 mm Hg on the average, through the course of the experiments. Muscle blood flow decreased by a factor of 3.5 on the average, with constriction. Since the arterial

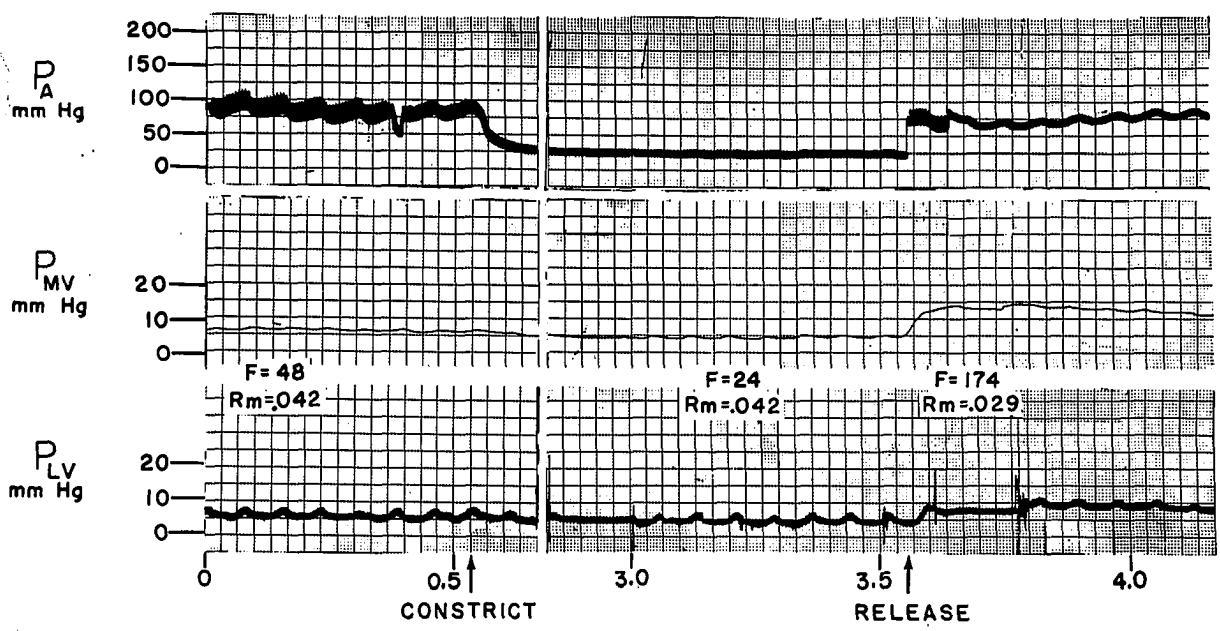

Fig. 3 -Typical pressure responses of the muscle vasculature, with measured blood flows and calculated resistances with reactive hyperemia. P_A = femoral artery pressure, P_{MV} = small muscle vein pressure, P_{LV} = large muscle vein pressure, F = muscle blood flow, R_M = muscle vein resistance.

TABLE 6

LOCAL EFFECTS OF PARTIAL CONSTRICTION AND RELEASE OF CONSTRICTION OF THE FEMORAL ARTERY ON THE MUSCLE VASCULATURE (n = 11)

	P_A mmHg	P_{LMV} mmHg	ΔP_{TM} mmHg	M.F. ml/min /100g S1.T.	R_{TM} mmHg /ml/min /100gS1.T.	ΔP_{ASMV} mmHg	R_{ASMV} mmHg /ml/min /100gS1.T.	P_{SMV} mmHg	ΔP_{MV} mmHg	R_{MV} mmHg /ml/min /100gS1.T.	T.F. ml/min /100g L.T.
CONTROL	103	7	96	8.2	15.91	91	14.95	12	5	0.72	10.8
PARTIAL CONSTRICT.	54	6	48	2.3	27.50	46	26.40	8	2	1.27*	3.8
RELEASE CONSTRICT.	86	8	78	17.4	6.30**	69	5.46**	17	9	0.72	18.5
POST-CONTROL	98	6	92	6.4	17.15	87	16.41	11	5	0.82	9.2

* $P < .05$ ** $P < .01$

P_A = femoral artery pressure, P_{LMV} = large muscle vein pressure, ΔP_{TM} = total muscle pressure gradient, M.F. = muscle blood flow in ml/min/100 grams of skinless tissue, R_{TM} = total muscle resistance, ΔP_{ASMV} = pressure gradient, artery to small muscle vein segment, R_{ASMV} = resistance, artery to small muscle vein segment, P_{SMV} = pressure small muscle vein, ΔP_{MV} = pressure gradient, muscle vein segment, R_{MV} = resistance, muscle vein segment, T.F. = total limb flow in ml/min/100 grams of limb tissue.

TABLE 7

LOCAL EFFECTS OF PARTIAL CONSTRICTION AND RELEASE OF CONSTRICTION OF THE FEMORAL ARTERY ON THE SKIN VASCULATURE (n=10)

	P_A mmHg	P_{LSV} mmHg	ΔP_{TS} mmHg	S.F. ml/min /100g S.T.	R_{TS} mmHg /ml/min /100gS.T.	ΔP_{ASSV} mmHg	R_{ASSV} mmHg /ml/min /100gS.T.	P_{SSV} mmHg	ΔP_{SV} mmHg	R_{SV} mmHg /ml/min /100gS.T.
CONTROL	103	11	92	26.1	4.23	81	3.78	22	11	0.36
PARTIAL CONSTRICT.	54	8	46	14.3	6.02	40	5.52	14	6	0.52*
RELEASE CONSTRICT.	85	11	74	21.2	4.08	68	3.80	17	6	0.30
POST-CONTROL	97	12	85	25.7	3.72	79	3.47	18	7	0.27

* $P < .05$ ** $P < .01$

P_A = femoral artery pressure, P_{LSV} = large skin vein pressure, ΔP_{TS} = total skin pressure gradient, S.F. = skin blood flow in ml/min/100 grams skin tissue, R_{TS} = total skin resistance, ΔP_{ASSV} Pressure gradient, artery to small skin vein segment, R_{ASSV} = resistance, artery to small skin vein segment, P_{SSV} = small skin vein pressure, ΔP_{SV} = pressure gradient, skin vein segment, R_{SV} = resistance, skin vein segment.

pressure decreased proportionately less than the muscle blood flow, the mean total muscle resistance (R_{TM}) and the mean artery to small muscle vein segment resistance (R_{ASMV}), increased by 11.59 and 11.45 mm Hg/ml/min/100 grams of skinless tissue respectively. However, these increases were not statistically significant ($P > .05$). On release of constriction the mean muscle blood flow was more than twice the control value and the calculated resistances R_{TM} and R_{ASMV} were significantly reduced below the control values ($P < .01$).

The muscle vein segment resistance (R_{MV}), which was significantly increased ($P < .05$), on constriction (Table 6) returned only to the control level on release of constriction. In these experiments the increase of blood flow on release of constriction was commensurate with the elevation in the muscle vein pressure that was observed. These results are consistent with those reported by Sharpey-Schafer (50). They appear to indicate that the venous vasculature is acting as something other than passive tubes in the face of the elevated blood flow in reactive hyperemia.

The mean large skin vein pressure (P_{LSV}), showed a decrease of 3 mm Hg with constriction (Table 7), then returned to the control level. The skin blood flow dropped to 54% of the control value in constriction, when simultaneously, muscle blood flow dropped to 28% of control (Table 6). However, on release of constriction the skin flow returned only to 80% of the mean control level (Table 7), while the average muscle blood flow (Table 7), exceeded the mean control value by more than 100%. The skin did not exhibit reactive hyperemia, suggesting that the muscle bed is the preferred route for flow following limb tissue ischemia.

Neither the mean total skin resistance (R_{TS}) or the artery to small skin vein segment resistance (R_{ASSV}) was significantly altered ($P > .05$), through the experiments. On the other hand, the skin vein resistance (R_{SV}) increased significantly during partial constriction ($P < .05$) a response also observed in the muscle vein segment (Table 6). Since the pressure gradients were diminished in both instances, the resistances calculated probably reflect a passive constriction in both beds.

Hematocrits in Exercise and Reactive Hyperemia

Vascular resistance is a function of the geometry of the vessels accomodating blood flow and the viscosity of the fluid. It was suggested that an increase in viscosity of the venous blood in exercise could account for the elevated muscle vein resistances observed. To investigate this possibility blood samples were drawn and hematocrits measured, as previously described. Table 8 shows the measured venous hematocrit values and the mean values for the various experimental states in eight experiments. For comparison, this procedure was followed in reactive hyperemia experiments as well as exercise.

In five of eight experiments there was a slight increase in the hematocrit with exercise that persisted postexercise. These changes were not significant ($P > .05$). During partial constriction of the femoral artery the venous hematocrits decreased from the control values in six of eight experiments. This change was barely significant at the .05 level. The mean venous hematocrit remained lower than the control on release of constriction and post-control though these changes were not significantly different from the control ($P > .05$). At the same

TABLE 8

HEMATOCRITS IN EXERCISE AND REACTIVE HYPEREMIA

(n = 8)

	EXERCISE EXPERIMENTS								
EXPERIMENT NO.	1	2	3	4	5	6	7	8	Mean %
CONTROL	30	42	43	42	44	40	39	28	38.5
EXERCISE	31	41	41	43	45	38	41	30	38.7
POSTEXERCISE	32	42	41	43	47	38	42	31	39.5
POST-CONTROL	31	43	42	42	47	38	38	29	38.7
	REACTIVE HYPEREMIA EXPERIMENTS								
CONTROL	33	43	42	40	45	37	41	32	39.0
PARTIAL CONSTRICT.	32	39	42	41	44	35	40	30	37.9*
RELEASE CONSTRICT.	32	40	41	39	44	39	40	29	37.9
POST-CONTROL	30	41	41	42	44	38	40	28	37.9

* $P < .05$

time the venous hematocrit decreased significantly ($P < .05$), during partial constriction, the muscle vein resistance (R_{MV}), increased significantly ($P < .05$) (Table 6). The decreased viscosity obviously was not a prominent factor affecting the muscle vein resistance.

Neuromuscular Block During Stimulation of the Femoral and Sciatic Nerves

While there is evidence to indicate that the stimulation parameters used were not of sufficient magnitude to stimulate sympathetic fibers coursing the femoral and sciatic nerve trunks, further proof was sought employing a technique of blocking skeletal muscle contractions. In accordance with the procedure described, using Succinylcholine Chloride (Anectine) as the blocking agent, seven experiments were performed. Tables 9 and 10 show the mean vascular responses for the muscle and the skin beds respectively.

In muscle (Table 9), stimulation of the limb prompted responses in muscle blood flow, in total muscle resistance, and artery to small muscle vein resistances that were similar to those of the first two series of experiments (Tables 1 and 2). The decreases in mean total muscle resistance and artery to small muscle vein segment resistance were significant at the .01 level. In this series the mean muscle vein resistance was not significantly different from the control value ($P > .05$), although in all seven experiments the calculated resistance value was greater than the control value. When skeletal muscle contractions were abolished with Succinylcholine Chloride, and while stimulation of the limb continued, all parameters measured tended to return toward control value. This was especially true for the pressure and the resistance measured in the muscle vein segment, as these values returned to the

TABLE 9

LOCAL EFFECTS OF STIMULATION AND NEUROMUSCULAR BLOCK ON THE MUSCLE VASCULATURE (n = 7)

	P_A mmHg	P_{LMV} mmHg	ΔP_{TM} mmHg	M.F. ml/min /100g S1.T.	R_{TM} mmHg /ml/min /100gS1.T.	ΔP_{ASMV} mmHg	R_{ASMV} mmHg /ml/min /100gS1.T.	P_{SMV} mmHg	ΔP_{MV} mmHg	R_{MV} mmHg /ml/min /100gS1.T.	T.F. ml/min /100g L.T.
CONTROL	93	6	87	8.9	12.02	82	11.30	11	5	0.57	11.0
EXERCISE	87	7	80	20.2	4.56**	59	3.60**	28	21	1.31	21.0
1 to 2 MIN. AFTER BLOCK	94	6	88	10.0	10.39	83	9.20	11	5	0.57	12.9

* $P < .05$ ** $P < .01$

P_A = femoral artery pressure, P_{LMV} = large muscle vein pressure, ΔP_{TM} = total muscle pressure gradient, M.F. = muscle blood flow in ml/min/100 grams of skinless tissue, R_{TM} = total muscle resistance, ΔP_{ASMV} = pressure gradient, artery to small muscle vein segment, R_{ASMV} = resistance, artery to small muscle vein segment, P_{SMV} = pressure, small muscle vein, ΔP_{MV} = pressure gradient, muscle vein segment, R_{MV} = resistance, muscle vein segment, T.F. = total limb flow in ml/min/100 grams of limb tissue.

TABLE 10

LOCAL EFFECTS OF STIMULATION AND NEUROMUSCULAR BLOCK ON THE SKIN VASCULATURE (n=6)

	P_A mmHg	P_{LSV} mmHg	ΔP_{TS} mmHg	S.F. ml/min /100g S.T.	R_{TS} mmHg /ml/min /100g S.T.	ΔP_{ASSV} mmHg	R_{ASSV} mmHg /ml/min /100gS.T.	P_{SSV} mmHg	ΔP_{SV} mmHg	R_{SV} mmHg /ml/min /100gS.T.
CONTROL	92	9	83	27.0	4.70	73	4.28	19	10	0.44
EXERCISE	88	10	78	30.2	3.95	69	3.52	19	9	0.35
1 to 2 MIN AFTER BLOCK	90	9	84	30.4	4.53	71	4.27	19	10	0.40

* $P < .05$ ** $P < .01$

P_A = femoral artery pressure, P_{LSV} = large skin vein pressure, ΔP_{TS} = total skin pressure gradient, S.F. = skin blood flow in ml/min/100 grams of skin tissue, R_{TS} = total skin resistance, ΔP_{ASSV} = pressure gradient, artery to small skin vein segment, R_{ASSV} = resistance, artery to small skin vein segment, P_{SSV} = small skin vein pressure, ΔP_{SV} = pressure gradient, skin vein segment, R_{SV} = resistance, skin vein segment.

identical control values. There would appear to be no evidence of additional sympathetic innervation due to stimulation of the limb. This is also borne out by the skin vascular responses (Table 10), measured simultaneously with those of muscle in six experiments. With stimulation the blood flow to the skin increased from 27.0 to 30.2 ml/min/100 grams of skin tissue as the three resistances calculated R_{TS}, R_{ASSV}, R_{SV} decreased. These changes were not significant ($P > .05$). The response pattern to stimulation was very similar to that shown previously (Table 3 and 4) for the skin vasculature. Following the injection of Succinylcholine Chloride the blood flow through the skin remained 3.4 ml/min/100 grams of skin tissue above the mean control value and resistances returned toward mean control values.

Local Effects of Mechanical Hyperemia and the Active Hyperemia of Exercise at Constant Perfusion, on the Vasculature of Skeletal Muscle.

To gain further insight into the response of the muscle vasculature of the limb to increased blood flow, a pump perfusion maneuver was employed as previously described. A typical response of muscle to this procedure is illustrated in Figure 4. As the muscle blood flow (F) was increased from 42 ml/min in stepwise fashion to 174 ml/min the arterial pressure (P_A) showed a slight tendency to fall at the highest flow. The perfusion pressure (P_P) increased 10 to 20 mm Hg with each increase in blood flow. The small muscle vein pressure (P_{MV}) showed similar increases with flow rate and the large muscle vein pressure varied no more than a mm Hg through the entire range of flows. The muscle vein resistance (R_m) shows a consistent decrease through the range of flows indicating that the muscle blood flow increased

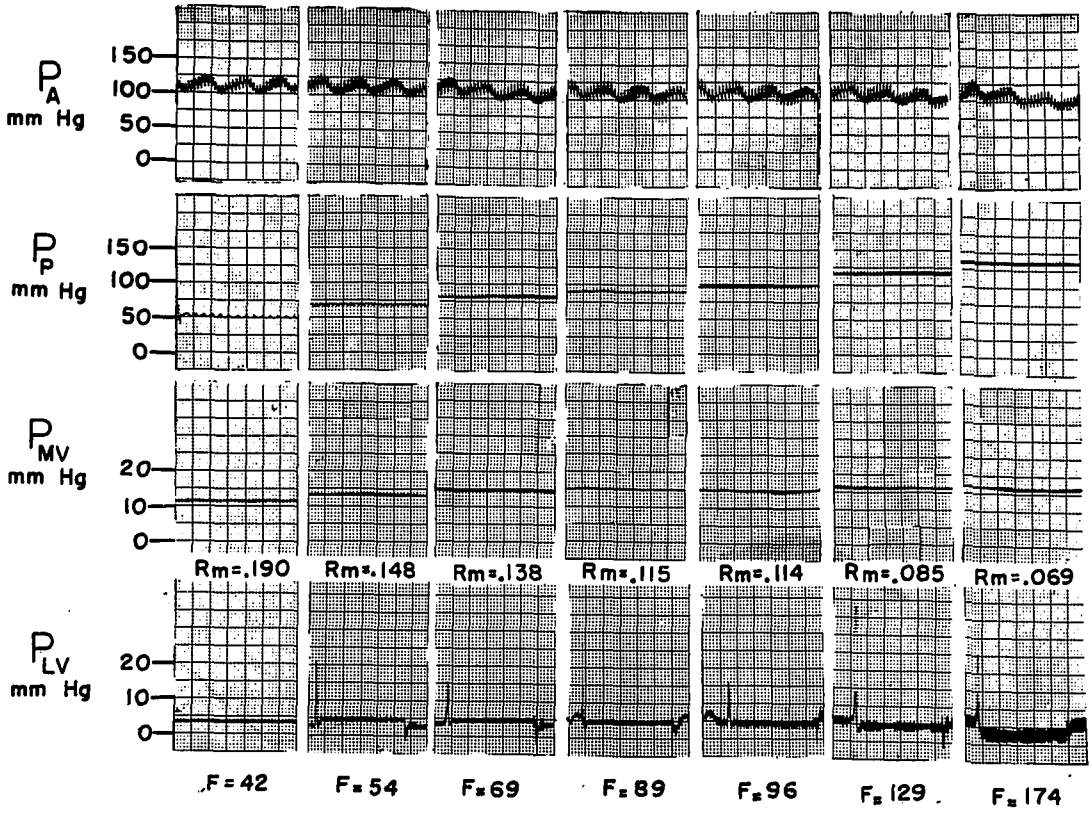

Fig. 4 -Typical pressure responses of the muscle vasculature, with measured blood flows and calculated resistances with mechanical hyperemia. P_A = femoral artery pressure, P_P = perfusion pressure, P_{MV} = small muscle vein pressure, P_{LV} = large muscle vein pressure, F = muscle blood flow, R_m = muscle vein resistance.

proportionately more than the muscle vein pressure gradient as flows were adjusted upward. This response resulted in the characteristic pressure-flow curve for the limb vasculature seen in Figure 5 (unbroken black line).

The average results for nine experiments, at five different blood flow levels, are shown in Table 11. As the mean blood flow was elevated from 3.6 to 13.9 ml/min/100 g. skinless tissue, the total muscle resistance (R_{TM}), the artery to small muscle vein resistance (R_{ASMV}) and the muscle vein resistance (R_{MV}) decreased in step-like fashion. These decreases in R_{TM} and R_{ASMV} from the lowest to the highest flow used were significant ($P < .01$). The mean difference in muscle vein resistance (R_{MV}) from the lowest to the highest flow was significant at the .05 level. A graphic plot of mean blood flow and the mean muscle vein resistance data conforms to the curve of Figure 5 (unbroken line). It will also be observed (Table 11), that the skin blood flow progressively increased with the elevation of flow rate. It is interesting to note (Table 11), that the muscle bed appeared to receive a higher proportion of the increase in flow at the higher flow rates. The muscle flow changed by mean increments of 2.3, 2.5, 2.8, and 2.7 ml/min/100 grams of skinless tissue and the skin in increments of 11.7, 10.9, 7.3 and 8.7 ml/min/100 grams of skin tissue.

In the same nine experiments the animals were subjected to nerve stimulation of the limb following control measurements at a blood flow level approximating a normal control value. A typical record of responses using this procedure is illustrated in Figure 6. The arterial pressure measured in the carotid artery remained nearly

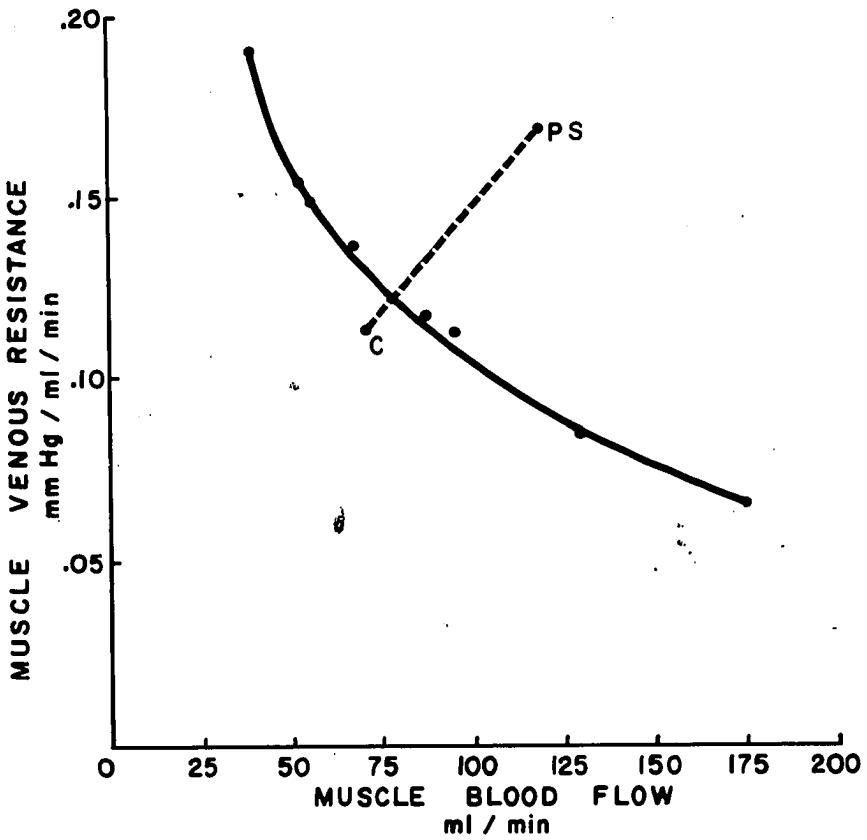

Fig. 5 -Relationship of muscle vein resistance to muscle blood flow with exercise. Data from constant perfusion-exercise experiment superimposed. C = Control, PS = Postexercise.

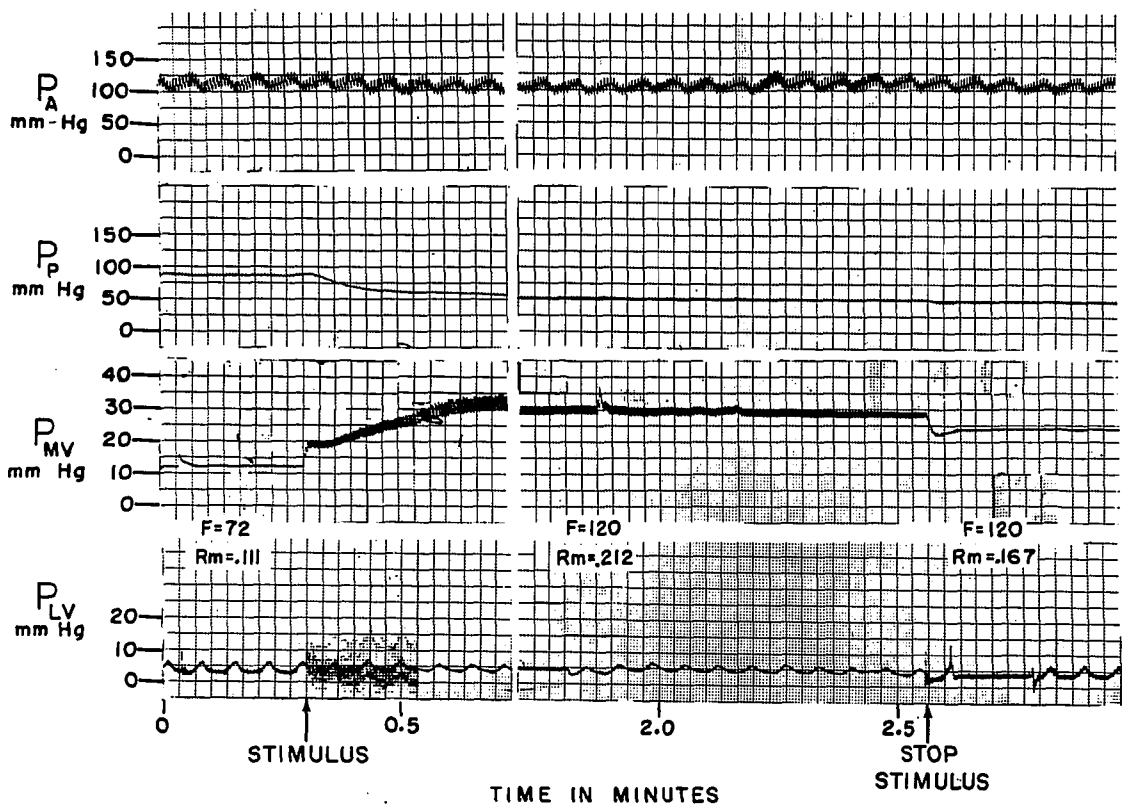

Fig. 6 -Typical pressure responses of the muscle vasculature, with measured blood flows and calculated resistances with exercise at constant perfusion. P_A = femoral artery pressure, P_{MV} = small muscle vein pressure, P_{LV} = large muscle vein pressure, F = muscle blood flow, R_m = muscle vein resistance.

TABLE 11

LOCAL EFFECTS OF MECHANICAL HYPEREMIA ON THE VASCULATURE OF SKELETAL MUSCLE

F.S.	P_A mmHg	P_P mmHg	P_{LMV} mmHg	ΔP_{TM} mmHg	M.F. ml/min /100g S1.T.	T_{TM} mmHg /ml/min /100gS1.T.	ΔP_{ASMV} mmHg	R_{ASMV} mmHg /ml/min /100gS1.T.	P_{SMV} mmHg	ΔP_{MV} mmHg	R_{MV} mmHg /ml/min /100gS1.T.	T.F. ml/min /100g L.T.	S.F. ml/min /100g S.T.
4 (n=9)	108	68	5	63	3.6	19.17	60	19.37	9	4	0.87	6.0	18.0
6 (n=8)	105	94	5	90	5.9	16.05	84	16.04	9	4	0.69	8.6	29.7
8 (n=9)	104	117	5	111	8.4	14.99	107	14.40	10	4	0.60	11.9	40.6
10 (n=9)	96	129	5	123	11.2	13.30	118	12.80	10	5	0.50	15.5	47.9
12 (n=7)	91	144	6	138	13.9	11.92**	133	11.53**	11	5	0.43*	19.0	56.5

* $P < .05$ ** $P < .01$

F.S. = flow setting, P_A = carotid artery pressure, P_P = perfusion pressure, P_{LMV} = large muscle vein pressure, ΔP_{TM} = total muscle pressure gradient, M.F. = muscle blood flow in ml/min/100 grams of skinless tissue, R_{TM} total muscle resistance, ΔP_{ASMV} = pressure gradient, artery to small muscle vein segment, R_{ASMV} = resistance, artery to small muscle vein segment, P_{SMV} = pressure, small muscle vein, ΔP_{MV} = pressure gradient, muscle vein segment, R_{MV} = resistance, muscle vein segment, T.F. = total blood flow in ml/min/100 grams of limb tissue, S.F. = skin blood flow in ml/min/100 grams of skin tissue.

constant at 115 mm Hg. On stimulation the perfusion pressure (P_P) decreased from approximately 87 to 50 mm Hg and remained steady through the postexercise period. The response of the small vein pressure (P_{MV}) to exercise was similar to that shown previously (Figure 2), in which a rapid increase in pressure was followed by a slower rise to a "steady state" value. On cessation of stimulation the pressure decreased immediately by 5 mm Hg but then remained well above the control value for sometime postexercise. A similar postexercise response was observed in four of nine experiments at constant flow. The large vein pressure (P_{LV}) showed little tendency to change through the course of the experiment. Blood flow (F) through muscle increased in exercise from 76 to 120 ml/min despite constant perfusion of the limb. This indicated a diversion of blood flow from the skin vasculature in exercise. Postexercise blood flow was sustained at the exercise level. As previously shown (Tables 1 and 2), the muscle vein resistance in this experiment (Figure 6), was above the control level in exercise and remained so postexercise.

Table 12 shows the mean values for nine experiments with constant limb perfusion. It will be observed that the mean control value of muscle blood flow for these experiments was 8.2 ml/min/100 grams of skinless tissue, which closely approximates the flow at setting No. 8 in Table 11, and the control blood flows in the spontaneous flow experiments (Tables 1 and 2). The vascular responses to exercise are nearly identical to those observed in the first two series of experiments (Tables 1 and 2). With constant perfusion the muscle blood flow could not rise to the levels observed in natural flow experiments; however, a diversion of flow from skin to muscle did occur, which decreased skin

TABLE 12

LOCAL EFFECTS OF EXERCISE AT CONSTANT PERFUSION ON THE VASCULATURE OF SKELETAL MUSCLE (n=9)

	P_A mmHg	P_P mmHg	P_{LMV} mmHg	ΔP_{TM} mmHg	M.F. ml/min /100g S1.T.	R_T mmHg /ml/min /100gS1.T.	ΔP_{ASMV} mmHg	R_{ASMV} mmHg /ml/min /100gS1.T.	P_{SMV} mmHg	ΔP_{MV} mmHg	R_{MV} mmHg /ml/min /100gS1/T.	T.F. ml/min /100g L.T.	S.F. ml/min /100g S.T.
CON.	94	112	5	107	8.2	15.40	104	15.10	8	4	0.51	11.6	36.2
EX.	94	46	6	40	12.2	4.16**	28	2.74**	18	11	1.37**	11.6	12.0**
P.E.	95	45	5	40	11.4	4.04**	30	3.12**	14	9	0.95**	11.0	9.5**

* $P < .05$ ** $P < .01$

Con. = control, Ex. = exercise, P.E. = postexercise, P_A = carotid artery pressure, P_P = perfusion pressure, P_{LMV} = large muscle vein pressure, ΔP_{TM} = total muscle pressure gradient, M.F. = muscle blood flow in ml/min/100 grams of skinless tissue, R_{TM} = total muscle resistance, ΔP_{ASMV} = artery to small muscle vein pressure gradient, R_{ASMV} = resistance, artery to small muscle vein segment, P_{SMV} = small muscle vein pressure, ΔP_{MV} = pressure gradient, muscle vein segment, R_{MV} = resistance = muscle vein segment, T.F. = total blood flow in ml/min/100 grams of limb tissue, S.F. = skin blood flow in ml/min/100 grams of skin tissue.

flow three-fold and raised muscle blood flow approximately 50% in exercise. There was a slight reduction in muscle flow postexercise but it remained 3.2 ml/min/100 grams of skinless tissue above the control value. Skin flow also diminished further postexercise, from the exercise level of 12.0 to 9.5 ml/min/100 grams of skin tissue. The changes in skin flow were significant ($P < .01$). The decrease in total blood flow through the limb postexercise cannot be explained. It may indicate increased loss of fluid from the vascular compartment triggered by increased capillary hydrostatic pressure.

Table 12 also shows that the muscle vein resistance was significantly increased in exercise and postexercise ($P < .01$). With nearly identical mean blood flows as those observed in control and postexercise states (Table 12), the mechanical hyperemia experiments (Table 11), resulted in a decrease in mean muscle vein resistance, from 0.060 to 0.050 mm Hg/ml/min/100 grams of skinless tissue, rather than an increase. This was observed in eight of nine mechanical hyperemia experiments. The broken line of Figure 6 indicates the direction of the mean small muscle vein resistance change with increased blood flow from control (C) to post-stimulation (PS) states. The postexercise resistance (PS) is observed to fall far off the line plotted for resistance as a function of flow rate in the hindlimb. This is further evidence that the muscle vein resistances measured in exercise, and immediately postexercise, results from some degree of increased activity of smooth muscle in the venous bed.

CHAPTER IV

DISCUSSION

Local Effects of Exercise, Reactive and Mechanical Hyperemia on the Vasculature of Skeletal Muscle

This study shows that the pressure in small muscle veins is elevated out of proportion to the increase in muscle venous outflow following local exercise, and in proportion to the increase in muscle venous outflow immediately following release of arterial occlusion. Since venous hematocrit changes could not explain these findings, and small muscle venous pressure rises proportionately less than muscle venous outflow during mechanical hyperemia, an active response of the smooth muscle in the veins is suggested. Without question, a part of the increased muscle vein resistance during exercise is due to the influence of the contracting skeletal muscles. This would cause a passive narrowing of the lumen of adjacent blood vessels and increase the resistance to flow. However, since the postexercise venous resistance remained elevated, there being no observable skeletal muscle contractions in this period, increased vasoactivity appears to be involved.

Several possibilities for explaining these effects as something other than a local change in smooth muscle activity were investigated. There was no evidence that the stimulation parameters used were sufficient

to fire sympathetic fibers which would contribute to increased vasomotor activity. Corroboration of this point is given by the failure of widely different stimulation parameters to elicit significant variations in venous responses in exercise. Furthermore, the skin data indicate no change, to a decrease in venomotor tone in response to stimulation, rather than the increase one would expect with increased sympathetic activity. In addition, when Succinylcholine Chloride was used to block skeletal muscle contractions during electrical stimulation of the limb, the parameters measured returned toward control values, giving no evidence of increased constrictor tone. The value of this evidence has recently been opened to question by the work of Burn and Seltzer (10). They demonstrated that selected neuromuscular blocking agents also blocked sympathetic post-ganglionic nerve endings. While they did not study Succinylcholine Chloride, they found that Decamethonium, which has an identical action on neuromuscular receptors, did block sympathetic activity in bath concentrations of 25 mg/liter. However, the block was only 50% complete in the phrenic nerve-diaphragm preparation of the rat after four hours in the bath. In the present experiments the concentration of injected Succinylcholine Chloride was 100 mg/liter. However, the bolus injection required to make the limb skeletal muscle quiescent during stimulation never exceeded 10 milliliters and this was diluted in blood perfusing muscle at the rate of 20.2 ml/min/100 grams of skinless tissue. In addition, the critical pressure and blood flow measurements were made within two minutes of the injection. Furthermore, when the still quiescent limb was stimulated at high intensity and duration (10 to 40 volts and 10 to 20 ms.), we were able to demonstrate a vasoconstrictor effect in muscle veins in four of seven experiments, and in

skin veins in six of seven experiments. This would indicate that (1) there was probably no sympathetic stimulation with the stimulation parameters used and, (2) if Succinylcholine Chloride has a sympathetic blocking action it is not effective at high stimulation intensity.

The elevated muscle vein resistance could conceivably result from a shunting of muscle vein blood to skin veins at a site downstream from the location of the small muscle vein catheter. Such an occurrence would lead to an underestimation of muscle blood flow and the overestimation of muscle vein resistance. If such a shunt were operative, it should be indicated by a decrease in oxygen content of the skin vein blood, assuming the increased oxygen consumption of exercise is confined to muscle. The oxygen contents of the dorsal and medial saphenous veins did diminish in exercise by 10 and 20% respectively (Table 5). However, the skin blood flow also decreased by 10% in the seven experiments reported. There was no indication that a sizeable portion of muscle vein blood is shunted to the skin in exercise.

It was also postulated that the high small muscle vein pressures recorded were flow related, i.e., not true lateral pressures. Besides the fact that the muscle vein catheter sites were observed to have good collateral circulation, subsequent experimental observations make this postulate untenable. In reactive hyperemia experiments blood flows were measured which approximated those seen in exercise. However, the muscle vein pressures measured were considerably lower per unit of flow than in the exercise experiments. Where muscle vein resistances assumed control values in reactive hyperemia, they exceeded control values in exercise by a factor of 1.5 to 2. When the hindlimb was mechanically perfused

at increasing blood flows, the flows increased out of proportion to the increases in muscle vein pressures, resulting in progressive decreases in muscle vein resistances.

While the muscle vein segment data are in accord with the exercise and reactive hyperemia responses reported by Sharpey-Schafer (50), they are not in agreement with those of Kjellmer (40), and Thulesius and Johnson (54). These investigators reported a dilitation of postcapillary vessels in exercise. Their data are based on isovolumetric and isogravimetric determinations of capillary hydrostatic pressure. Both techniques necessitate the alteration of normal vascular dynamics for this determination. Kjellmer (40), e.g., had to raise large muscle vein pressure to calculate the capillary filtration coefficient and then the capillary pressure. Furthermore, to make these calculations, it was assumed that 80% of the change in large vein pressure is transmitted to the capillary. Landis and Pappenheimer (43), appear to question such an assumption, stating that the variability of normal capillary pressure is such, that one cannot make a meaningful comparison of the increment in capillary pressure that corresponds to any given increment in venous pressure. Kjellmer admits to the possibility of an error of up to 20% in his calculation of capillary hydrostatic pressure. The necessary alteration of the large vein pressure to calculate capillary hydrostatic pressure could be responsible for another potential source of error. Yamada and Burton (59), first demonstrated the existence of a venivasomotor reflex, in which filling of finger veins resulted in a reflex precapillary constriction. More recently, Patterson and Shepherd (47), found that stretching vessels of normal, sympathectomized and

chronically denervated forearms by venous constriction was followed by constriction of the resistance vessels. If such a response occurred with venous constriction in Kjellmer's preparation, the capillary pressure would tend to be underestimated, as would the postcapillary resistance. It is possible that such a mechanism would be even more active in exercise than the resting state, since the precapillary vessels would be more widely dilated in this state and more susceptible to such a venivasomotor reflex. The work of Thulesius and Johnson (54), has not been reported in detailed form though the isogravimetric technique used has been described (32). It is difficult to conceive that an accurate interpretation of dynamic vascular events in exercise could be derived from a procedure necessitating a stoppage of blood flow during the maneuver.

Since the capillary pressure must exceed muscle vein pressure, the present data indicate that a two to three-fold increase in capillary hydrostatic pressure occurs in exercise. While this would help explain the efflux of fluid from the vascular compartment in exercise, one is faced with the problem of describing the mechanism for the increased vasoactivity of the muscle veins. One can only offer conjecture on this subject at the present time. Grant (25), showed that while sympathectomy of a limb reduced constrictor tone and increased blood flow, it did not affect the ability to increase the limb blood flow in response to muscular contractions. Such work led to the generally accepted view that the hyperemia of exercise is a localized phenomenon not induced by vasomotor nerves. While this intrinsic vasomotor activity is usually associated with the precapillary vessels, there is evidence that under certain conditions, postcapillary vessels exhibit intrinsic activity

which may be opposite in direction from that exhibited by precapillary vessels.

Hanson and Johnson (32), demonstrated a local arteriovenous reflex in the intestine. They showed that a progressive decrease in the arterial pressure resulted in an increase in venous resistance. They postulated an axon reflex mechanism with an adrenergic mediator, with receptors located on the arterial side and effectors on the venous side. However, in subsequent work (33), these investigators were not able to demonstrate this mechanism in the dog hindlimb.

The predominance of opinion attributing the arteriolar dilitation of exercise to a tissue metabolite (37), (40), leads one to suspect the same type of mechanism as the causative factor in muscle vein constriction. Indeed, there is evidence to suggest that the same substance may be responsible for both effects. Haddy (30), has demonstrated that even small infusions of histamine administered intra-arterially, will raise small vein pressure due to its dilator effect on the precapillary vessels. With larger infusions histamine raised small vein pressure by direct action on the vasculature and through stimulation of an adrenal discharge. Anrep et al. (2), had earlier suggested that histamine was the precapillary dilator substance in exercise, since muscle effluent blood was found to contain significantly higher levels of histamine than was found in the resting state. This view was subsequently questioned when it was shown that the dilator response was not diminished following the administration of anti-histamine (37). In four experiments, not reported here, infusions of Phentolamine 50 μg/min., failed to indicate an increase in adrenergic activity in the muscle veins

in exercise. While histamine or any other agent cannot be implicated here, Haddy's data demonstrates the dual effects which may be induced either directly or indirectly, by an endogenous substance, and lends credibility to the view that a precapillary dilator metabolite may be responsible for the increased venoactivity observed in exercise.

In reactive hyperemia experiments the release of partial occlusion was followed by a muscle vein pressure rise commensurate with the increase in the muscle blood flow. This response is apparently indicative of an increase in the vasoactivity of muscle veins, since the characteristic response to increasing blood flows in the mechanical hyperemia experiments was a pressure rise not commensurate to the increase in flow.

This study also shows that exercise of the hindlimb is followed by a three to four-fold decrease in the total muscle resistance, measured from the femoral artery to the large muscle vein. Despite the small fall in the pressure gradient, the muscle blood flow increased by a factor of 2.2. This observation, i.e., a fall in total vascular resistance has been observed by a number of investigators (16), (24), (36), but the mechanism for it has defied description.

As the present and other studies show (25), (40), the dilitation does not depend on the integrity of central nervous pathways. Gaskell (23), was the first to postulate that muscle blood vessels were opened by vasodilator metabolites liberated from skeletal muscle fibers. Since that time various substances have been implicated as active in the process but established proof for any one is lacking. An increased lactate level in exercise was suggested as the triggering mechanism but this appeared questionable when Rigler (48), reported that

exercise hyperemia was unaffected when the formation of lactate was prevented by iodoacetic acid. Golwitzer-Meier (24), has presented evidence that the hydrogen ion concentration is not involved. The tissue hypoxia theory has been advanced as a likely mechanism but it too has its detractors for reasons summarized by Shepherd (51). Hilton (37), found the response was unaffected by anti-histamines and also suggested that ATP and bradykinin were not involved. Fleisch and Sibul (20), studied the vasodilator properties of some seventy intermediary products of metabolism and found extremely weak activity in a few. Under the same experimental conditions acetylcholine was much more potent.

Kjellmer (40), has focused on the possibility that the potassium ion is responsible for the arteriolar dilitation in exercise and provides evidence in support of this assertion. He found that the action of potassium caused identical responses to those he observed in exercise i.e., precapillary dilitation and virtually no change in the activity of the postcapillary vessels. In the present study, the postcapillary activity increased in response to exercise. Assuming that this represents the true conditions of the veins in exercise it is unlikely that it is potassium induced. Emanuel et al. (19), found that potassium salts in infusions of less than 8 mEq/l. dilated precapillary vessels while the postcapillary vessels remained unchanged. Higher infusions produced an arterial constrictor effect but increased dilitation in small vessels. Kjellmer (41), also observed arterial constriction with high infusions of potassium. Rudko and Haddy (49), recently demonstrated that potassium levels do not rise in venous blood following release of a four minute occlusion in the dog hindlimb. To the extent that some

common arteriolar dilator mechanism might be suspected in exercise and reactive hyperemia this evidence detracts from the liklihood of a potassium mechanism. However, such evidence hardly precludes a potassium mechanism from consideration in exercise hyperemia.

Local Effects of Active, Reactive and Mechanical Hyperemia on the Vasculature of the Skin

The data relating to the skin vascular bed showed a significant decrease only in the muscle vein resistance in the second series of fifteen exercise experiments. The total, and the artery to small muscle vein segment resistance diminished with exercise but the changes were not significant. Skin blood flow declined with exercise in one series and increased in the other by a nearly identical magnitude. This change was small and the results would agree with those of Coles and Cooper (12), who found that the exercise hyperemia was confined to the muscle tissue. Work by Wallace (56), also indicated that flow through the skin did not increase in local exercise of the hand. The apparent skin dilitation observed probably reflects alterations in skin dynamics sufficient to preserve its normal blood flow in the face of a pronounced dilitation in the muscle bed. This was possible with a 15 to 16% decrease in total skin resistance as the total muscle resistance declined by approximately 65%. There was no indication of the vasoconstriction of skin vessels observed by Christensen *et al.* (11), and Barger *et al.* (3), in exercising humans, and by Page *et al.* (45), in forearm vein segments during exercise. In their investigations the vasculature retained its central nervous innervation. Furthermore, with the exception of the last study mentioned, the exercise involved considerable of the body musculature which

would necessitate some redistribution of the total blood supply. Centrally supplied autonomic fibers apparently fulfill this function according to Folkow and Mellander (21). In the present work the limb was denervated and the exercise involved only a limb segment. Even though denervated the limb vasculature showed ability to redistribute its blood supply in the constant perfusion-exercise experiments. When the blood flow to muscle became grossly insufficient in exercise, a large diversion of flow from skin to muscle occurred. In one experiment the skin flow was completely curtailed postexercise. The blood flow through the muscle bed increased 50% on the average, in these experiments while the skin flow decreased to 33%. This diversion of flow from skin is apparently due to dilitation in the skeletal muscle bed without dilitation in the skin. Indeed, the skin vessels apparently passively constrict, for the perfusion pressure diminished, but proportionately less than the decrease in skin flow.

Assuming that the decrease in skin vein resistance represents a true alteration in vascular activity, its significance remains questionable since the decline in total, and artery to small skin vein resistance also occurred. There is probably little overall effect on the critical capillary hydrostatic pressure.

Numerous investigators (7), (12), (58), have demonstrated reactive hyperemia in the skin vascular bed. When the parallel beds of muscle and skin were simultaneously deprived of their blood supplies in this study, the skin did not exhibit reactive hyperemia. On release of constriction the skin flow returned to only 80% of the control value, while the muscle blood flow more than doubled. Two to three minutes

after release of constriction the flow was slightly less than control. Coles and Cooper (12), have demonstrated that when the forearm temperature was reduced in humans, reactive hyperemia was mostly confined to the deeper muscle tissues. When the forearm was warm, on the other hand, the hyperemia occurred in the skin as well as the deeper tissues. The lack of the hyperemic response in this study was probably due, in part, to a cooling effect. In the course of the experiments the limb skin retracted considerably after sectioning, and a large area of muscle and subcutaneous tissue was exposed which would facilitate cooling. Furthermore, the occlusion of the femoral artery was not complete in these experiments and there is evidence (Tables 6 and 7), that the skin blood supply was not compromised as much as the muscle supply during occlusion. The data show that the skin flow diminished by 45% while the muscle flow decreased by 72%. This fact, combined with the normally low metabolic requirements of the skin apparently contributed to the absence of the hyperemic effect in this bed.

CHAPTER V

SUMMARY AND CONCLUSIONS

The effect of exercise on veins was studied in an attempt to help explain changes in blood volume that are observed to occur in exercise. For comparative purposes the effect of reactive and mechanical hyperemia on veins was also investigated. Vascular responses in muscle and skin were observed in forty dogs with denervated hindlimbs. Blood flow determinations were made in both beds as well as pressure measurements at sites in the femoral artery, large and small muscle veins, and the large and small skin veins. Vascular resistances were calculated for the segments from the femoral artery to the small muscle and skin veins respectively, from the small muscle and skin veins to the large muscle and skin veins respectively, and from the femoral artery to the large muscle and skin veins respectively. Appropriate pressure and blood flow measurements were made in the control state, during exercise (simulated by faradic stimulation of the femoral and sciatic nerve trunks) immediately postexercise, (3 to 5 seconds), and post-control. To ascertain whether or not increased sympathetic activity occurred with stimulation, skeletal muscle activity was blocked with Succinylcholine Chloride during stimulation in seven experiments. In a number of experiments of the exercise series the oxygen contents of muscle and skin blood were determined and the hematocrits were measured. Hematocrits were also measured in a number of reactive hyperemia experiments.

In this series, pressure and flow measurements were made in the control state, during partial constriction of the femoral artery, on release of constriction and in the post-control state. In another series the same vascular measurements were made as the blood flow through the limb was progressively increased with a pump (mechanical-hyperemia), and when the blood flow was held constant as the limb was exercised.

An increase in the muscle venous resistance was observed in exercise that could not be attributed solely to the passive action of the skeletal muscle on the adjacent vasculature, since the vasoactivity persisted postexercise. Venous hematocrit determinations appeared to rule out increased viscosity as a factor in the increased muscle vein resistances. Changes in muscle vein dynamics in reactive hyperemia and mechanical hyperemia indicated there was little likelihood that an artifact in the experimental preparation was responsible for the high muscle vein pressures measured in exercise. In addition, it is unlikely that increased sympathetic activity, resulting from stimulation of the limb nerve trunks, could be a causative factor, or that muscle-to-skin shunts could be involved. The response of the skin vasculature to exercise was characterized by an apparent decrease in the skin vein resistance that did not persist postexercise.

Venous resistance in muscle did not change during reactive hyperemia. Since muscle venous resistance fell during mechanical hyperemia, increased muscle venoactivity following release of arterial occlusion is suggested.

These findings suggest that there is an increase in vasoactivity of muscle veins in exercise and a similar but less pronounced response

in veins in reactive hyperemia. These responses may contribute to the rise in capillary hydrostatic pressure and hence to fluid efflux from the capillary.

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