HIGHLIGHTED TOPIC | Skeletal and Cardiac Muscle Blood Flow

Ideas about control of skeletal and cardiac muscle blood flow (1876–2003): cycles of revision and new vision

Loring B. Rowell
Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, Washington 98195

Rowell, Loring B. Ideas about control of skeletal and cardiac muscle blood flow (1876–2003): cycles of revision and new vision. J Appl Physiol 97: 384–392, 2004; 10.1152/japplphysiol.01220.2003.—This perspective examines origins of some key ideas central to major issues to be addressed in five subsequent mini-reviews related to Skeletal and Cardiac Muscle Blood Flow. The questions discussed are as follows, 1) What causes vasodilation in skeletal and cardiac muscle and how much is vasomotor (vasoconstrictor) control of muscle vascular conductance and muscle blood flow significantly blunted in exercise by muscle metabolites and what might be a dominant site of action? 2) What reflexes initiate neural control of muscle vascular conductance so as to maintain arterial pressure at its baroreflex operating point during dynamic exercise, or is muscle blood flow regulated so as to prevent accumulation of metabolites and an ensuing muscle chemoreflex or both? 3) To what extent is neural control of muscle blood flow (via muscle pumping) to muscle blood flow, including its effect on cardiac output? 4) Is neural (vasoconstrictor) control of muscle vascular conductance and muscle blood flow significantly blunted in exercise by muscle metabolites and how strong is the continuity of science. Since 1876, the value and importance of these ideas persist; without knowledge of them, we risk needless repetition and loss of the way toward better ones.

JOHN HUNTER stated that “blood goes where it is needed” (1794). John Hunter’s intuition was often superb; he must have wondered how a system “knew” where flow was needed and how the right amount got to the right place. He must have suspected that metabolism (need) was involved. Sir William Harvey pointed to the importance of mechanical factors in 1628. Vasomotor nerves were discovered by F. Pourfois du Petit in 1727, and Hunter may have pondered neural vasodilation as well. Experimental glimpses of metabolic, neural, and mechanical control of muscle blood flow (MBF) began late in the 19th century. Enthusiasm for these three ideas waxed and waned cyclically with periodicity depending on satisfaction of each generation with new vs. old answers. These ideas are the backbone of this historical perspective, as are four related questions. 1) What causes the vasodilation? 2) What is muscle’s mechanical contribution to its own blood flow, including its effect on cardiac output? 3) To what extent is neural (vasoconstrictor) control of MBF blunted by muscle’s metabolism? 4) What reflexes initiate neural control of muscle vascular tone?

A historical perspective exposes a chain of ideas that reveals the ability to build on the findings of others and thus provide that strength that is the continuity of science. Since 1876, the value and importance of these ideas persist; without knowledge of them, we risk needless repetition and loss of the way toward better ones.

JOHN HUNTER stated that “blood goes where it is needed” (1794). Published posthumously.

Address for reprint requests and other correspondence: L. B. Rowell, Box 357290, Dept. of Physiology and Biophysics, University of Washington School of Medicine, Seattle, WA 98195.

METABOLIC VASODILATION IN SKELETAL MUSCLE
Metabolites, Myogenic Reactions, and Osmolality

The causes of hyperemia in active skeletal muscle and in cardiac muscle have been sought for over a century. Latschenberg and Deahna (in 1876) and Gaskell (in 1879) proposed that muscle vascular tone is inhibited by metabolites released during contractions. Although the earliest studies focused on causes of reactive hyperemia after arterial occlusion, which is similar but not the same as exercise hyperemia, many findings were important, particularly those of Lewis and Grant (33) in 1925 and Fleisch and colleagues (18, 19) in the 1930s. In 1879, Roy and Brown disproved the view that reactive hyperemia was caused by paralysis of vasomotor nerves; denervation did not prevent it. Also, over the past decades, significant neurogenic vasodilation in active human skeletal muscle, a recurrent theme, was gradually ruled out (25). In 1902, Bayliss postulated that vasodilation might be linked to a myogenic reaction to reduced vascular transmural pressure during contractions. Mohrman and Sparks (38) reported a small myogenic-like “vasodilation” with brief tetanic contractions, probably partly attributable to passive refilling of vessels emptied by compression, as was clearly so with reactive hyperemia.

Thomas Lewis [as cited in Lewis and Grant (33)] was the first to apply quantitative methods to investigate hyperemia. His plethysmographic measurements of human forearm blood flow confirmed the metabolic hypothesis and refuted the myogenic hypothesis by demonstrating reactive hyperemia in response to either arterial or venous occlusion. Lewis’ proposal...
that metabolites causing vasodilation must be relatively non-diffusible is important in considering how vasodilation is caused and maintained, especially when based on venous concentrations of metabolites and when (or if) metabolites appear in venous drainage. Lewis saw his main problem, which persists today, as the inability to define changes in muscle per se separated from other tissues. This stemmed from the presence of collateral vessels and mixed venous drainages from various stressed and unstressed tissues.

Although Fleisch and coworkers’ pump perfused their cat hindlimbs, their extensive and thorough studies of vasoactive properties of anions of a large number of organic acids that are normal intermediates of metabolism are still, 70 years later, regarded as classics. They and Lewis were the first to show the minor effects of reduced arterial O2 content. Fleisch and Sibul (18) considered vasodilation due to increased H+ concentration to be important. Lewis felt that vasodilation attributed to CO2 was due to change in pH and not CO2 per se. Fleisch and Weber (19) found phosphorylated “metabolites” (compounds) and high-energy phosphates to be potent vasodilators (along with H+ concentration); adenosine compounds were especially powerful vasodilators (in 2003, we are still on Fleisch’s track).

Of particular importance is the observation of Fleisch and Sibul (18) that combinations of metabolites elicited greater vasodilation than predicted by simple summation. The potential role of combinations of substances on metabolic vasodilation reappeared in the demonstration of Mellander and Lundvall (cited in Ref. 37) that increased interstitial osmolality produced by accumulated metabolites could itself cause vasodilation. In 1970, Skinner and Costin (56) revealed that the combined effects of K+, hyperosmolality, and decreased Po2 exceeded the sum of their individual effects.

Important reviews by Haddy and Scott in 1968 (22), Mellander and Johansson in 1968 (37), and Shepherd in 1983 (52) summarized evidence that includes, for example, K+, H+, O2, CO2, phosphate ions, adenosine, adenine nucleotides, intermediates of the Krebs cycle, vasoactive peptides, lactate, and so on. These reviews (37, 52) also listed the essential criteria that must be met by any putative mediator of exercise hyperemia. So far, no combination of these substances has mimicked exercise hyperemia (31); even worse, these substances lacked any sustained effect as contraction continued (57). Venous and interstitial K+ concentration decreases with duration of exercise, owing to activation of the Na+-K+-ATPase pump (57). Hyperosmolality is gradually diminished by capillary fluid exchange. Thus vasodilator stimuli seem to disappear, whereas vasodilation continues, suggesting either that we are not measuring the “correct” vasodilators or that substances that initiate vasodilation with exercise are not those that sustain it. Bear in mind that in many studies venous concentrations of metabolites are exaggerated because MBF is often restricted by the experimental procedures. So far, the evidence that all of these metabolites together must cause the hyperemia of exercise is largely circumstantial.

Local Neural Influences

Local neural influences were proposed by Hilton in 1959 (cited in Ref. 51) in which excitation of intrinsic neurons within the blood vessel wall spread vasodilation through arteries within active muscle. Honig and Frierson (24) thought that these neurons released peptidergic transmitters that initiate the rapid onset of vasodilation with contractions (metabolic vasodilation was correctly assumed to be too slow). Segal and colleagues (cited in Ref. 51) proposed that an intramuscular arteriolar network functions like a syncytium over which vasodilation can be propagated so that diffuse vasomotor stimuli can yield summated microvascular responses. Experiments of Segal and Duling advanced ideas by Honig and Frierson but revealed that arteriolar vasodilation is spread from cell to cell by electronic propagation across gap junctions rather than by intrinsic neurons (cited in Ref. 51).

The Vascular Endothelium

In 1980, the accidental discovery of Furchgott and Zawadzki (cited in Ref. 20) of the role of vascular endothelium as a modulator and/or initiator of vasomotor responses has, thanks to their perceptive follow up, begun a new chapter (20). Some vasodilators exert their effects on vascular smooth muscle by stimulating the release of nitric oxide (NO). An increase in flow velocity or shear stress in the arteries and arterioles will elicit an endothelium-dependent vasodilation. In skeletal muscle, prostaglandins appear to be important mediators of this vasodilation rather than NO (28).

Here, two postulates may merge: the role of adenosine as a muscle vasodilator (still questioned) and the importance of endothelium derived factors. Marshall (35) found that, in hypoxia, muscle cells contribute little to adenosine release, but adenosine is released from the vascular endothelium and acts on A1 receptors to cause significant NO-dependent vasodilation. In this case, the vasodilation serves mainly to decrease heterogeneity of intramuscular flow distribution. Acting similarly, other local vasodilators such as acetylcholine leaked from motor nerve endings (51) or ATP released from red blood cells (14) may play important roles in local vasodilation and its coordination with local demands rather than in altering global flow to the muscles.

Conversely Rådérgran and Hellsten (cited in Ref. 43) found that, in normoxic, active human muscle, adenosine does not appear to regulate vasodilation. Use of adenosine agonists and antagonists and NO synthase inhibitors yielded no convincing evidence of significant regulation of MBF by adenosine or NO. In most studies that employed NO synthase inhibitors to abolish effects of NO on human forearm blood flow during arm exercise, no effects on MBF were seen, but there are some effects at rest and postexercise [see Rådérgran for recent review (43)].

Apparently, when muscles are electrically stimulated to contract, adenosine may play a role in vasodilation. The abnormal patterns of fiber recruitment and force development can cause local areas of ischemia (29, 45). Is there a missing vasodilator or dilators? Is the conclusion that the mix of vasodilators already described cannot explain the high MBF observed during exercise justified? Because flow is pressure dependent, what we really seek is the degree of vasodilation or the muscle vascular conductance (MVC). The problem is that active muscle is a pump (see below) that adds hydraulic energy to the system. Therefore, “conductance” is really a virtual conductance, only part of which is due to vasodilation. Perhaps the metabolite contribution added to that of the muscle pump will prove sufficient to explain MBF during exercise.
META BOLIC VASODILATION IN CARDIAC MUSCLE

This section focuses on a question: do skeletal and cardiac muscles differ significantly in their mechanisms of metabolic control of blood flow?

Cardiac muscle has little capacity for anaerobic metabolism, and since arterial–venous \( \dot{V}O_2 \) difference is \( \approx 15 \text{ ml/100 ml at resting heart rate (HR)} \) (cardiac muscle has no inactive state) coronary blood flow and metabolism must be closely matched. However, the matching is similar for human quadriceps muscle during mild to peak exercise in both normoxia and hypoxia; femoral venous \( \text{PO}_2 \) and \( \text{O}_2 \) contents parallel those in the coronary sinus across the range of \( \dot{O}_2 \) uptake (\( \dot{V}O_2 \)) (16, 48) [this is not true in whole body exercise because sympathetic vasoconstriction reduces flow in active muscles and thereby raises muscle \( \text{O}_2 \) extraction (47)].

The traditional view is that, in skeletal muscle, unlike cardiac muscle, metabolism is partly anaerobic at onset of exercise ("\( \text{O}_2 \) deficit") and again becomes partly anaerobic at some "anaerobic threshold" as metabolic rate rises. This view is damaged by the discoveries by Jobis and Stainsby (1968), Connett et al. (1983, 1984, 1986), and Conley et al. (1998) (all cited in Ref. 11) that muscle glycylisis and lactate production occur under fully aerobic conditions. Also, at onset of exercise, intramuscular \( \text{PO}_2 \) and \( \text{O}_2 \) extraction do not change immediately (\( \text{PO}_2 \) often rises transiently) (5). Afterward, \( \text{PO}_2 \) falls (and \( \text{O}_2 \) extraction increases), but it does not reach values that limit \( \dot{V}O_2 \) up to peak values (11), as is also true in cardiac muscle (16).

Surprisingly, at peak blood flows per 100 g, \( \dot{V}O_2 \) and \( \text{O}_2 \) extraction appear to be similar for both cardiac and skeletal muscle (peak flows = 250–400 ml/100 g \( \cdot \text{min}^{-1} \)) (31) despite the far greater capillary density (16) and apparently less potential for diffusion limitation for \( \text{O}_2 \) in the heart than in skeletal muscle (unless average capillary mean transit time is shorter in heart muscle).

Perspectives on what agents might dilate coronary vessels differ from those concerning skeletal muscle. Cardiac investigators conclude that "the" mechanism for coronary vasodilation is unknown. This conflicts with mainstream ideas concerning skeletal muscle vasodilation, which hold that many or even all substances released from active muscle cells are vasoactive and together might explain the "metabolic vasodilation" and in conjunction with mechanical factors might explain the rise in MBF. The absence of valves in coronary veins suggests that no cardiac muscle pump exists. Nevertheless, compression of myocardial vessels could occur in a manner, both temporally and spatially, such that additional force could drive more blood out of muscle as it does to a small extent during leg exercise in patients lacking venous valves (6).

The coronary physiologist has focused mainly on \( \text{O}_2 \), \( \text{CO}_2 \), ions, osmolality, \( \text{NO} \), prostaglandins, and adenosine and has concluded that none will suffice individually to explain metabolic vasodilation. What about their combined effects along with those offered by Fleisch in the 1930s? An interesting argument is that blockade of one putative coronary vasodilator may be ineffective because some other vasodilators simply increase their concentration to make up the deficit. Unless the deficient agent is adenosine (uniquely sensitive to tissue \( \text{PO}_2 \)), what would be the stimulus to raise the others?

Various tests for potential coronary vasodilators have yielded essentially the same findings in skeletal muscle (3, 52, 62). Adenosine was a strong candidate for coronary vasodilation (Berne, 1963) (cited in Ref. 16) owing to the close link between its production and low cellular \( \text{PO}_2 \). It is an effective coronary vasodilator in ischemic or hypoxic hearts and contributes to vasodilation in hypoxic skeletal muscle (35) but not in either organ in normoxic and steady-state conditions (62).

A final comparison of the two circulations reveals the dominance of \( \alpha_1 \)-adrenoceptors on the large resistance arterioles of the heart and oxidative skeletal muscle (see below), whereas the small arterioles controlling capillary perfusion and flow distribution in the heart have \( \beta \)-adrenoceptors (62). Sympathetic noradrenergic stimulation in the heart causes these small vessels to vasodilate while constricting the large arterioles. In skeletal muscle, the small arterioles possess \( \alpha_2 \)-adrenoceptors, which are made less effective by metabolites. Thus, in both circulations, the net effects of sympathetic noradrenergic stimulation on large as opposed to small arterioles are similar. Other than the lack of venous valves and some \( \beta \)-adrenergic control of coronary arteriolar resistance, functionally significant differences in control of coronary and skeletal muscle circulations are not obvious, either because control of neither is understood or because they are not different.

THE SKELETAL MUSCLE PUMP: HOW WELL DOES IT WORK?

The muscle pump first received attention from William Harvey in 1628. John Hunter (1794) described the importance of muscle contraction in reducing orthostatic edema. More precise observations were made by Sadler (1869) and by Gaskell (1877) who observed a large rise in blood flow at the beginning of contraction, low flow during sustained contractions (or none depending on mode and force of contraction), and high flow during relaxation (36). Burton-Opitz in 1902 and later Anrep and von Saalfeld (2) used the only available (crude) "flowmeters" to measure more precisely the patterns of flow just described (see references in Ref. 36).

Experimental studies on humans by Leonard Hill (1909), D. R. Hooker (1911), and August Krogh (1929) all revealed that, when upright humans begin to walk, pressure in superficial (skin) veins of the ankle fell suddenly below hydrostatic pressure (cited in Ref. 36). In 1936, Beecher, Field, and Krogh (4) deduced that most venous return from superficial leg veins was drawn via (1–2 mm diameter) perforating veins into deep muscle veins where average (per step) pressure was lower and could fall to negative values at the instant of each muscle relaxation. In 1949, Pollack and Wood (41) saw that it took six to seven walking steps to reduce ankle vein pressure from 90 to \( \approx 25 \text{ mmHg} \). This slow decline was thought to be a consequence of the cutaneous venous blood being forced through the small perforating veins to deep veins. Note that according to Gray’s Anatomy of the Human Body (20a) “during relaxation of calf muscles [after contraction] blood is actually aspirated from the superficial into the deep veins.” This was demonstrated angiographically in the human calf in 1962 (cited in Ref. 53). The point is that aspiration of blood through small high-resistance perforating veins must require substantial negative pressure in the deep veins, which are securely tethered to
surrounding muscle and thus suddenly pulled open while empty when muscle relaxes (Bader 1963 [cited in Ref. 47]).

The actual pressure generated by the muscle pump is unknown; however, in 1949 Barcroft and Dornhorst (cited in Ref. 23) showed that contracting muscles could increase their venous outflow against back pressures of 90–100 mmHg. In 1966, Stegall (58) estimated that the muscle pump provides about one-third of the energy for muscle perfusion in upright humans. He assumed that muscle venous pressure was reduced to 20 mmHg between contractions rather than to the large negative values calculated by Sheriff et al. (53) and Toska and Ericksen (60).

The volume of blood mobilized from human muscle veins by the muscle pump has been estimated by both Sheriff and Ludbrook to be ~450 ml with rhythmic contractions in zero load conditions (cited in Ref. 47). For perspective, when an upright human starts to walk, within two to four heart beats, the load conditions (cited in Ref. 47). Flamm et al. (17) demonstrated in cycling humans theinal pumps make an unknown contribution to this translocation before re

and pelvic organs are suddenly translocated back to the heart before reflexes have time to assist. The respiratory and abdominal pumps make an unknown contribution to this translocation (47). Flamm et al. (17) demonstrated in cycling humans the effectiveness of muscle pumping, which reduced the steady-state volume of technetium-99m-labeled red blood cells in the legs by 22–30% and raised heart and lung volumes by 20–30%.

Can the Muscle Pump Raise MBF by Its Effects on the Heart?

In the 1950s, Rushmer among others dismissed any importance of the muscle pump in maintaining central venous pressure (CVP) and end-diastolic volume (EDV) and cardiac stroke volume (SV). Their view was that the heart by itself could provide the blood flow required for exercise by simply increasing its rate and force of contraction (cited in Ref. 47). Conversely, in 1962 Guyton et al. (21) argued that the heart by itself cannot raise its output more than a few percentage points unless some “event” in the peripheral circulation translocates blood volume from the vasculature back to the heart. In accordance with Guyton et al., Sheriff et al. (55) showed in conscious dogs that any attempt to significantly raise cardiac output at rest by ventricular pacing was partially counteracted by the fall in CVP and SV owing to the flow-dependent redistribution of blood volume from central to peripheral vessels. Furthermore, similar attempts to raise cardiac output above its normal level in voluntarily exercising dogs were again counteracted by a fall in CVP and SV because any rise in flow went mainly to nonpumping organs (55).

We have a paradox; cardiac output is a determinant of CVP, EDV, and SV because an increase in blood flow increases peripheral vascular volume at the expense of central vascular volume, which in turn reduces CVP, EDV, and SV (i.e., total volume is constant). However, EDV is also a determinant of SV and cardiac output (Starling’s law). Perhaps the greatest contribution of Guyton was getting us to understand the negative effect of increased cardiac output on EDV and SV and also to realize this effect could only be counteracted by another pump in the peripheral circulation to reduce its volume (e.g., see Ref. 21). It works as long as muscle venous valves are competent. Otherwise, cardiac output, EDV, and SV cannot rise normally with exercise (6).

Can Contractions per se Increase MBF?

A new wave of challenges to traditional concepts about the muscle pump focus on whether it can actually raise MBF by increasing the arterial-venous pressure difference across the muscle (30). In 1987 and 1996, Laughlin and colleagues (29, 31) and Sheriff and colleagues (24a) reviewed the evidence. Laughlin and colleagues emphasized problems associated with electronically induced aberrant contractions, namely markedly reduced peak MBF and ineffective muscle pumping. They noted that peak conductance in resting muscle “maximally” vasodilated with drugs was far below virtual peak “conduc-tance” during voluntary contractions (as though pumping raised flow).

One event that has spurred discussion is the large and almost instantaneous rise (1–2 s) in virtual MVC at onset of dynamic exercise followed by a secondary rise in ~5 s, probably owing to metabolic vasodilation (43, 53, 61). Is the fast response caused by the muscle pump or by virtually instantaneous vasodilation (and diffusion)? It is neither neurogenic, myogenic, nor due to withdrawal of sympathetic vasoconstriction (53). It is also not caused by release of endothelial factors, K+ osmolality, adenosine, or leakage of neuronal acetylcholine (all are too slow except for K+). It is also not caused by release of endothelial factors, K+ osmolality, adenosine, or leakage of neuronal acetylcholine (all are too slow except for K+). (12, 43, 53, 57). Alternatively, sudden aspiration of blood through the muscle by the muscle pump could cause O2 delivery to transiently exceed muscle VO2, thus delaying the rise in O2 extraction and the fall in muscle PO2. This apparently happens (3, 5).

A particularly revealing event accompanied the onset of dynamic exercise when Sheriff et al. (53) kept cardiac output constant at resting levels (pacing with atrioventricular block). The usually fast rise in virtual MVC with exercise was accompanied by a 40-mmHg fall in mean systemic arterial pressure (SAP) in 1 s and a rise in CVP rather than the fall that would attend vasodilation. The muscle pump must have withdrawn blood volume from its arterial supply, thereby lowering arterial pressure before any vasodilation occurred. A large negative pressure in small muscle veins would appear necessary (53, 60).

Muscle contractions per se can raise MBF. Sheriff and Van Bibber (54) devised an ingenious experiment in which contracting porcine hindlimbs were perfused either at high pressure from the aorta or by contracting and pumping blood around a surgically constructed short circuit and thereby perfusing themselves, even when the arterial-venous pressure difference across the muscle was zero. True, the self-perfused muscle received venous blood, which should weaken contrac-
tions, but this also strengthens the point. Also, in these experiments, there was essentially no hydrostatic column favoring the pump.

The idea that muscle contractions can by themselves raise MBF is again challenged as is the concept of a pump within nondependent muscles or of any muscle pump at all (see Ref. 30). Nevertheless, history reveals the necessity of a muscle pump if cardiac output is to rise normally with exercise. This does not require that contractions raise MBF. It does require muscles to return to the right ventricle what they receive from the left with sufficient force and speed to maintain thoracic blood pressure and volume and cardiac output regardless of posture.

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NEURAL CONTROL OF MBF AND METABOLIC INHIBITION
OF VASOCONSTRICITION

Graded exercise is accompanied by proportional increases in sympathetic nerve activity (SNA), which redistributes blood flow and maintains SAP (47). Vasoconstriction was generally assumed to be confined to inactive regions. If active muscle were also a target, would it vasoconstrict as well? The answers come from multiple sources that initially employed electrical stimulation of cat or dog hindlimbs to simulate exercise. The vasoconstrictor response to increased SNA in active muscle seemed to be reduced (Rein, 1930; cited in Ref. 44) and occasionally almost abolished (e.g., Refs. 27 and 44). Dissociated responses depended on 1) magnitude and duration of muscle contractions, 2) magnitude of vasodilation and how it was estimated, 3) frequency of sympathetic nerve stimulation, 4) perfusion technique (constant flow vs. constant pressure vs. heart perfused), and 5) type of “exercise.”

Although in humans vasoconstriction clearly occurs in resting muscle during exercise (8), only recently has evidence pointed to augmented tonic SNA to active muscle (1, 10, 26, 39, 46, 47, 64). In 1984, Andersen and Saltin (1) reported that peak MBF in a mass of muscle too small to tax cardiac pumping capacity (~2 kg of quadriceps muscle) can reach ~250 ml·100 g⁻¹·min⁻¹. Similar peak flows in 15 kg of muscle would overwhelm cardiac pumping capacity. Even greater values for peak MBF in humans and other mammals (31, 48) reveal two key points: 1) skeletal muscle is a “sleeping giant” whose blood flow must be under tonic vasoconstrictor constraint if hypotension is to be averted, and 2) commonly reported estimates for “maximal” MBF ranging from 50 to 80 ml·100 g⁻¹·min⁻¹ (31, 37, 45) are clearly underestimates (caused in part by electrical stimulation) (29, 45).

Evidence for Tonic Sympathetic Vasoconstriction in Active Muscle

Stoppage of SNA or its effects on blood flow to active muscle by 1) anesthetic blockade of sympathetic nerve fibers (26), 2) activation of the arterial baroreflex (10, 59, 64), and 3) acute local blockade of α₁-adrenoceptors (39) revealed substantial tonic vasoconstriction in active muscle that increased in proportion to work rate as revealed by the progressive increments in MBF with blockade. Systemic blockade of SNA (53) and clinical dysautonomia (Marshall, Schirger, and Shephard, 1961, and Bevegård et al., 1967) (cited in Ref. 47) caused severe hypotension with even mild exercise and in dogs quickly led to syncope as work intensity rose (53); in all cases, loss of sympathetic tone in active muscle was the major cause. Clearly, regulation of SAP is not possible during exercise without tonic vasoconstriction in muscle.

Further evidence includes directly measured muscle SNA, which rises in proportion to exercise intensity (50), as does spillover of norepinephrine from active muscle, which accounts for most of total spillover (15, 32).

Is Tonic Vasoconstriction of Active Muscle Blunted by Sympatholysis?

The question is difficult; the answer depends on where we look and how we look. We continue to argue as to whether constriction of the resistance vessels, which control MBF, is blunted by metabolites. Over a wide range of metabolism, vasoconstriction is not overridden no matter whether it is initiated by electrical stimulation or by reflex activation (23, 31, 46). For example, during bilateral carotid occlusion, 40% of the rise in SAP was via vasoconstriction in exercising hindlimbs (10). As cardiac output and total vascular conductance rise with exercise, a much greater absolute change in conductance (percent changes are often not instructive) is necessary to change SAP by a given amount. Active muscle is the only organ with sufficient conductance to significantly raise SAP during exercise, and its ability to do so persists despite “sympatholysis” (10).

Is the concept of sympatholysis valid? Technically, it is despite the implication of destruction in the term “lysis.” One difficulty is that when changes in MVC during muscle contractions (high MBF) are compared with changes during rest, absolute changes in MVC and resistance at any given level of SNA are vastly different. When baseline MBF is high, vasoconstriction causes large changes in MVC, suggesting no sympatholysis, but only small changes in resistance, suggesting there is sympatholysis. Here, only MVC reveals the magnitude of active changes in MBF and vascular tone that relate directly to control of SAP. This problem is now recognized. It is possible that when sympatholysis does occur it requires a greater increase in SNA to maintain SAP than would be required without this attenuation. Nearly 70 years have been spent trying to sort out these problems.

The problem of constant flow vs. constant pressure perfusion. With constant pressure perfusion, vasoconstriction decreases flow but this vasoconstriction lessens as metabolites accumulate faster and flow partially recovers; whereas with constant flow, vasoconstriction is augmented throughout exercise (49). In 1968, Rowlands and Donald (49) detailed other important problems (rarely cited) in interpreting sympatholysis, such as 1) the time dependency of delayed vasoconstriction when this phenomenon is evident; 2) how responses are affected by vessel diameters that affect vasoconstriction according to the length-tension relationship (e.g., vessels can develop greater tension when distended during exercise than at rest); and 3) frequency of sympathetic stimulation has greater effects during exercise than at rest, again depending on infusion technique. Their superb experimental skill put sympatholysis in better perspective.

Differential control of large and small (precapillary) arterioles. Perhaps the most important insight came in the 1960s when Bjorn Folkow and his colleagues (see Refs. 9, 27) observed differential effects of neural and local humoral agents on large (resistance) arterioles and the small arterioles in skeletal muscle that control capillary perfusion. For example, Cobbold et al. (9) and Kjellmer (27) saw that sympathetic nerve stimulation increased resistance and reduced capillary filtration coefficient in cat hindlimbs. However, as muscle resistance vessels remained partially constricted, capillary filtration coefficient was restored presumably due to relaxation of “precapillary sphincters” (i.e., terminal arterioles). Kjellmer (27) saw that the rise in resistance with nerve stimulation was less during exercise than at rest, but recent calculation of MVC from his data revealed its decrements were larger during exercise than at rest (47).
If sympatholysis occurs mainly in the small precapillary arterioles rather than in resistance vessels, we could maintain reduced MVC and keep SAP at the operating point of the baroreflex (see below) and also support increased capillary perfusion in the active regions of the muscle, i.e., sympatholysis in the right place. This is where matters have headed. Several recent studies, notably those of Faber and colleagues, e.g., in 1991, 1992, and 1995 (cited in Ref. 23), showed that acidosis impairs \( \alpha \)-adrenergic vasoconstriction in microvessels of rat muscle. In contrast to \( \alpha_1 \)-adrenoceptors, \( \alpha_2 \)-adrenoceptors are highly sensitive to metabolic inhibition. The resistance arterioles contain both receptor types, whereas the small terminal arterioles are controlled primarily by \( \alpha_2 \)-adrenoceptors. In theory, this distribution of adrenoceptors could foster maintained vasoconstriction in resistance arterioles and sympatholysis in small precapillary arterioles. Thomas, Hansen, and Victor (1994) (cited in Ref. 23) explored metabolic inhibition of resistance vessels in rat hindlimbs and found vasoconstriction to be preserved in active soleus muscle (oxidative fibers) and in gastrocnemius-plantaris muscle (glycolytic fibers) during mild contractions; however, during maximal contractions, vasoconstriction was abolished only in glycolytic muscle by impaired \( \alpha_2 \)-mediated vasoconstriction and presumably not by impaired \( \alpha_1 \)-receptors [which may in part be so in humans (44a)]. It appears that \( \alpha_2 \)-adrenoceptors dominate control of resistance vessels in glycolytic muscle. Additional results were ably reviewed by Hansen (23). In an evolutionary sense, speed seems to have been favored over endurance.

Research in this area has grown exponentially in the past decade. For example, recent findings from Van Teeezen and Segal (63), based on direct measurements of diameters of microvascular branches in skeletal muscle, revealed that as contractile activity and SNA increase, vasoconstriction of the large resistance arterioles persists as does reduced total muscle perfusion. Conversely, in the small terminal arterioles, vasoconstriction is antagonized. Thus we have maintained MVC and blood pressure and up to a point maintained capillary perfusion.

In retrospect, one must wonder how so many have observed such marked total sympatholysis, especially in muscles that contain predominantly sympatholysis-resistant oxidative fibers. Is the problem really solved? Remember, relative distributions of \( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptors are dependent on muscle fiber types and species; e.g., in humans, muscle fiber types are mixed, and the above generalization may not strictly apply (see Ref. 44a).

**REFLEX CONTROL OF MBF**

The rises in muscle SNA and norepinephrine spillover in proportion to the severity of exercise (31, 47) parallel the progressive rise in total SNA and vasoconstrictor tone in active muscle and most other organs, except for the central nervous system (47). What reflexes might initiate this rise in SNA, and what error signal(s) is being corrected by this rise?

**Muscle Chemoreflexes and Mechanoreflexes**

A primary candidate for over 30 yr has been the signals from muscle afferents that detect chemical changes in active muscle (called muscle chemoreflexes). The basic idea originated with Zuntz 118 yr ago. Mechanoreflexes from mechanosensitive muscle afferents are also initiated but so far appear to fit no cardiovascular regulatory scheme (47). A long history of controversy has left two main questions: is the primary error corrected by the autonomic nervous system? 1) a mismatch between MBF and metabolism (a flow error) or 2) a mismatch between cardiac output and total vascular conductance (a pressure error)?

So far, a tonically active muscle chemoreflex that contributes to tonic SNA during mild to heavy dynamic exercise has not been demonstrated. Muscle chemoreflexes are activated in conditions that cause muscle ischemia such as static contractions or occlusive arterial disease. Increased SNA was commonly associated with putative anaerobic metabolism and lactic acid release (47). Recent research reveals no evidence of anaerobic metabolism or critically low muscle PO2 in normal dynamic exercise (see above). Thus, under normal conditions, there is no obvious error signal [lactate release is clearly not a flow-dependent error, unless MBF or PO2 are reduced far below normal (11)]. The idea that a muscle chemoreflex is initiated during severe dynamic exercise under free flow conditions lacks rigorous experimental tests. Another point is that chemosensitive muscle afferents are thermonensitive and respond vigorously over a physiological range of muscle temperatures (47). The functional significance is unexplored.

**Arterial Baroreflexes**

Inasmuch as the capacity of active muscle to vasodilate can (depending on mass) so greatly exceed the pumping capacity of the heart, the potential for pressure errors is great. Loss of muscle vasoconstrictor tone in whole body exercise causes severe hypotension (see above). Historically, however, the reasons for rejecting a primary role for arterial baroreflexes have been mostly reasonable ones.

The earliest objection to a role for baroreflexes was that HR and SAP rose together with exercise in opposition to Marey’s Law (1861), which states that HR and SAP are inversely related; thus the reflex “must be turned off” with exercise. The next issue was whether SAP immediately rose with exercise (meaning no baroreflex opposition) or transiently fell and then rose. In the latter case, the baroreflex would be required to restore SAP after its fall and could thus explain the rise in HR and cardiac output. This idea had two problems: 1) often SAP rose immediately with exercise, and 2) when SAP did fall, it was restored to levels at or above the preexercise level. Complete restoration would require infinite reflex sensitivity.

More support for an inactive baroreflex came during the 1960s and 1970s from studies on dogs with arterial baroreceptor denervation (34, 65). These studies revealed no obvious deficit in SAP control after an abnormally slow initial response (noted in more detailed studies). Finally, ill-fated attempts to evaluate baroreflex sensitivity from HR, and especially from the ECG R-R interval, gave problems that are extant. First, the gain or sensitivity of the baroreflex is proportional to the gain of HR plus the gain of total peripheral resistance responses. Second, control of HR reveals neither quantitatively nor even qualitatively the ability of the baroreflex to control SAP in exercise, a point made often by Kiichi Sagawa (cited in Ref. 47). Worse yet, when baroreflex sensitivity was assessed by suddenly raising SAP with a pressor drug (in humans) and measuring the change in R-R interval, the more severe the
exercise, the higher the baseline HR and the smaller the change in interval per unit of change in SAP; this was not because, as concluded, the baroreflex became less sensitive: it was because of the mathematical relationship between interval and HR (as with resistance and conductance).

Because baroreflex sensitivity incorporates the sensitivity or gains of both HR and vascular resistance, both of these variables must be evaluated. One way of achieving this is by measuring the change in SAP (which includes HR and resistance) in response to a given change in pressure within a baroreceptor (the stimulus). In 1966, Bevegard and Shepherd (7) determined the sensitivity of the human carotid sinus reflex by applying negative pressure to the sinus (simulates hypertension) and measuring the change in SAP. Baroreflex sensitivity was unaffected by moderate exercise.

In a series of classic experiments during the 1980s by Donald and colleagues at the Mayo Clinic and by Ludbrook and coworkers in Australia (reviewed in Refs. 47 and 65), the carotid sinus was isolated and its pressure controlled so as to produce complete stimulus-response curves over a physiological range of SAP. These curves gave the best measure of baroreflex sensitivity (which unfortunately could not often include the aortic receptors). These curves also revealed whether the operating point (often wrongly called “set-point”) of the reflex had shifted (as in “resetting”). Together, these experiments revealed the following: 1) the sensitivity of the baroreflex is the same during rest and exercise; 2) denervation of the baroreflex prevents the rise in SAP and SNA at the onset of mild exercise and delays and blunts the rise in heavy exercise [this rise in SAP probably stems from activation of a muscle chemoreflex by low MBF (47, 65)]; and 3) prevention of the normal rise in carotid sinus pressure forces SAP [and SNA, see DiCarlo and Bishop (13)] to rise to extreme levels as though resting sinus pressure were suddenly perceived as hypotension by the central nervous system (i.e., as though the operating point of the reflex were higher) (Walgenbach and Donald cited in Ref. 65).

In 1993 and 1994, Potts et al. (42) and Papelier et al. (40) constructed complete carotid sinus stimulus-response curves from humans during mild to severe (Papelier) exercise, which again revealed constant reflex sensitivity from rest across the work rates and most importantly demonstrated an upward resetting of the reflex to higher operating pressures in proportion to work intensity.

It is now clear that, inasmuch as the skeletal muscle circulation comprises 70–85% of total vascular conductance over its range of exercise performance and has a capacity to vasodilate much more, tonic vasoconstriction of muscle is critical to the maintenance of SAP, which in turn is sensed and regulated by the arterial baroreflex. Furthermore, upward resetting of the baroreflex requires vasoconstriction in active muscle to raise SAP. The baroreflex appears to be a vital controller of MBF as it tonically opposes excessive vasodilation to maintain SAP. Conversely, a muscle chemoreflex can protect muscle from hypoperfusion.

**SUMMARY**

Despite substantial progress since 1876, we still face the problems that are summarized in this section. Because of the evolution of ideas over this time, we are closing in on some solutions, particularly in the areas of neural and reflex control, which are also summarized below.

Identification of which candidates for metabolic vasodilation explain the rise in MBF requires first that we quantify the mechanical contributions of muscle contractions to total MBF. Contributions of specific metabolites to vasodilation might then be quantified, but simple addition of their separate effects is not likely to explain total vasodilation. Dose responses of multiple combinations of metabolites and other factors will probably be needed. Problems could be less daunting for coronary blood flow if any mechanical contributions to flow are small relative to those to MBF. Meanwhile, the search for “the missing vasodilator” persists as another alternative.

Quantification of metabolic vasodilation in muscles of normally exercising subjects is not only confounded by the muscle pump but also by concurrent tonic vasoconstriction that reduces MVC and MBF so as to maintain SAP at the operating point of the arterial baroreflex. This vasoconstriction and precise regulation of SAP occur despite any sympatholysis. However, this metabolic inhibition of vasoconstriction rather than blunting vasodilation of large-resistance arterioles may predominantly inhibit vasoconstriction of small terminal arterioles that control capillary flow, presumably by differential effects of metabolites on $\alpha_2$- vs. $\alpha_2$-adrenoceptors. This combined “protection” of both MVC and capillary flow may not apply in general because relative distributions of $\alpha_2$- and $\alpha_2$-adrenoceptors depend on muscle fiber type and species; e.g., in humans, muscle fiber types are mixed. Alternatively, if sympatholysis also affected resistance vessels, SNA would have to rise enough to overcome sympatholysis because maintenance of SAP requires maintained reduction in MVC by vasoconstriction.

The extent to which the muscle pump can raise MBF is not known, but it need not raise MBF to be an effective pump. Its pumping effectiveness is revealed by its counteraction of the positive effect of increasing cardiac output on peripheral vascular volume, which in turn reduces CVP, EDV, and SV. By the muscle pump’s sustained reduction in muscle blood volume and its translocation of this volume to the thorax throughout exercise, CVP, EDV, and SV and thus cardiac output can rise normally. This does not occur in patients lacking venous values.

Control of MBF in exercise combines these metabolic, neural, and mechanical components with a resultant MVC that is closely regulated by the arterial baroreflex. Furthermore, the increases in SAP and in SNA to muscle (and to most other organs) coincide with upward resetting of the baroreflex to higher pressures as exercise intensity increases. Inasmuch as these changes in SNA and MVC require a normal baroreflex, this reflex appears to dominate neural control of MBF in exercise. Alternatively, this neural control could be dominated by a muscle chemoreflex if active muscle becomes underperfused and ischemic; we have no experimental evidence for any tonic control of SNA by this reflex during any intensity of normal dynamic exercise under free-flow conditions.

**REFERENCES**


The document contains scientific literature on the control of skeletal and cardiac muscle blood flow, with a focus on the role of endothelium in responses of vascular smooth muscle. The text discusses various studies on the effects of exercise, sympathetic control, and metabolic factors on blood flow regulation. Key authors mentioned include Hansen J., Janicki JS, Sheriff DD, Robotham JL, Wise RA, Feigl EO, Beecher HK, Field ME, Krogh A, and many others. The references span from historical perspectives to contemporary studies, covering a wide range of topics from endothelial function to the role of myoglobin in striated muscle.


