

## Skeletal muscle blood flow capacity: role of muscle pump in exercise hyperemia

M. HAROLD LAUGHLIN

*Department of Biomedical Sciences, College of Veterinary Medicine, and The Dalton Research Center, University of Missouri-Columbia, Columbia, Missouri 65211*

LAUGHLIN, M. HAROLD. *Skeletal muscle blood flow capacity: role of muscle pump in exercise hyperemia*. Am. J. Physiol. 253 (Heart Circ. Physiol. 22): H993-H1004, 1987.—An appreciation for the potential of skeletal muscle vascular beds for blood flow (blood flow capacity) is required if one is to understand the limits of the cardiorespiratory system in exercise. To assess this potential, an index of blood flow capacity that can be objectively measured is required. One obvious index would be to measure maximal muscle blood flow (MBF). However, a unique value for maximal MBF cannot be measured, since once maximal vasodilation is attained MBF is a function of perfusion pressure. Another approach would be to measure maximal or peak vascular conductance. However, peak vascular conductance is different among skeletal muscles composed of different fiber types and is a function of perfusion pressure during peak vasodilation within muscle composed of a given fiber type. Also, muscle contraction can increase or decrease blood flow and/or the apparent peak vascular conductance depending on the experimental preparation and the type of muscle contraction. Blood flows and calculated values of conductance appear to be greater during rhythmic contractions (with the appropriate frequency and duration) than observed in resting muscle during what is called “maximal” vasodilation. Moreover, dynamic exercise in conscious subjects produces the greatest skeletal muscle blood flows. The purpose of this review is to consider the interaction of the determinants of muscle blood flow during locomotory exercise. Emphasis is directed toward the hypothesis that the “muscle pump” is an important determinant of perfusion of active skeletal muscle. It is concluded that, during normal dynamic exercise, MBF is determined by skeletal muscle vascular conductance, the perfusion pressure gradient, and the efficacy of the muscle pump.

microspheres; maximal oxygen consumption; cardiac output; arterial pressure; function hyperemia

THE HYPEREMIA THAT OCCURS when quiescent skeletal muscle is stimulated to contract rhythmically represents one of the largest increases in perfusion seen in the tissues of the normal mammal. The magnitude of this hyperemia may account for the attention it has received over the past two centuries (10, 20, 27, 28, 35, 50, 54, 57). In view of this extensive literature, it is surprising that the mechanism of vasodilation is not well understood. It is clear that exercise hyperemia is primarily a local phenomenon, and its magnitude is related to the high basal vascular tone of the resistance vessels. This accounts for the fact that skeletal muscle vascular beds possess such a large potential for increased blood flow

(i.e., a large blood flow capacity) (20, 27, 54, 56). Much of the interest in skeletal muscle blood flow capacity stems from studies concerning the potential of skeletal muscle vasculature for blood flow in pathological conditions and from studies conducted to compare the relative importance of different control systems in determining muscle blood flow.

The lack of knowledge of the blood flow capacity of skeletal muscle also underlies the long-standing controversy concerning the primary determinants of maximal oxygen consumption during exercise and the mechanisms by which physical conditioning may increase maximal oxygen consumption (31, 37, 50, 51, 53). One theory

indicates that maximal oxygen consumption is determined by the ability of skeletal muscle to consume oxygen (i.e., a biochemical limitation), whereas another indicates that maximal oxygen consumption is primarily determined by the capacity to deliver oxygen in blood to active skeletal muscle (i.e., a transport limitation). Depending on "design features," the ability to transport blood to active muscle could be determined by maximal cardiac output and/or by the capacity of the skeletal muscle vasculature for blood flow (blood flow capacity). The two key questions stemming from this controversy are, What is the blood flow capacity of skeletal muscle? and What are the determinants of "maximal muscle blood flow during exercise"?

The purpose of this paper is to consider the determinants of blood flow to skeletal muscle during normal dynamic exercise and to analyze approaches used to estimate the blood flow capacity of skeletal muscle. The questions, What is blood flow capacity? and How can it be quantified? are considered first. Some differences among the methods used to study muscle blood flow in active skeletal muscle are then considered with emphasis on approaches to the measurement of muscle blood flow capacity. Finally, the available data concerning the muscle pump and the potential role of this mechanism in the perfusion of skeletal muscle during exercise are discussed.

### *Blood Flow Capacity of Skeletal Muscle*

Most reviews written on the subject of skeletal muscle blood flow indicate that maximal blood flow in mammalian skeletal muscle is in the range of 50–150 ml·min<sup>-1</sup>·100 g muscle<sup>-1</sup> (10, 18, 20, 27, 54, 56–58). However, some investigators contend that muscle blood flows during exercise must be greater than these estimates indicate (35, 50–52). Several recent reports indicate that muscle blood flows during exercise are three to four times these supposed "maximal" values (Table 1). Thus "maximal muscle blood flow" may be greater than many believe. A major cause of this controversy is the definition (or lack thereof) of the term maximal muscle blood flow.

The term maximal muscle blood flow is ill defined and often abused in the literature. The term maximal muscle blood flow is often used to describe the highest flow measured in a series of experiments (27, 35). Application of the term maximal to a value for blood flow implies that the value is the highest possible. Such a maximal value must therefore be a unique value that is stable and reproducible. Maximal values for biological variables are often indicated by a plateau as in the relationship between whole-body oxygen consumption and exercise intensity or in a dose-response curve for a vasodilator drug. At the very least, blood flow is determined by two factors: perfusion pressure and vascular conductance. Thus, if maximal vasodilation is attained, then blood flow becomes a function of perfusion pressure. As a result, it is only possible to measure a unique maximal muscle blood flow under a given set of conditions (33). Therefore a unique value for maximal blood flow cannot be determined.

In general, the term maximal muscle blood flow has

been used to describe what is referred to in this review as blood flow capacity. The blood flow capacity of vascular beds can be estimated and compared among groups with the proper experimental design and with precisely defined conditions (i.e., proven maximal vasodilation with blood flow measured at specific and varied perfusion pressures) (33, 37, 48). Using this approach, Laughlin and Ripperger (37) estimated blood flow capacity of resting skeletal muscle by producing maximal papaverine vasodilation and determining the relationship between perfusion pressure and flow as shown in Fig. 1. It is then possible to compare the pressure-specific blood flow capacity among muscles. As described below (see *Caveat*), the fact that maximal papaverine vasodilation was attained (i.e., plateau in the papaverine dose-response curve) does not necessarily mean that further vasodilation could not be produced via other methods. Therefore I refer to this as peak papaverine vasodilation.

Another approach that has been used to estimate blood flow capacity has been to determine peak vascular conductance (blood flow/pressure). However, vascular conductance even during maximal vasodilation is also related to perfusion pressure (due to the distending effect of increased transmural pressure). For example, Reid and Johnson (48) determined the relationship between vascular conductance and perfusion pressure in dog diaphragm muscle and demonstrated that once maximal vasodilation had been attained, vascular conductance was observed to be a linear function of perfusion pressure (48). The effects of pressure on vascular conductance will be most apparent when examined over a large range of pressures as was done by Reid and Johnson (48). If the relationship between perfusion pressure and vascular conductance is determined for a maximally dilated vascular bed, it is possible to compare the blood flow capacity of different vascular beds, as reflected in peak vascular conductances calculated for each vascular bed, at a given perfusion pressure. As an example, Fig. 2 depicts the peak vascular conductances (perfusion pressures of 130 mmHg, venous pressures assumed = 0) determined in four different preparations: 1) isolated, perfused rat hindquarters vasodilated with papaverine; 2) rat muscles performing isometric twitch-type contractions; 3) rat muscles performing isometric trains of tetanic contractions; and 4) rats running on a motor-driven treadmill. It is important to emphasize that these data are from the same muscles of the same species under these various conditions. These data illustrate another important consideration in relation to understanding skeletal muscle blood flow capacity. That is, the peak vascular conductance for a specific perfusion pressure varies (and/or blood flow capacity varies) in skeletal muscle tissue according to the fiber type composition of the muscle.

Blood flow is often assumed to be distributed homogeneously within and among the active skeletal muscles. However, the data presented in Fig. 3 and Table 1 indicate that blood flow is not evenly distributed within and among skeletal muscles during exercise in conscious mammals. Rather, blood flow is much higher in some muscles and areas of muscles than in others. These blood flow distribution patterns appear to be related to 1) the

TABLE 1. *Muscle blood flow during exercise in conscious mammals*

Source	Species	Muscle	Type of Exercise	Blood Flow, ml·min <sup>-1</sup> ·100 g <sup>-1</sup>	Method	P <sub>a</sub> , mmHg
Armstrong & Laughlin (5)	Rat	G <sub>r</sub>	Treadmill	467	Microspheres	130
		G <sub>w</sub>		68		
		VL <sub>r</sub>		495		
		VL <sub>w</sub>		102		
Musch et al. (42)	Dog	SM	Treadmill (max)	289		
		BF		340		
		G		208		
Armstrong et al. (3)	Pig	VL <sub>r</sub>	Treadmill (max)	185	Microspheres	150
		VL <sub>w</sub>		143		
		Brach		290		
		Glut		202		
Manohar (39)	Pony	Glut	Treadmill (max)	253	Microspheres	155
		Triceps brachii		227		
Armstrong & Laughlin (unpublished observations)	Horse	VL <sub>r</sub>	Treadmill (max)	140	Microspheres	145
		VL <sub>w</sub>		60		
	Steer	VL <sub>r</sub>	Treadmill (max)	137	Microspheres	145
		VL <sub>w</sub>		56		
		Glut		185		
Andersen & Saltin (1)	Human	Quad	1 Leg estension	250	Thermodilution	130
Rowell et al. (52)	Human	Quad	1 Leg extension	273	Thermodilution	135
	Human	Quad	1 Leg extension (hypoxia)	309	Thermodilution	135

Data are means. Muscles are red and white gastrocnemius (G<sub>r</sub> and G<sub>w</sub>, respectively); red and white vastus lateralis (VL<sub>r</sub> and VL<sub>w</sub>, respectively); semimembranosus (SM); biceps femoris (BF); gastrocnemius (G); brachialis (Brach); deep gluteals (Glut); and quadriceps muscle group (Quad).

blood flow capacity of muscles composed of the different muscle fiber types (Fig. 1) (34, 37, 38), 2) the muscle fiber recruitment patterns within and among the muscles (4, 7, 34, 35), and 3) neurohumoral effects on the muscle vascular beds (3, 35). The well-known fact that all muscle fibers are not uniformly active during normal dynamic exercise (6, 12, 19, 22, 60) is often ignored in considerations of muscle blood flow during exercise. This important fact should not be overlooked because a value for blood flow obtained from mixed muscle will underestimate the flow that existed in a high-flow area of the muscle mass and overestimate flow in low-flow areas.

The data presented in Fig. 2 also indicate that the various methods used to estimate potential or peak vascular conductance yield different values. Similarly, the blood flow data depicted in Figs. 2 and 3 indicate that the type of muscle stimulation used in studies of active hyperemia has an important influence on the estimates of blood flow capacity. Before a discussion of the differences among measurements of blood flow capacity and/or vascular conductances in active muscles, it will be helpful to consider some of the differences between the experimental preparations.

*Approaches to Study of Exercise Hyperemia*

Perhaps the most obvious difference between the various experimental methods of stimulating muscles (used as models of exercise) and an active skeletal muscle in a

conscious exercising animal is the fact that the muscle in the model of exercise is not in its normal environment. Another important consideration is the type of contractions produced by the stimulation parameters.

In locomotory exercise the contractions are rhythmic; with the muscles active (contracted) during 55–70% of the stride cycle and relaxed the remainder of the time (19, 22). When speed is increased, both durations decrease so that the percent time spent in each state is relatively constant. In models of muscle activity, the stimulation parameters will determine the time-averaged metabolic rate (tension-time index) as well as the relative amounts of time spent in contraction and relaxation (27). It is also important to determine whether the stimulation parameters used will activate autonomic nerves leading to sympathetic vasoconstriction (38). As will be discussed below, the amount of time spent in contraction and relaxation is important because blood flow is impeded during muscle contraction and, as a result, most (if not all) blood flow occurs during relaxation.

Many of the classic in vitro/in situ studies of the relationships between muscle contraction (exercise) and blood flow have used twitch-type contractions. Hudlicka (27) reported that in this model of exercise, muscle blood flow is determined by the number of contracting fibers and the frequency of stimulation. Hudlicka also indicated that repeated rhythmic single-twitch stimuli produce larger increases in muscle blood flow than do repeated

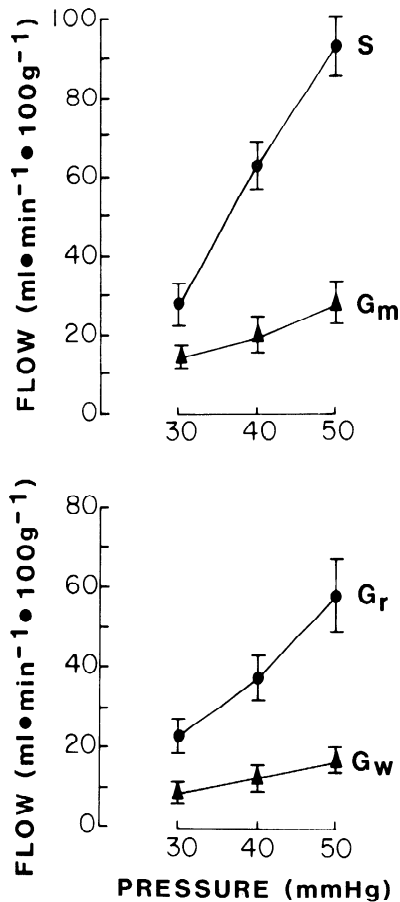


FIG. 1. Relationships between regional muscle blood flow and perfusion pressure in soleus (S) and mixed ( $G_m$ ), red ( $G_r$ ), and white ( $G_w$ ) portions of the gastrocnemius muscle of control Sprague-Dawley rats. Data are means  $\pm$  SE ( $n = 18$ ) from Laughlin and Ripperger (37) and unpublished data from groups of control rats.

short-lasting tetanic stimuli or sustained tetanic contractions and that maximal blood flow was usually produced by stimulation frequencies of 4–6 Hz (27). The interactions of these factors can be appreciated from the experiments of Folkow and Halicka (17). They found that as stimulation frequency was increased from 1 to 4 Hz in cat gastrocnemius muscle, blood flow increased from 10 to 46 ml·min<sup>-1</sup>·100 g<sup>-1</sup>; as frequency was further increased to 60 Hz (tetanic contractions), blood flow tended to decrease. The results of Mackie and Terjung (38) in rat skeletal muscle illustrated in Fig. 3 also indicate that twitch-type contractions produce the highest blood flows in rat fast-twitch glycolytic muscles (white gastrocnemius, Fig. 3). However, their results (Fig. 3) also indicate that high-oxidative fast- and slow-twitch rat muscle had much higher blood flows during trains of tetanic stimulation (100-ms duration, 100 Hz, 120 tetani/min) than the highest flows produced by twitch-type contractions in these types of muscle (38). This type of muscle stimulation (tetanic trains) produces contraction patterns more similar to normal recruitment and represent stimulus durations below those needed to activate autonomic nerves (38). Thus, in these models of exercise, the stimulation parameters that produce the highest muscle blood flow (and/or peak vascular conductance) may vary will muscle fiber type.

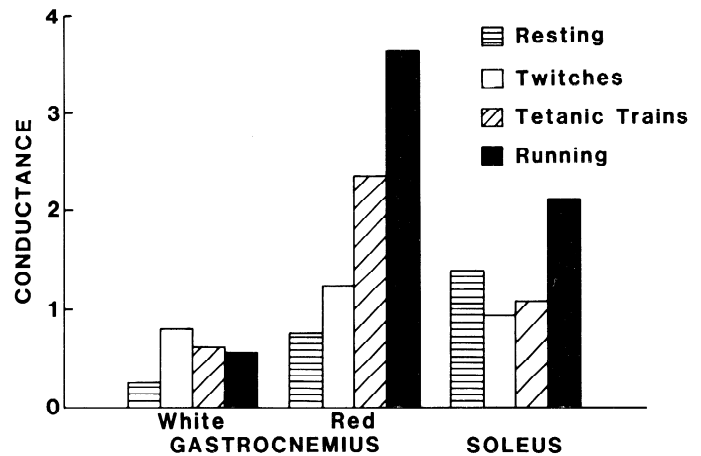


FIG. 2. Vascular conductances determined at a mean perfusion pressure of 130 mmHg. Data from muscles during maximal papaverine vasodilation (resting) are from Laughlin and Ripperger (37). Conductances were calculated for perfusion pressures of 130 mmHg with equations derived from linear regression analysis of relationships between vascular conductance (for each muscle) and perfusion pressure, correcting for effects of predicted viscosity differences. Data for twitch and tetanic stimulation conditions were calculated from data of Mackie and Terjung (38); data for run condition were for rats running at 105 m/min taken from Armstrong and Laughlin (5). It is important to remember that these calculations of conductance are based on two assumptions: 1) venous pressures = 0, and 2) all blood flow is the result of a pressure gradient (i.e., kinetic energy is negligible).

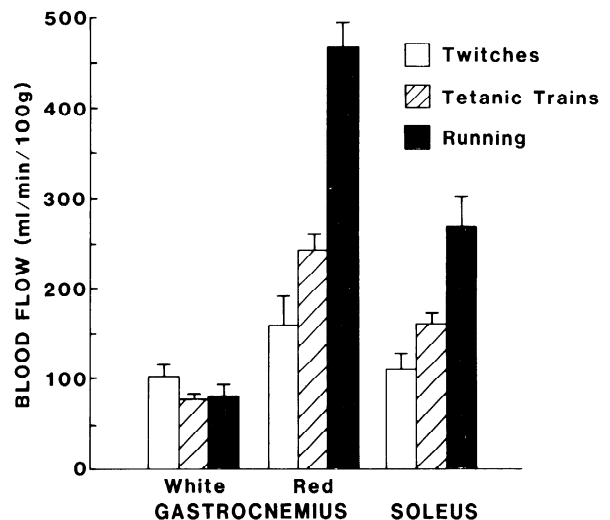


FIG. 3. Peak blood flows to 3 types of rat skeletal muscle during 3 different types of contraction. Data for muscles during twitch and tetanic stimulation conditions are from Mackie and Terjung (38) and those for running rats are from Armstrong and Laughlin (5). Blood flows for twitch-type stimulation were taken after 10 min of contraction, and flows for tetanic stimulation were taken after 1 min of contraction (38).

A related consideration is that many *in vitro/in situ* models of exercise use a muscle or a group of muscles that are supplied by arteries and veins that can be easily isolated and/or muscles that are thin and can therefore be transilluminated for study. In the attempt to apply these data to exercising subjects or to whole body stress such as shock, it is then often assumed (though less often is this assumption stated) that these muscles "represent" all skeletal muscle. In other words, it is assumed that mammalian skeletal muscles are homogeneous. Depending on the species, mammalian skeletal muscles are ac-

tually quite heterogeneous within muscles and among muscles throughout the body (2, 7, 53). Moreover, the normal recruitment patterns of skeletal muscles during dynamic exercise are heterogeneous (4, 6, 12, 19, 22, 53). In the aforementioned models of exercise, the muscles are generally stimulated so that all fibers within the muscle are activated (27, 38). As mentioned above and shown in Table 1 and Fig. 3, muscle blood flow is also distributed heterogeneously within and among muscles during exercise in conscious subjects (3, 5, 34–36), and some muscles (primarily the high-oxidative extensor muscles) have higher blood flows than the “average” muscle blood flow. Thus the fact that skeletal muscles are not homogeneous must be kept in mind when skeletal muscle blood flow and blood flow capacity data obtained from any model and/or preparation are being interpreted and/or extrapolated to intact animals.

Another important difference between some models of muscle activity and normal exercise is that arterial pressures are often higher in normal exercise. Intense exercise in conscious subjects is usually accompanied by increases in mean arterial pressure (5, 34, 42, 52). Not all investigators present the perfusion pressure data from their experiments (35). In general, the *in vitro/in situ* studies are conducted under constant flow or constant pressure conditions. Given the choice between constant-flow or constant-pressure (free-flow) conditions, it is clear that the latter is most physiological (54, 57). One common approach used to correct for differences in perfusion pressures among various experiments is to calculate vascular conductances (48). Since conductance varies with perfusion pressure, it is best to determine the relationship between perfusion pressure and vascular conductance and then calculate the (peak) vascular conductance for any specific pressure as described above (see Fig. 2) (48).

There are many other potentially important differences among the various preparations used to study blood flow in active muscles. These differences include the effects of anesthesia, surgical trauma, regional hypoperfusion due to damaged and/or occluded vessels, basal vascular tone, autonomic influences, maximal oxygen consumption per gram of skeletal muscle, and other mechanical and/or chemical factors. Although these differences among preparations are important, I would like to focus on variations among the preparations and methods used to estimate vascular reserve (and/or blood flow capacity or potential vascular conductance) that alter the contribution of the muscle pump. These variations are the result of mechanical differences inherent in the way that muscles are stimulated to contract.

The data presented in Fig. 2 clearly show that 1) peak vascular conductances determined at specific perfusion pressures are different in muscles composed of different fiber types (i.e., values in resting muscle differ among different fiber types), 2) these peak vascular conductances obtained in fast-twitch (red and white gastrocnemius) muscles during papaverine vasodilation are less than those seen during muscle contraction, and 3) the peak vascular conductances determined for slow- and fast-twitch high-oxidative muscles during normal exer-

cise are greater than those obtained with the models of exercise. These observations raise several critical questions. For example, Why do blood flow and vascular conductance appear to be greater in contracting muscles? and Why does “peak” vascular conductance appear to vary with the type of muscular contraction? Let us consider the hypothesis that muscle blood flow and vascular conductance appear greater in contracting muscles than in maximally dilated quiescent muscles, because the muscle pump is only functional in rhythmically contracting muscles and in addition, that muscle blood flow and calculated vascular conductances are greater during normal exercise than in models of exercise because the muscle pump is most efficient during locomotory exercise in conscious subjects.

### *Muscle Pump*

In this review the term muscle pump refers to propulsion of blood from the vasculature of skeletal muscles during the contraction of the muscles (also known as the venous pump). Muscular contraction can raise intramuscular pressures to 200 or 300 mmHg (24, 29, 30, 44), and the resultant compression of the veins causes blood to flow out of the compressed segments. In as much as the venous valves are all oriented toward the heart, blood can only flow out of the compressed venous segments in one direction. If the muscle maintains a tetanic contraction, then the net effect is to increase the resistance to blood flow through the muscle. This appears to result primarily from compression of large arteries and veins passing through muscles and/or fasciculi, since capillaries and precapillary resistance vessels do not appear to be compressed during muscle contraction (21). Rhythmic contractions cause a pumping action on the veins in that the potential and kinetic energy imparted to the venous blood during muscle contraction causes blood to flow out of the veins during contraction (venous outflow), and the pump is refilled during muscle relaxation (15, 16, 46, 47, 49, 55, 59).

The muscle-pump hypothesis emerged in the 1940s (10, 47, 49, 54, 55, 59). The dynamics involved in the muscle pump can perhaps be best appreciated from the classic work of Pollack and Wood (47) as shown in Fig. 4, which shows that in these human subjects, who were standing on a treadmill, venous pressure at the ankle averaged ~90 mmHg. With the first step (start of exercise) venous pressure was increased. However, during the next four to five steps, venous pressure decreased progressively to a mean value of ~25 mmHg and remained depressed at this level for as long as the exercise continued. When exercise was stopped, it took ~30 s for ankle venous pressure to go back up to 90 mmHg. Thus, during treadmill exercise, the local (in the dependent limb) perfusion pressure gradient is increased due to the effective decrease in the pressure in the veins. These data suggest a potential role for the muscle pump in normal muscle perfusion in humans during exercise.

The idea that the muscle pump may be important in providing blood flow to muscles during exercise is well established in the literature (11, 15, 16, 43, 46, 47, 49, 53, 59) yet often ignored. Surprisingly, the increase in re-

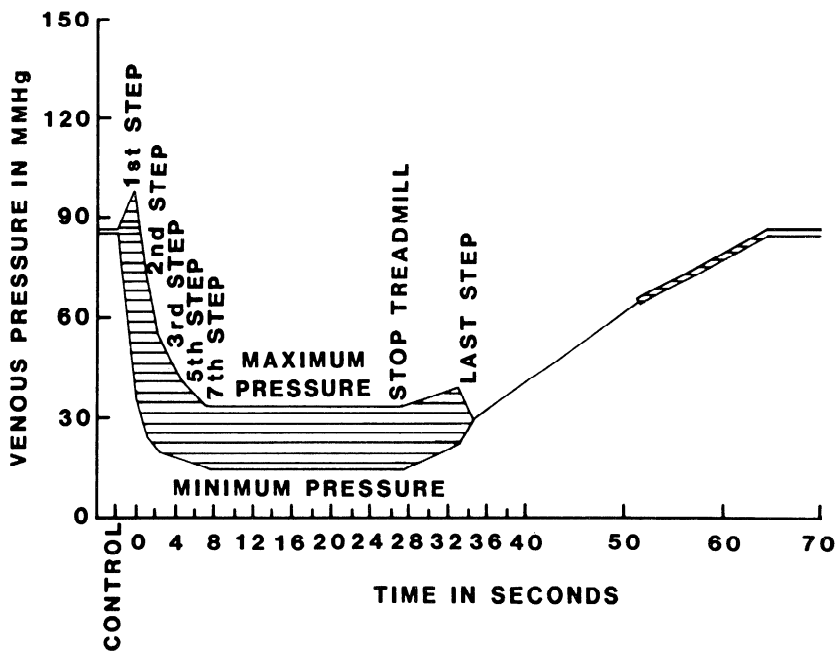


FIG. 4. Average (10 subjects) changes in ankle venous pressures as a function of time during sustained treadmill exercise at a speed of 1.7 mph with no incline. Figure was redrawn from Pollack and Wood (47).

sistance to blood flow produced by sustained muscle contraction and the expected effects of the muscle pump on venous return seem to be better appreciated (21, 26, 28, 30, 45, 57, 58). Based on studies conducted on feline calf muscles performing rhythmic exercise, Folkow and co-workers (15) proposed that the muscle pump may be of great importance in normal exercise and noted that the muscle pump may decrease venous pressures by 55–65 mmHg in the dependent legs of humans during heavy rhythmic exercise (16). Stegall (59) proposed that ~30% of the total energy necessary for the perfusion of skeletal muscle is provided by the muscles during lower limb exercise. The observations of Bevegård (11) and Pollack et al. (46) made on patients with venous valvular defects are also consistent with the idea that the muscle pump is an important mechanism for assisting venous return and providing perfusion of skeletal muscle during exercise.

The results of Folkow et al. (15) are also quite valuable in developing an understanding of the effects of the muscle pump on blood flow. They showed that when the calf muscle preparation of cats is stimulated with tetanic trains (60 Hz) all venous outflow occurred during contraction, whereas arterial inflow occurred during relaxation (each tetanic contraction lasted for 250 ms). The sequence of events occurring within this vascular bed and blood flow in the arterioles, capillaries, and small veins can only be deduced from their data. Since the capillaries do not appear to be compressed during tetanic contraction (21), blood probably starts to flow out of the capillaries at the start of muscular relaxation, and flow continues through the capillaries throughout relaxation as the venous system is refilled.

Figure 5 is redrawn from Fig. 6 of Folkow et al. (15). Figure 5 shows the pressures measured in the superficial muscle vein, the femoral vein, and the vena cava in cats with dependent limbs. Notice that the calf muscles were located 33 cm below heart level, producing a vena canal

pressure of 25 mmHg. Folkow et al. (15) reported that the muscle pump did not appear to facilitate muscle blood flow in this preparation unless there was a positive venous pressure. The top line in Fig. 5 shows the pressures observed during contractions, whereas the bottom line shows the pressures observed between contractions. Folkow et al. (15) stated that venous compression and therefore pressures would be expected to be greater in deeper muscle veins. The measurements of intramuscular pressure by Kirkebo and Wisnes (29) support this proposal. Figure 5 also reflects a hypothesis concerning the effects of these events on the vessels deep within the muscles (open symbols). The pressures are shown to be even higher in the deep veins during contraction. The events that would be observed immediately on relaxation of the muscle, as illustrated in Fig. 5, in these deep venous segments are also speculation on my part. However, it is clear from the data of Folkow et al. (15) that pressures fall throughout the muscle venous system on relaxation of the muscle and that the magnitude of this transient pressure decrease is greatest as one progresses from the vena cava toward the muscle. Therefore, I propose that in the smallest veins the pressures could even be negative as shown in Fig. 5. This notion is consistent with the facts that the muscles relax rapidly (50–100 ms) and that the 200- to 300-mmHg compressive force has been suddenly removed. It is possible that the relaxing muscle pulls open the empty collapsed veins, thus causing transmural pressure to be negative. The magnitude of the pressure fall observed in these veins and the period of time the pressures remain depressed will be determined by how fast blood can flow from the arterial side through the capillaries and into the empty venous segments. In experiments of Folkow et al. (15), it took up to 0.7 s for blood to refill the veins (as reflected in the time course of the return of venous pressures to precontraction values). Pollack and Wood (47) showed that the time course was 20–30 s in humans after mild

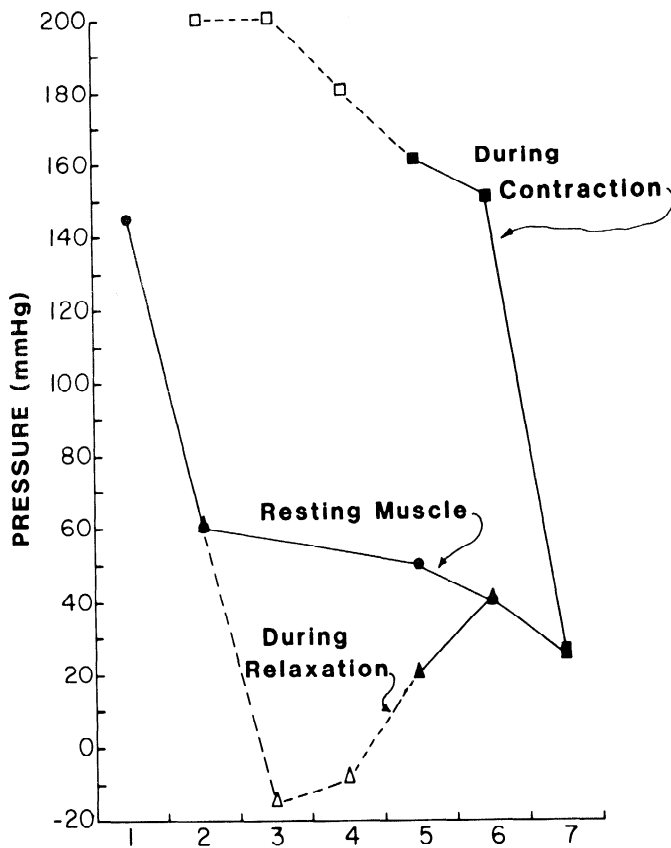


FIG. 5. Illustration of effects of muscle contraction on pressures in different segments of vasculature of calf muscles of dependent cat limbs. Data shown with solid symbols and lines are from Fig. 6 of Folkow et al. (15). Open symbols and broken lines are hypothetical data points. Vascular segments from left to right are 1, arterial pressure; 2, capillary; 3, venules; 4, deep muscle veins; 5, superficial muscle veins; 6, femoral vein; and 7, vena cava. Capillary pressure (2) represents sum of normal capillary pressure of 35 mmHg (13, 14, 20, 32) plus 25 mmHg due to hydrostatic column.

treadmill exercise (Fig. 4). Thus the time course may vary among species and among types of rhythmic muscle activity. Since arterial inflow continues throughout the relaxation period and there is generally no femoral venous outflow during relaxation (15), it is clear that the venous segments do not refill instantaneously. It appears that after contraction, there is a wave of venous segment filling (and venous pressure elevation) moving from the first set of venous values out to the systemic veins. If enough time is allowed between contractions, then the effect is dissipated. If on the other hand, another contraction occurs before the venous segments are completely refilled, then the venous pressures would remain depressed. Some segments of the venous system may continue to have near zero or negative pressures as shown in Fig. 5. In the preparation of Folkow et al. (15) one 250-ms tetanic contraction per second appeared to keep the venous segments from refilling, in that there was no venous outflow during relaxation. We have observed that (4, 36) rats running at 60 m/min have a stride or stroke frequency of 3.55 Hz. Gruner and Altman (22) indicate that rats spend an average of one-third of the stride cycle in the swing phase and two-thirds in the stance phase.

Thus these data indicate that there is even less time for venous segment refilling in rats during treadmill exercise suggesting that deep muscle venous pressures may remain depressed.

The relationship between venous pressure and the muscle pump seen in humans (16, 59) and isolated cat muscle (15) may present a problem for the proposed role of the muscle pump during exercise in rats. It is clear that the hydrostatic column results in high venous pressures in independent limbs of humans and that exercise causes decreases in these pressures (Fig. 4), but there is a very small or no hydrostatic column in rats. So how can the muscle pump work in rats? Although it is clear that positive venous pressures are necessary for the muscle pump to work, it is not clear how much above zero the venous pressures must be. The relationship between venous pressure and muscle pump efficacy has not been described in detail for any species. It seems reasonable that an optimum venous distending pressure exists and that this pressure will be different in different species (i.e., more pressure would be necessary to distend the veins in humans as compared with rats). It is clear that venous pressures in exercising rats are positive (8). Since data describing pressures throughout the venous tree in exercising rats are not available and since the correct venous pressure to measure (i.e., central, femoral, small vein, venous capillary) is unknown, further speculation does not seem appropriate. Finally, these interrelationships may all be different during locomotory exercise as compared with isolated cat muscles (15).

*Effects of type of muscle activity.* The muscle pump may be more effective in locomotory exercise than in the in situ/in vitro models of exercise. This notion is based on two major differences between the way muscles contract in these types of activity: the sequence of muscle fiber activation and the type of contraction. In most models of exercise, all fibers within the muscle or muscles being studied are activated simultaneously. On the other hand, in locomotion, the time during the stride cycle at which different muscles and groups of muscles are active varies so that each muscle has a unique time (or times) of activity (6, 12, 19, 22, 60). Even within a muscle, it appears that the recruitment of fibers is not simultaneous in locomotory exercise (22). Thus, in locomotory exercise the rhythmic contractions are more sequential, allowing a greater potential for the muscle pump. The sequential activation of skeletal muscles in locomotory exercise may provide for a more effective pumping action on the veins of the skeletal muscle in the limbs somewhat like a wave of contraction traveling from the apex to the base of the heart is most efficient for cardiac pumping. Although it is clear that the heart is an extreme example of the effects of sequential activation, this example illustrates the concept that the efficacy of any such pump is not only determined by the maximal pressure developed but perhaps equally (if not more importantly) by the spatial and temporal sequence of the pressure development and by the precontraction vascular volume (similar to the ventricular end-diastolic volume) (15, 16).

A second major difference between locomotory exercise and models of exercise is that locomotion includes muscle



contractions during active lengthening and shortening phases of the stride cycle as well as passive lengthening movements (12, 22, 35). The extensor muscles actively shorten during the push-off phase of the stride cycle. This would be expected to squeeze blood out of the small veins toward the heart (15). In locomotion, impact with the ground can produce muscle tensions and pressures within the muscles that are often higher than the tension the muscles can produce in shortening contractions (60). During the swing phase of the stride cycle when the limb is being returned to position for the next step and the muscle is being stretched, dramatic decreases in pressure may occur in the microvasculature thereby facilitating the inflow of arterial and capillary blood into the small veins. I presume that this filling begins between the first set of venous valves and the capillaries. However, the distribution of pressures throughout the microcirculation and the sequence of venous refilling under these conditions is unknown.

The spatial distribution of the fibers from a given motor unit within muscles would be expected to decrease the impact of the muscle pump on muscle perfusion. However, single motor units are generally not activated during locomotion. Rather, many motor units with fibers distributed in similar locations within the muscles appear to be activated at similar times (6, 12, 22). Although the effects of locomotory gait on muscle flow have not been studied in detail, Pollack and Wood (47) observed that the efficiency of the muscle pump appeared greatest (as reflected in ankle venous pressures) at a treadmill speed of 1.7 mph in their 10 human subjects and that this efficiency was not influenced by the incline of the treadmill. Thus, when their subjects exercised on a 20° incline or at treadmill speeds of 2.6 and 3.3 mph, the average ankle venous pressures averaged 22–24 mmHg (decreased 60–65 mmHg) much like the responses shown in Fig. 4. Pollack and Wood (47) proposed that the muscle pump would be less efficient during exercise at treadmill speeds <1.7 mph based on their observations of the changes seen during slowing of the treadmill at the completion of exercise bouts. Currently available data do not allow a detailed analysis of the effects of stride frequency, stride length, and other gait-related factors on the muscle pump. This important area deserves further study.

*Role of muscle pump in exercise hyperemia.* The data for the highest blood flows measured in three types of rat skeletal muscle with three types of activity (twitches, tetanic trains, and treadmill exercise presented in Fig. 3) are consistent with the hypothesis that the muscle pump represents one mechanism to explain why muscle blood flow is higher during treadmill exercise than in *in vitro/in situ* models of exercise. It is also possible that the reason that muscle blood flows in high-oxidative muscle tissue (soleus and red gastrocnemius muscles) are higher during tetanic trains of contraction as compared with twitch contractions is that trains of brief tetanic contractions are associated with a more efficient muscle pumping action. One possible reason that trains of tetanic contractions do not produce similarly elevated blood flows (compared with twitch contractions) in the

white gastrocnemius muscle could be that the white muscle is located superficially in the leg. Kirkebo and Wisnes (29) have shown that the increment in muscle tissue pressure is greater in deep than in superficial regions of the contracted calf muscles of rats. Therefore, the veins within the white muscle may be exposed to a smaller increase in tissue pressure and perhaps less muscle pumping action. On the other hand, the muscle-pump component of flow to the white muscle may be relatively less because of lower vascularity (lower venous blood volume per gram of muscle) and the resultant lower “stroke volume.” When this approach is taken one step further, blood flows to the high-oxidative muscles may be higher during treadmill exercise than during trains of tetanic contractions (Fig. 3), again because of a greater contribution of the muscle pump to perfusion during locomotory exercise. The data presented in Table 1 suggest that the magnitude of blood flows presented in Fig. 3 for rats are similar to those seen in other mammals under similar conditions.

Mackie and Terjung (38) used synchronous activation of motor nerves resulting in simultaneous activation of all fast and slow muscle fibers within the muscles. As discussed above, the normal muscle activation patterns could produce a more efficient pumping action on the vasculature. The tetanic contractions elicited in these studies (38) were isometric (as are most *in vitro/in situ* experiments), whereas treadmill exercise includes lengthening and shortening contractions. It is reasonable that changes in muscle length (as described above) during the stride cycle would also produce a more effective muscle pump. Thus these data are consistent with the importance of the muscle pump during normal exercise.

Another approach to quantifying the apparent effect of the muscle pump on muscle perfusion is to consider the vascular conductances calculated under the different conditions as illustrated in Fig. 2 [one reason for conducting the studies that produced the data from resting muscle tissue presented in Figs. 1 and 2 (37) was to gain an appreciation for the potential or maximal vascular conductance in skeletal muscle in the absence of any mechanical effects]. Given that the data presented in Fig. 2 represent perfusion pressure specific conductances, if it is assumed that all four preparations are in a state of maximal vasodilation (i.e., all vascular smooth muscles are relaxed), then the difference between the estimates of vascular conductance can be attributed to the contractile activity of the skeletal muscle. The data from the white fast-twitch muscle indicate that the peak calculated vascular conductance is about the same for each type of rhythmic muscle contraction, whereas the peak vascular conductance of resting muscle is less. These data suggest that any type of rhythmic muscle contraction can produce a similar amount of muscle pump contribution to perfusion in fast-twitch glycolytic muscle. However, the data indicate that the situation is different for the high-oxidative muscle tissue. The slow-twitch (soleus) and fast-twitch (red gastrocnemius) high-oxidative rat muscle appear to have the highest conductance during treadmill exercise. The fast-twitch high-oxidative muscle vascular conductance shown in Fig. 2



progressively increases from left to right (resting vasodilated < twitch-type contractions < tetanic contractions < treadmill exercise). The calculated vascular conductance for the soleus muscle was quite similar in papaverine-vasodilated resting muscles and during twitch and tetanic type contractions, whereas running produced an apparently greater vascular conductance in the soleus. Thus all three types of skeletal muscle appear to have greater vascular conductances during rhythmic contractile activity than during papaverine vasodilation in resting muscle. Furthermore, locomotory exercise produces the greatest value for vascular conductance in the soleus (slow-twitch oxidative) and red gastrocnemius (fast-twitch oxidative-glycolytic) muscles.

Although I have used calculated vascular conductances in this analysis (Fig. 2), it is clear that if these differences among conductance values are the result of the muscle pump, the apparent increase in vascular conductance observed during contraction is actually the result of increased energy imparted to the blood by the muscle contraction and not due to increased diameter of resistance vessels. If we return again to the results of Folkow et al. (15), the peak venous outflow observed during contraction ranged between 80 and 170 ml/min under various conditions. Although the diameter of the flow probes used is not given, the size of the veins in this preparation suggests that the velocities of flow were very high during the "spurt" of blood. This observation serves to emphasize the fact that the muscle pump may facilitate blood flow by at least two mechanisms: decreased venous pressures and increased total kinetic energy in the system. Thus the total energy gradient available to force blood through the muscle vascular bed is increased. Because of the assumptions used to calculate the vascular conductances presented in Fig. 2, this increased energy appears to be increased conductance. These considerations should make it clear why one cannot apply Ohm's law across a vascular circuit that is broken up by a pump that adds energy (the muscle pump).

Not all investigators have considered the effects of perfusion pressure (transmural pressure) on the estimates of vascular conductance. As indicated above, a unique maximal vascular conductance cannot be determined. However, for the sake of argument, assume that one can measure a unique value for maximal vascular conductance in skeletal muscle. The literature indicates that calculated peak vascular conductances in skeletal muscle are in the range of  $0.18\text{--}1.2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1} \cdot \text{mmHg}^{-1}$  (9, 17, 25, 27, 28, 40). In isolated perfused rat hindquarter preparations (as used in Fig. 1) the estimates are in the range of  $0.1\text{--}0.2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1} \cdot \text{mmHg}^{-1}$  (32, 37). Thus a conservative estimate of maximal vascular conductance for resting muscle appears to be 1.4 (indeed, the value for soleus in Fig. 2 is the highest value for muscle vascular conductance of which I am aware). If we assume that this is maximal conductance for average skeletal muscle, then it would take a perfusion pressure of 179 mmHg to drive muscle blood flow at a rate of  $250 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$  ( $1.4 = 250/P$ ). Since arterial pressures are usually in the range of 130–150 mmHg in rats during exercise, the muscle pump appears to provide

$\sim 30\text{--}50 \text{ mmHg}$  of additional energy (kinetic and/or potential) during dynamic exercise in rats (arterial pressures are  $\sim 130 \text{ mmHg}$  in the studies included in Figs. 2 and 3). This represents 27% of the total estimated energy used in muscle perfusion and is close to the estimate of Stegall in humans (59). It is important to realize that if we had used 0.2 for the average conductance value rather than 1.4 then the apparent muscle pump effect would be even greater. Thus this is a conservative estimate. Similar calculations (using the appropriate data for the specific muscles shown in Figs. 1–3) indicate that during treadmill exercise in rats, the muscle pump may provide as much as 30 and 60% of the total energy for perfusion of the soleus and red portion of the gastrocnemius muscles, respectively.

*Effects of muscle contraction on fluid balance.* Another important effect of the muscle pump during vasodilation associated with muscle contraction and/or exercise relates to fluid balance within the muscles (20). If a resting muscle or rat hindquarter preparation is maximally vasodilated and perfused at an arterial pressure of 130 mmHg (similar to the perfusion pressure seen during intense exercise), the result is an increase in mean capillary pressures, massive filtration, edema formation, and ultimately, zero flow (14). This is observed because the arterial pressure at which no net fluid filtration is seen (isogravimetric conditions) across the capillaries of maximally dilated skeletal muscle preparations are consistently in the range of 30–50 mmHg (14, 32, 37). Therefore, during vasodilation in resting skeletal muscle, any increase in arterial pressure above these levels (30–50 mmHg) will cause the filtration of fluid from blood to tissue. This increased filtration causes increased tissue pressure, which reduces arterial transmural pressure and therefore reduces flow. During maximal exercise when the resistance vessels are dilated, blood flows are extremely high, and perfusion pressure is increased, it would be expected that fluid balance would be a problem. The pumping action of muscle contraction on lymph vessels and lymph flow have been known for years (10, 20, 55). Tissue pressures are also increased during the muscular contraction of exercise thus decreasing the net filtration forces across the capillary wall (20). Thus another reason that apparent peak blood flows are higher during muscle contraction as compared with maximal vasodilation of resting muscle may be the effects of the muscle pump on fluid balance in the muscle.

*Caveat.* The rationale applied to the data in Fig. 2 up to this point has been based on the assumption that maximal vasodilation was attained in the resting skeletal muscle (37). Although it is clear that Laughlin and Ripperger (37) attained maximal papaverine vasodilation, it is difficult to establish that all smooth muscles are relaxed in such a preparation when the vasodilators are given in the arterial blood (27, 33, 54, 56). For example, vasodilators may be more effective in producing relaxation when the agents approach the smooth muscle cells from the tissue rather than diffusing through the vessel walls. Also, given the fact that perfusion is heterogeneous in resting muscle before and after vasodilation, it is possible that the concentrations of drug vary

throughout the vasculature of the rat hindquarters. There is also evidence that vascular smooth muscle myogenic effects may be involved in producing vasodilation during muscle contraction (28, 50, 54, 56, 57). In addition, combinations of vasodilators often produce greater vasodilation than the maximal effect produced by any one agent (33), and it appears that exercise hyperemia is a result of an orchestration of multiple vasodilator factors. Thus it is possible that active muscle releases some, as yet to be determined, vasodilator that produces the added vasodilation (28, 36, 50, 55, 57–59). Although these problems are not unique to the experiments of Laughlin and Ripperger (37), the notion that it is not possible to obtain maximal vasodilation (or the degree of vasodilation seen in active muscle) in resting muscle preparations with intra-arterial infusions must remain as one possible explanation of the differences in vascular conductance between resting and active muscles as illustrated in Fig. 2.

#### *Skeletal Muscle Blood Flow Capacity and Determinants of Maximal Muscle Blood Flow*

Now we come full circle to ask, What is skeletal muscle blood flow capacity? and What are the major determinants of muscle blood flow during exercise? In reference to muscle blood flow capacity, it is clear that flow capacity is different in different types of skeletal muscle (Fig. 1) and will vary within a given type of muscle depending on the methods used for estimating flow capacity (i.e., pharmacological vasodilation of resting muscle or one of the methods of studying exercise hyperemia) (Fig. 3).

We know from Poiseuille's law that blood flow is the result of the interaction of the driving force (pressure gradient plus kinetic energy) and the conductance of the vascular bed being considered. Thus

$$BF = (P_a - P_v) \times MVC \quad (1)$$

where BF is blood flow,  $P_a$  is arterial pressure,  $P_v$  is venous pressure, and MVC is the muscle vascular conductance measured at  $P_a$ . On the basis of the data of Folkow et al. (15), it seems reasonable to include the contribution of the muscle pump to the driving force for blood flow by reflecting a decrease in  $P_v$ . It is possible that  $P_v$  in the small veins just before the first value is negative. When Eq. 1 is considered, there are three major determinants of maximal blood flow:  $P_a$ ,  $P_v$ , and maximum MVC. As stated above,  $P_a$  is often increased during intense dynamic exercise. This may be one component of the controversy in the literature about maximal blood flow in skeletal muscle. Many in vitro/in situ models of exercise use perfusion pressures considerably less than 130 mmHg. The third term in Eq. 1, MVC, can be determined for any given muscle (37, 48). There is evidence that peak MVC is related to muscle fiber type (27, 35, 37, 38), the oxidative capacity of the muscle, and the state of training of the subject (31, 35, 37).

The determination of the appropriate  $P_v$  and separation of the direct effects of  $P_v$  and the effects of the muscle pump on "effective"  $P_v$  is at the heart of this discussion. The efficacy of the muscle pump and there-

fore the magnitude of the decrease in  $P_v$  in Eq. 1 could be influenced by at least six factors: 1) the type of stimulation for the contractions (twitch, sustained tetanus, tetanic trains, or normal muscle fiber recruitment), 2) type of exercise and the magnitude of muscle-length changes during the exercise (isometric, swimming, sprinting, jogging, etc.), 3) muscle fiber type and location within muscles and muscle groups (deep vs. superficial), 4) vascular arrangement within the muscles being considered, 5) function of the venous valves (e.g., varicose veins, venous hypertension, or congestive heart failure) (11, 46), and 6) the effects of gravity and/or the venous transmural pressures (15, 16). It is clear that under some circumstances (i.e., isometric, sustained contractions, or when venous pressures are less than or equal to zero) the net effect of contraction is decreased MVC (i.e., contraction impedes blood flow), whereas under other circumstances the net effect is to decrease  $P_v$  (i.e., contraction facilitates blood flow).

In conclusion, the term maximal blood flow is a misnomer and it is not possible to measure a unique maximal muscle blood flow. However, it is possible to estimate the potential of the vascular bed of skeletal muscle for blood flow as reflected by perfusion pressure specific vascular conductances and/or blood flows. It appears that blood flow capacity is different in skeletal muscle composed of different fiber types. Also, with similar arterial pressures, peak blood flow to skeletal muscle during rhythmic contractions is greater than can be produced in pharmacologically dilated resting skeletal muscle. Two major causes of this difference appear to be 1) variations in the mechanical effects of contractions and the efficacy of the muscle pump during the different types of muscle contraction, and 2) the fact that the maximal effect of vasodilating drug may not represent complete vasodilation throughout the vascular bed. The available data do not prove that the muscle pump is a significant determinant of the perfusion of contracting skeletal muscle, but are consistent with this hypothesis. Therefore, I believe this hypothesis deserves further consideration. If this hypothesis is correct, then during normal dynamic exercise skeletal muscle blood flow is determined not only by vascular conductance and the perfusion pressure gradient but also by the contribution of the muscle pump.

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