Relation Between Blood Flow and Contraction Force in Active Skeletal Muscle

By Leo Hirvonen, M.D., and Ralph R. Sonnenschein, M.D., Ph.D.

Observation of the effects on contractile ability of skeletal muscle as affected by induced alterations in its total blood flow might yield insight into the role of vasomotor innervations, whether constrictor or dilator, in the regulation of blood flow, and hence of performance, of active muscle. Additionally, it might prove possible to infer the actions of vasomotor nerves and pharmacological agents on the partition of total flow within the active muscle between the "nutritional" flow, i.e., that component of total flow involved in the exchange of nutrients with the tissue, and "non-nutritional" flow. Such observations constitute the present report.

Methods

The experiments were performed on cats weighing 1.9 to 3.5 Kg., anesthetized, after initial etherization, with intravenous chloralose (50 mg. per Kg. body weight) augmented with urethane as required. After cannulation of the trachea, one hind limb was shaved and skinned completely. The subsequent procedure varied according to which of the following preparations was used. In the first, the "isolated" preparations, blood flow was measured in active muscles only, while in the others, the "combined" preparations, flow to the entire musculature of the leg was followed.

"ISOLATED" GASTROCNEMIUS-SOLEUS PREPARATION (FIGURE 1)

All attachments of the thigh muscles to the tibia were ligated and sectioned. The tibialis group of muscles was ligated at each end and removed in toto. All branches of the femoral artery except for the direct supply of the gastrocnemius-soleus muscles were ligated. A ligature was placed around the ankle to occlude circulation of the paw. The tibial nerve was exposed for the placement of stimulating electrodes. After heparinization of the animal (Upjohn, 500 to 700 U.S.P. units per Kg.), the femoral artery was cannulated and arterial flow was redirected to it from the opposite femoral artery. Flow in this closed system was measured with a drop counter, as described by Lindgren,1 and recorded in terms of intervals between successive drops or pairs of drops. In this method, the arterial flow is diverted through a cannula system to a plastic chamber. In the latter, blood falls as uniform drops from an orifice at the top through a layer of low density, low viscosity, liquid silicone where it interrupts a light beam which activates a photo-cell circuit. The blood is returned through a cannula to the distal arterial segment. No contamination of the blood ordinarily occurs with the immiscible silicone, and the system offers little resistance to flow. Measurement is limited to the maximum rate which allows separate drops to form, approximately 30 ml. per minute.

The systemic arterial pressure was recorded in the femoral artery while the local perfusion pressure was recorded from the cannula distal to the drop chamber, both pressures being monitored with Statham P23A transducers. A screw clamp on the cannula proximal to the drop chamber served for the control of the perfusion pressure. Intrarterial infusions were made through arm of the distal cannula using an infusion pump (Harvard Apparatus Co.). The leg was held rigidly in place by pins screwed into the femur and tibia. A thread was led from the ealeaneus to a tension transducer (Grass Instrument Co., FT10). A bipolar platinum stimulating electrode was placed on the tibial nerve. The leg was then recovered with its skin. Temperatures in the esophagus and in the muscle were measured by indwelling thermocouples and maintained at relatively constant levels by an electric heating pad under the animal and by an adjustable heat lamp directed at the leg.

The tibial nerve was stimulated twice every second by a Tektronix type 161 pulse generator gated by a Grass Model S4 stimulator so as to give with each stimulation a train lasting 60 msec. of monophasic square wave impulses each of 0.02-msec. duration, spaced at intervals of 5 msec. The amplitude of the pulses was adjusted in order to give maximal response as detected by the force transducer, which generally required 0.5 to 1.0 volts. The duration of the individual impulses, 0.02 msec., was short enough so that autonomic fibers should not have been excited. The stimulus

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TABLE 1
Comparison of Effects of Sympathetic Stimulation (S), Clamping (C), Norepinephrine (N), and Epinephrine (E) on "Isolated" Gastrocnemius Preparation

<table>
<thead>
<tr>
<th>Type of response*</th>
<th>No. of animals</th>
<th>Type of response</th>
<th>No. of animals</th>
<th>Type of response</th>
<th>No. of animals</th>
<th>Type of response</th>
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</table>

* S < C means that for equivalent reductions in flow the reduction in muscle force is less during sympathetic stimulation than during clamping.

which produced maximal muscle response did not induce overt autonomic or somatic reflexes.

When indicated, the ipsilateral sympathetic chain was exposed at the level of L3 to L5 and prepared for stimulation with a bipolar platinum electrode. After the appropriate level for producing vasoconstriction in the leg was determined by stimulation, the sympathetic trunk was cut central to the electrode. The sympathetic chain was stimulated by means of a Grass Model S5 stimulator with 2-msec. monophasic square wave impulses at 10 to 15 c.p.s.; the intensity was adjusted in each case to give the desired change in flow. With few exceptions, this stimulation was not accompanied by general cardiovascular changes.

For hypothalamic stimulation of the vasodilator center, the head was fixed in a stereotaxic instrument, the scalp reflected, and a section of skull removed to allow insertion of a stainless steel electrode, 0.4 mm. wide, insulated except at the tip. Monopolar stimulation was effected by 50 to 70 c.p.s. monophasic square wave pulses of 2-msec. duration at 1.5 to 3 volts, delivered by a Grass Model S5 stimulator. The hypothalamus was explored in the area bounded by the standard stereotaxic coordinates AP +13 to +11, lateral 1 to 3, and vertical 0 to —4 mm., until maximal dilator effect was obtained. This general area corresponded with that previously described.2 The criterion for acceptability of a dilator response was that, during hypothalamic stimulation, the sympathetic chain being intact and the muscle at rest, an increase in arterial flow should occur with essentially no change in arterial pressure. When possible the cholinergic nature of the hypothalamic dilator effect was tested by the intravenous administration of atropine sulphate (U.S.P.) at 0.5 to 1.5 mg. per Kg. body weight.

Synthetic L-norepinephrine (Levophed Bitartrate, Winthrop-Stearns, Inc.) and synthetic L-epinephrine (Winthrop-Stearns) were dissolved in 0.9 per cent NaCl in concentrations of 1.0 or 10.0 μg. of base per ml. During intra-arterial infusions of these agents, the maximum volume rate was 0.5 ml. per min.

Recordings of pressures, flow, and muscle force were made with Offner type 133 amplifiers and Dynograph.

"COMBINED" PREPARATIONS

Quadriceps as the Active Muscle

With the exception of the following details, the preparation and methods were as above. Flow was measured in the external iliac artery of one leg. Collateral circulation was controlled by ligation of all appropriate arteries. Adequacy of the control of collateral circulation was tested, when possible, at the end of each experiment by intra-aortic injection of 5 to 10 ml. of India ink during occlusion of the iliac artery of the test leg. In the course of some experiments, the existence of functional collaterals was ruled out by the absence of muscle response during total clamping of the perfusion system.

The patellar tendon and fascial connections of the quadriceps to the tibia were cut. A thread was led, from a hole drilled in the patella, to the force transducer and the distal end of the femur was held rigidly in place by an inserted pin. The femoral nerve as it passed from within the iliopectus muscle was prepared for stimulation and its branch to the sartorius muscle was cut.

Gastrocnemius-soleus as the Active Muscle

Measurement of flow and control of collateral circulation were as with the quadriceps preparation; fixation of the leg, measurement of muscle force and stimulation of the tibial nerve were as in the "isolated" gastrocnemius preparation.

Results

CHARACTERISTICS OF THE MUSCLE RESPONSE AND THE ACCOMPANYING ACTIVE HYPEREMIA

When stimulation of the tibial nerve was begun, the force of the gastrocnemius-soleus reached a high level which then declined with-
in several minutes to a relatively constant steady state of about 1.0 to 1.5 Kg. This muscle response corresponded with a steady rate of flow usually three to six times the resting rate. This steady state of muscle response and flow often might continue during one-half hour of continued stimulation. After a variable period of time, in spite of constant arterial pressure, the preparation deteriorated; the resting flow might be lower than previously and the degree of active hyperemia especially was reduced; the muscle response in turn declined commonly to around 400 mm., considerably less than it had been in the earlier steady-state condition. In view of these changes, comparisons were made only of procedures which were performed within a short time of each other, where initial flow and muscle force were essentially the same. As contrasted with the "isolated" gastrocnemius preparation, the usual level of resting flow in the "combined" preparations was higher, while the increase in flow during activity was proportionately lower. This would be expected in view of the fact that the flow to all the muscles of the leg was being measured and only a portion of the musculature was active. The usually observed muscle force was initially in the order of 0.5 to 1.0 Kg. for the quadriceps. Otherwise, the course of change in flow and muscle force with time was similar to that described for the "isolated" gastrocnemius preparation.
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TABLE 2
Comparison of Effects of Sympathetic Stimulation (S), Clamping (C), and Norepinephrine (N) in "Combined" Preparations

<table>
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<th>Type of response</th>
<th>Quadriceps</th>
<th>Gastrocnemius</th>
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<th>Quadriceps</th>
<th>Gastrocnemius</th>
<th>Number of animals</th>
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<tr>
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</tr>
</tbody>
</table>

*Two types of response in same animal.

minute; norepinephrine generally had a stronger effect than epinephrine on a weight basis. The marked diminution in flow and in muscle force produced by sympathetic stimulation or by infusion of norepinephrine or epinephrine was consistently observed.

With one exception, the effects of all procedures on the relationship between muscle force and flow were essentially identical (table 1 and fig. 3). In general, the relationship between flow and muscle force over the major part of the range was approximately linear. The first decrement in flow was often associated with a less than proportional decrease in muscle force. This generally occurred only in the early part of the experiment when both the resting flow and the flow during activity were at a relatively high level.

"Combined" preparations. Comparison of the effect of sympathetic stimulation and clamping on the relationship between flow and muscle force in the quadriceps preparation revealed that, with one exception, the two procedures either had equal effects (table 2, fig. 4A and D) or that the sympathetic stimulation reduced flow more than it did contraction force (table 2, fig. 4B). Results in table 2 indicate that norepinephrine had either the same effect as clamping or reduced contraction more than flow; examples are seen in figure 4B, C and D. In no case was the depressant effect of norepinephrine on muscle force less than that of clamping. The comparisons among the effects of the various procedures in each animal were made by observing the plotted results. When the relationships were close as in figure 4A and D, these were noted as showing equal effects of the procedures. When obvious differences such as in figure 4B and C existed, then the effects of sympathetic stimulation or of norepinephrine were noted as "less than" or "greater than" clamping according to whether the muscle response for a given flow was greater or less than that during clamping, through most of the range of the induced diminution of flow. The distributions of responses obtained in the gastrocnemius preparation were similar to those of the quadriceps (table 2) and indicate no important differences between these two muscles.

The several procedures used to reduce flow
in the active "isolated" gastrocnemius produced essentially identical linear reductions in muscle force. Dilator action of epinephrine in small doses as seen in resting muscle (e.g., Lundholm) did not appear in the active muscle.

In the "combined" preparations, the situation was different, in that there were both contracting and resting components of the muscle mass whose blood flow was being measured. The differences in effects on the flow-force relationships induced by sympathetic chain stimulation and by norepinephrine infusion, as contrasted with their similarity in the "isolated" preparation, may be ascribed to quantitative differences in actions of these agencies on the vessels of contracting and of resting muscles. The mechanisms underlying such differences remain to be elucidated. The actions of both sympathetic stimulation and norepinephrine, or epinephrine, cannot be explained on the basis of the Orbeli effect (e.g., Biilbring and Burn), since in the "isolated" gastrocnemius no evidence for augmentation of muscle force was observed.

CAROTID PRESSOR REFLEX

In considering the effects of artificial stimulation of the sympathetic chain, as described above, it appeared desirable to make a comparison with the more physiological stimulation induced by bilateral occlusion of the carotid arteries. Fourteen experiments, all yielding similar results, were performed as illustrated in figures 5 and 6. In the first phase of the experiment, both carotid arteries were occluded for about two minutes, while perfusion pressure was maintained constant by adjustment of the clamp on the arterial cannula; systemic arterial pressure rose by an average of 30 mm Hg (range 20 to 55 mm Hg). In the second phase, lasting one to two minutes, the cannula clamp was released and the perfusion pressure allowed to increase while occlusion of the carotids was maintained.

With the muscle at rest, flow decreased during the first phase by an average of 20 per cent; in the second phase, with increased perfusion pressure, flow increased by an average of 25 per cent above the preclamping value. When the muscle was active, only 5 to 10 per cent decrease in flow occurred in the first phase; in the second phase, the average increase in flow was about 15 per cent.

In the first phase, muscle force was unchanged or decreased a few per cent. In the second phase, muscle force increased so that it was equal to, or slightly above, its initial level.

It is apparent that a small vasoconstrictor influence occurs in active as well as resting muscle during evocation of the carotid sinus reflex; this is considerably less than can be induced by sympathetic chain stimulation, as also shown by Mercker and Schoedel. If the perfusion pressure is allowed to increase freely, an increase in flow with associated enhancement of muscle force may occur, as previously noted by Rein and Felix.

EFFECTS OF STIMULATION OF THE SYMPATHETIC VASODILATOR SYSTEM

Little has been known of the functional significance of the sympathetic vasodilator system, whose basic characteristics have been
investigated and reviewed by Uvnäs and his collaborators. The observations of Hyman et al. and Rosell and Uvnäs suggest that, in resting muscle, the dilators act to increase "non-nutritional" blood flow. These findings raise the question of the action of the dilator system in active muscle both on blood flow and on performance of the muscle. The following experiments were performed with this question in mind.

"Isolated" Gastrocnemius Preparation

Ten experiments out of 23 trials met the criterion for acceptability of the vasodilator response. In these, hypothalamic stimulation, with the muscle at rest, was associated with, at most, 10 mm Hg increase in mean arterial pressure, in most cases with no increase or a slight decrease. The flow in the resting muscle, 1.6 to 6.2 ml./min., was increased by an average of 80 per cent (range: 38 to 186 per cent). In four additional experiments, included for comparison, hypothalamic stimulation consistently produced a pressure rise of 15 to 55 mm Hg with an associated increase in flow of 67 to 245 per cent.

When the muscle was active, with its flow at a correspondingly higher level (9 to 22 ml./min.), hypothalamic stimulation, when unaccompanied by rise in arterial pressure, produced little or no increase in flow and no increase in muscle force (figs. 7 and 8). In those experiments where the predominant effect of the hypothalamic stimulation was a rise in pressure, either from the beginning or after repeated stimulations (fig. 8), an increase in flow and an increase in muscle response might occur. A single case (fig. 9) showed unusual results in that a large increase in muscle force occurred associated with a dilator effect. It is noteworthy that in this experiment the initial muscle force and associated flow were considerably less than usual.

"Combined" Quadriceps Preparation

This series includes eight experiments. Hypothalamic stimulation increased the flow by 97 (46 to 250) per cent. When the quadriceps muscle was active, the flow was about twice as high as at rest, and hypothalamic stimulation produced on an average 25 (4 to 36) per cent increase in the flow of the leg musculature. The corresponding changes in muscle force were no greater than ± 6 per cent. In the later stages of two experiments, as the levels of the flow and muscle force decreased, the vasodilation was associated with a relatively greater enhancement of muscle force. The same effect occurred in two other experiments where an increased pressor response also appeared. In two cases, a small but definite decrease (3 to 12 per cent) in muscle force was repeatedly observed coincident with 10 to 30 per cent increase in flow.

In four experiments, flow was restricted by a reduction in perfusion pressure of 25 to 40 mm Hg; this was associated with a reduction of muscle force and blood flow. The effect of vasodilator stimulation was unchanged by this procedure. In one experiment of this series and one of the gastrocnemius series, hypothalamic dilator stimulation was started
Summary of individual carotid clamping experiments. Arterial and cannula pressures shown schematically as mean values.

About 40 seconds prior to the onset of muscle activation and continued for the first 50 to 80 seconds of the muscle response; the muscle response was allowed to continue for another minute. No difference was seen in the pattern of initial fatigue as compared with activation of the muscle in the absence of dilator stimulation.

As a rule, dilator stimulation in the "isolated" preparation had little or no effect on total arterial flow or force of contraction in a briskly responding active muscle, with vessels already maximally dilated by local factors, presumably metabolic. A different situation obtained in those cases where the vessels did not respond as well to the action of local factors. When this occurred, as in some of the cited experiments, activation of the dilator system did induce further local dilation with improvement in flow and muscle performance. The greater observed increase in flow in the "combined" preparations during dilator stimulation was likely due to increase in flow in the inactive muscles. Such an increase in flow in the inactive muscles might have brought about the occasionally observed reduction in muscle force, through shunting a significant amount of flow away from the active muscles.

Discussion

Before any interpretation of the results can be made, the characteristics of one aspect, in particular, of the experimental procedure must be considered. It was necessary that the peripheral nerve being stimulated to activate the muscle be left intact so that centrally initiated vasomotor activity could be conducted to the vasculature of the muscle. As a result of this, the possibility existed that stimulation of the peripheral nerve might have effects other than the desired one of activating the muscle. One obvious possibility was that afferent fibers might be stimulated and might bring about reflexes which could complicate the picture. Two observations...
suggest that this factor played no important role. First, the intensity of stimulation of the peripheral nerve required to produce maximal muscle response was below the threshold for producing overt cardiovascular or skeletal muscle reflexes. Secondly, previous observations by Sonnenschein\textsuperscript{13} indicated that the vascular response in muscle, stimulated in the same manner as in the present experiments, was essentially unaltered when the peripheral nerve was decentralized. It is also unlikely that the mode of somatic nerve stimulation, especially with respect to the shock duration, interfered with conduction along autonomic fibers in the nerve, or initiated activity in these fibers. The present study indicates that conduction of centrally initiated vasoconstrictor impulses, either through stimulation of the sympathetic chain or through reflex activation, was apparently unaffected by stimulation of the peripheral nerve in the manner used. Damage of perivascular nerves during cannulation is of little importance, according to Rein,\textsuperscript{4} the observation in our experiments of potent vasomotor effects on sympathetic chain and hypothalamic stimulation supports this contention. Thus, while no absolute answer can be given, it appears unlikely that any of these undesirable effects of stimulation of the peripheral nerve occurred.

A major question toward which interpretation of the present results may be directed is that of distribution of blood flow within skeletal muscle with respect to the "nutritional" and "non-nutritional" components of flow. The question arises because of various lines of evidence that such a distribution occurs in resting muscle and that it may be altered by various procedures. For example, changes in oxygen consumption of resting muscle during stimulation of vasoconstrictor\textsuperscript{14} and vasodilator\textsuperscript{12} innervations have been ascribed to a shunting of blood into areas of low metabolic rate or through arterio-
venous anastamoses which are not functional in nutritional exchange with the muscle tissue itself. Similar inferences from clearance studies have been drawn for certain effects of vasomotor innervation and epinephrine injection. Through use of microparticle injections and anatomical procedures, evidence for the presence of anastamoses in muscle has been obtained; these vessels could conduct the "non-nutritional" flow.

Essentially no information of similar nature has been available on the distribution of blood flow in actively contracting muscle. The present results may be interpreted to this end if the assumption is made that the ability of a muscle to perform its work, as measured by its maximum contraction force, is an index of its nutritional flow. Such an operational definition of nutritional flow seems valid, for the work performed by the muscle under steady-state conditions (with the qualifications noted below) ought to reflect the exchange of nutrients and metabolites between the blood and the tissue. "Non-nutritional" flow is thus that component of total flow which, when changed, has no effect upon muscle performance. This concept of nutritional flow does not presuppose any particular anatomical arrangement of vessels. Of course, reduction in muscle force may also follow from effects of neuromuscular transmission or upon the muscle itself and these effects must be controlled. Further, the muscle will have a maximum utilization of nutrients, beyond which further supply will be ineffective in enhancing its performance; this was apparently the case in the experiment when it was possible to restrict the blood flow to a certain extent with little or no change in muscle force before the usual linear flow-force relationship became evident.

With the above qualifications it can be inferred that, in general, neither those procedures in which total flow was restricted nor hypothalamic vasodilator stimulation produced a change in the distribution of flow in the active muscle. The fact of the linearity in the flow-force relationship is the essential support for this conclusion; the discrepancies seen in the "combined" preparations have been otherwise explained above.

The results on the sympathetic vasodilator system are of special interest with respect to its physiological function. The fact that in briskly contracting skeletal muscle, with a high level of active hyperemia, vasodilator activation produced no change in total blood flow or in muscle force suggests that, in the intact animal, this system plays no role in the maintenance of flow or performance in skeletal muscle in good condition. This view is compatible with the concept of Abrahams et al. that the dilator system, acting in concert with other cardiovascular mechanisms, plays a role in the adjustment and distribution of the cardiac output during the defense reaction prior to the onset of, rather than during, muscular activity. In fatigued muscle, the system may, however, have an enhancing effect on flow and performance, if one may extrapolate from our experimental observations on the "deteriorated" preparations where the degree of active hyperemia and muscle force had declined to a low level and where hypothalamic stimulation increased both blood flow and force.

It then appears that a fundamental difference exists in the responses of the vasculature of resting and active skeletal muscle. While a change in the balance between "nutritional" and "non-nutritional" flow occurs under various influences when the muscle is at rest, this is not the case when the muscle is actively contracting. One might postulate two sets of vessels, one more intimately involved than the other in nutritional exchange with the muscle fibers. With the muscle at rest, a differential action of vasomotor innervation may be effective in altering the ratio of resistances in the two sets of vessels, and hence of flow through them. When the muscle is actively contracting, however, the potent dilating action of metabolic products may negate any action of vasomotor innervation on local vessels and hence prevent a reapportionment of flow among the two sets.
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of vessels. Change in total flow, as with sympathetic constrictor action, may still occur, however. This may be explained by making the additional postulate of a second locus of vasonomotor effect on resistance vessels upstream from the two differentiated sets of vessels. This scheme is only one of several possibilities which could explain the observed differences. These observations make clear the danger inherent in carrying over to tissues in full functional activity concepts of vascular behavior derived from the study of these tissues at rest.

Summary

The relationships between blood flow and contraction force in intermittently contracting cat skeletal muscle during alterations of flow by various procedures were studied.

When flow only to the active gastrocnemius-soleus was measured, mechanical reduction in perfusion pressure, sympathetic chain stimulation and intra-arterial norepinephrine and epinephrine infusion were found to have essentially identical effects in producing reduction in muscle force proportionate to that in blood flow. When flow in the whole leg muscle was measured while either the gastrocnemius-soleus or the quadriceps was active, varying results were obtained with these procedures which could be ascribed to differences in response of vessels in active and resting muscles. During the carotid sinus reflex some vasoconstrictor activity occurred in active muscle. On the assumption that the maximal muscle force is an index of the nutritional component of the flow, it may be inferred that, in general, those procedures in which total flow was restricted produced no alteration in distribution of nutritional and non-nutritional flow within the active muscle.

Blood flow and muscle force were generally unaffected by concomitant stimulation in the hypothalamus of the sympathetic vasodilator system. An increase in flow and force occasionally was observed when these were at low levels, or when a rise in arterial pressure occurred. The sympathetic vasodilator system produces no alteration in distribution of flow and would seem to play no role in the maintenance of blood flow and performance of normal active muscle.

A fundamental difference appears to exist in the responses of the vasculature of resting and active skeletal muscle; this difference is related to the interplay of specialized effects of the vasonomotor innervations and the action of vasodilator metabolites.

References


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