REGULATION OF INCREASED BLOOD FLOW (HYPEREMIA) TO MUSCLES DURING EXERCISE: A HIERARCHY OF COMPETING PHYSIOLOGICAL NEEDS

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Joyner MJ, Casey DP. Regulation of Increased Blood Flow (Hyperemia) to Muscles During Exercise: A Hierarchy of Competing Physiological Needs. Physiol Rev 95: 549–601, 2015; doi:10.1152/physrev.00035.2013.—This review focuses on how blood flow to contracting skeletal muscles is regulated during exercise in humans. The idea is that blood flow to the contracting muscles links oxygen in the atmosphere with the contracting muscles where it is consumed. In this context, we take a top down approach and review the basics of oxygen consumption at rest and during exercise in humans, how these values change with training, and the systemic hemodynamic adaptations that support them. We highlight the very high muscle blood flow responses to exercise discovered in the 1980s. We also discuss the vasodilating factors in the contracting muscles responsible for these very high flows. Finally, the competition between demand for blood flow by contracting muscles and maximum systemic cardiac output is discussed as a potential challenge to blood pressure regulation during heavy large muscle mass or whole body exercise in humans. At this time, no one dominant dilator mechanism accounts for exercise hyperemia. Additionally, complex interactions between the sympathetic nervous system and the microcirculation facilitate high levels of systemic oxygen extraction and permit just enough sympathetic control of blood flow to contracting muscles to regulate blood pressure during large muscle mass exercise in humans.

I. INTRODUCTION

A. Major Theme

The major theme of this review is that during large muscle mass exercise like running or cycling there are two potentially competing physiological needs. First, because the metabolic costs of muscle contraction can be high and prolonged, skeletal muscle blood flow needs to be matched to the metabolic demands of the contracting muscles. Second, regulation of blood pressure is also needed to ensure there is adequate perfusion pressure to all organs. The idea that these two important physiological needs “compete” arises when the mass and vasodilator capacity of skeletal muscle are considered in the context of the maximum values for cardiac output seen during exercise. This raises the possibility that vasodilation in the contracting muscles might outstrip cardiac output and threaten blood pressure regulation (68, 301, 392, 393).

The potential competition between vasodilation and blood pressure regulation outlined above has emerged as a major new idea in integrative physiology over the last 30 or so years (392). However, there were hints that this was an issue as early as the 1960s (301). In this review we consider the many factors that contribute to the homeostatic and regulatory mechanisms operating to meet the two main physiological needs emphasized above. We also make the case that during heavy exercise sympathetic modulation of the peripheral circulation (including contracting skeletal muscle) operates in a way that 1) maintains arterial blood pressure at a minimal “acceptable” level of ~100 mmHg, 2) facilitates the perfusion of a large mass of active muscle, and 3) increases oxygen extraction across the contracting skeletal muscles. These three points reflect an integrative perspective that we and others have been developing over the last 15 or so years (68, 392).

B. Structure of This Review

With our high level perspective as a background, we will work our way down from ideas related to oxygen consumption, cardiac output, skeletal muscle blood flow, and blood pressure...
regulation. To explore our first physiological need, we describe the range of oxygen consumption observed in humans and focus on the large increases in oxygen consumption that can occur during large muscle mass rhythmic exercise. We then discuss the magnitude of the cardiac output required to deliver this oxygen to the contracting muscles, and how blood flow is distributed to the microcirculation to meet the demand for oxygen by the active muscles. Our rationale for this top down approach is that in an era of reductionism, many scientists and trainees are less familiar with fundamental concepts related to whole body oxygen consumption, cardiac output, and blood flow distribution. Therefore, a synthesis of key facts and concepts is needed to frame the overall discussion of exercise hyperemia. We also start at the systemic level and “work down” because our own research has focused on integrated issues related to whole body oxygen consumption, skeletal muscle blood flow, and oxygen delivery to contracting muscles in conscious humans.

The second physiological need we identified is the ongoing need to regulate arterial pressure when the demand for oxygen by the exercising skeletal muscle is increased by several orders of magnitude, and as a result skeletal muscle blood flow is very high. So, in addition to considering the heart as a pump, the blood vessels as a delivery system, and the skeletal muscle as the end user, we must also consider the overall need of the organism to maintain an arterial pressure sufficient to perfuse the brain and other vital organs. This is especially important in humans who are upright and have a large brain located above heart level, which lowers cerebral perfusion pressure. Thus the autonomic nervous system serves as a regulator of blood pressure and is also critical in the regulation of skeletal muscle blood flow during exercise. The list below enumerates eight major questions. Additional key points and subsidiary questions will be used as needed to further frame our exploration of these issues.

What is the range of oxygen consumption in humans?

How is the oxygen delivery generated to meet the demands of the contracting muscles?

What fraction of cardiac output goes to skeletal muscle during exercise?

What are peak values for skeletal muscle blood flow?

How is blood pressure regulated when blood flow to contracting skeletal muscles is very high?

What are the local blood flow responses to muscle contraction, and what mechanisms cause them?

How does the sympathetic nervous system control blood flow to both inactive and contracting skeletal muscles?

Can this information be coherently integrated, and what perspectives do we have?

For each of these topics, we will emphasize data from studies in healthy humans. Complementary examples from animal models, comparative physiology, and human pathophysiology will be used as warranted to illuminate or reinforce key points. In general, we will also attempt to relate most elements of the review to rhythmic or dynamic exercise performed with a large mass of contracting muscles like running or cycling for a few minutes or more, which is typically referred to as aerobic exercise. While important insights can be gained by considering the physiological responses to small muscle mass exercise and static exercise, our overall goal is to present an integrated picture related to exercise as locomotion (16).

Of note, in preindustrial societies, prolonged movement including running was required for the purposes of hunting, foraging, herding, eluding predators, and muscle-powered agriculture. Along these lines, there are provocative arguments for evolutionary adaptations that favored the emergence of human endurance exercise capacity in the context of our traditional ways of life. For example, so-called persistence hunting requires continuous movement for many hours while running game animals to exhaustion (52, 279). More recently, there has also been a focus on the health consequences of inactivity and the powerful health benefits of regular aerobic exercise (50, 325).

While we work our way down from systemic responses to the factors in contracting skeletal muscle that cause blood flow to rise during exercise, these responses are so integrative it is unsatisfying to merely provide a linear catalog of them. Therefore, we adopted a narrative approach, and there may be digressions into topics and mechanisms that have already been covered in detail, or that will be covered in depth subsequently. This approach might seem unconventional, but exercise hyperemia is complex and our goal is to impart the readers with an appreciation of this complexity.

Before embarking on this intellectual journey, we would like to alert the readers’ attention to six key publications that have informed our thinking and provide foundational integration and synthesis on the topics we are addressing. These include Handbook of Physiology chapters by Barcroft (25) and Shepherd (431), the seminal monographs by Shepherd (432) and Rowell (390, 391), and also a critical review article by Clausen (91). While our goal is to provide a comprehensive state-of-the-art survey of contemporary knowledge, equally important is the need to identify important unresolved issues related to muscle blood flow and exercise hyperemia. Ultimately, questions stimulate the generation of new knowledge and insight.
C. Foundational Concepts and Definitions

There are a number of concepts critical to integrating ideas about skeletal muscle blood flow and blood pressure regulation during exercise. Because they are essential for the extended discussion of the topics that follow, we will outline them here.

Exercise and electrically induced muscle contraction are not synonymous. In both cases, metabolic activity in the muscles increases. However, exercise is associated with a variety of parallel cardiovascular and respiratory responses associated with generating the effort required for the orderly recruitment of motor units that cause the muscles to contract (121, 390, 391). The most obvious examples are the increases in heart rate, blood pressure, and ventilation that can occur almost instantaneously at the start of exercise via so-called “central command.” With electrical stimulation of peripheral nerves, central command is bypassed, and the recruitment of motor units is either reversed or more random (157, 273, 465, 474). This may reflect in part lower input resistance for depolarization in large axons when external current is applied. When the muscle is stimulated directly, contraction can be caused by either direct electrical effects on the muscle cells or by stimulating branches of motor nerves in the muscle (318, 338). In both cases, the effects of electrical stimulation on how the contraction is evoked is dependent on the specifics of the experimental paradigm, and the general conclusion is that it differs from voluntary exercise. In the final analysis, exercise always includes contraction, but contractions can be generated in the absence of exercise.

Static and dynamic exercise are not the same (16). Static (sometimes called isometric) exercise usually refers to sustained contractions lasting seconds to minutes with limited muscle shortening. The prototypical static exercise is a sustained handgrip performed at some fraction of maximum voluntary contraction for a period of perhaps a minute or longer. The prototypical dynamic (or rhythmic) exercise is something like running or cycling that features brief contractions performed over and over again. Due to the ease of measuring forearm blood flow and the ability to give high doses of drugs locally via the brachial artery, rhythmic handgripping is also a frequently used model to study exercise hyperemia. This approach permits blood flow responses to be “pharmacodissected” without causing marked effects on systemic blood pressure that might engage cardiovascular reflexes and confound the local effects of the drug. In other words, the forearm can be used as an in vivo bioassay system in humans. In most of the studies we will cite, rhythmic forearm exercise means perhaps 20–30 contractions/min separated by 1–2 s between contractions. However, some studies have used longer periods of “static” contraction with a few seconds between (280, 511). Is this a model of static exercise or dynamic exercise? The dividing line is not always clear. Another important caveat is that blood flow and hence oxygen delivery to the contracting muscles can be restricted or absent during isometric or static contractions as contraction compresses the muscle vessels leading to a reliance on high-energy phosphate stores and glycolysis to generate ATP in support of the ongoing contractions (28, 470). This contrasts with the aerobic ATP production and corresponding requirement for increased blood flow during rhythmic contractions.

Large versus small muscle mass exercise needs to be considered when interpreting experimental results. Handgripping is obviously small muscle mass exercise since <1 kg (out of perhaps 20–30 kg) of muscle is being activated. The obvious problem with this model is that humans do not “run with their arms,” and the purpose of the forearm and hands are very different from the big locomotor muscles of the lower extremities. For example, many of the motor units in the hand and forearm may contain only a few muscle fibers consistent with the need for precision movements by the upper extremity (310). During one leg rhythmic knee extension (kicking) exercise, it is possible to isolate 2–3 kg of contracting muscle (408). In contrast, running and cycling are obviously large muscle mass exercise because they use ~50% of total muscle mass. Activities like cross country skiing, rowing, and swimming might be characterized as whole body exercise. The points about small and large muscle mass exercise are critical for our later discussion about how skeletal muscle vasodilation is “managed” during heavy exercise to regulate mean arterial pressure. This is important because mean arterial pressure is “the” regulated variable in the cardiovascular system (301), and the brain is above heart level in upright humans. Finally, concerns about electrical stimulation aside, rhythmic handgripping and one leg kicking might have more in common with isolated muscle preparations than whole body exercise when considered in light of the mass of the contracting muscles.

The words peak or maximum are context specific during exercise (389). In general, maximum means the highest value recorded under any circumstance. For example, the highest oxygen consumption (VO2) value for most untrained or recreationally active humans can be observed during progressively faster walking or running uphill on a treadmill to exhaustion. Lower peak VO2 values (except in athletes like canoeists who are arm trained) are typically seen during incremental arm cranking. Thus the highest value obtained during a running-based test might be described as VO2max for that individual. In contrast, the highest value seen during incremental arm cranking would be the peak VO2 for that specific activity. Only in athletes with highly trained arms and legs (e.g., rowers and cross country skiers) is the addition of arm exercise to heavy leg exercise required to evoke VO2max, whereas in most humans running is a sufficient stimulus (36, 422, 459). Finally, during exercise at VO2max the forces generated by the contracting mus-
Vascular resistance or vascular conductance as a calculated index of vascular tone?

Vascular tone can be expressed as either resistance (pressure/flow) or conductance (flow/pressure). From an analytical perspective, it is important to note that there is a curvilinear relationship between pressure and flow at a given resistance, whereas the relationship between pressure and flow at a given conductance is more linear (270, 342). These relationships will have important implications later when we discuss conceptual issues related to sympathetic vasoconstriction in contracting muscles and the effects of even modest vasoconstriction on arterial pressure. In both cases, these derived terms are used to understand what is happening to the caliber of the blood vessels in the muscle vascular bed. While some investigators report blood flow values, some vascular resistance, and some vascular conductance, we tend to favor the use of conductance because it is linearly related to flow. However, much of the literature is framed in the context of Darcy’s law where pressure = flow/resistance, so some interpretive flexibility is required here (55).

2. Absolute or relative values for exercise related variables?

Under some circumstances we will discuss whole body oxygen consumption or skeletal muscle blood flow using absolute values typically expressed in terms of liters per minute. In other cases, these values will be either expressed as per kilogram of body weight or per 100 g of muscle. In some cases (especially when the fitness or training status of groups is different), things are expressed on a relative basis as a fraction of \( V_{\text{O}_2\text{max}} \). In general, our goal in using absolute, normalized, or relative units is to highlight the values that provide the most physiological insight. We also seek to clarify issues that can be confused by factors like differences in body size. For example, the heart rate response to exercise at a given fraction of \( V_{\text{O}_2\text{max}} \) is generally similar for young healthy people independent of fitness status; in contrast, the heart rate response to a given absolute work load can vary dramatically and be much lower in trained versus untrained subjects (390, 391).

3. What do the categories untrained, exercise trained, and elite mean for exercise related studies?

For the purposes of this review, untrained (sometimes also called sedentary) refers to humans who participate in no formal leisure time exercise and also do not perform regular heavy physical labor. The term trained can include individuals who are casual exercisers perhaps doing 30 min/day of moderately vigorous activity most days. It can also include committed recreational athletes who participate in local competitions. Elite refers to highly competitive endurance athletes who typically train intensely for several hours per day year round for many years. TABLES 1 AND 2 provide a summary of estimates for so-called reference man and woman and also values for trained subjects and elite athletes.

Most of the preceding concepts reflect highly contrived laboratory situations. Much human activity might be described as intermittent with periods of fast and slow locomotion with occasional brief but high force efforts interrupted by periods of relative rest. This was certainly our history when more of our economic activity was labor intensive and our diversions were active as opposed to screen based (17, 49, 355). One reason there has been so much experimental emphasis on the physiological responses to running and cycling is because these activities are amenable to controlled laboratory-based studies with treadmills and cycle ergometers.

D. Muscle Blood Flow and Metabolism Are Closely Matched During Exercise

Muscle blood flow is closely matched to the metabolic demands of contraction. As shown in FIGURE 1, this matching occurs across a range of intensities from rest to heavy exercise and during both small and large muscle mass exercise. It is also seen in response to both single contractions and more prolonged exercise lasting for hours.

The action of muscle contraction on bony levers generates movement, movement is a requirement of life, and energy is required to fuel this movement. In vertebrates, movement in general and locomotion in specific is caused by the recruitment of skeletal muscle motor units and contraction of skeletal muscle fibers with subsequent coordinated movement of the limbs (63, 142, 209). It is fueled by ATP, and ATP sources include high-energy phosphate stores, anaerobic metabolism, or the aerobic generation of ATP by the
For periods of exercise lasting minutes or longer, aerobic generation of ATP by the mitochondria is critical and requires oxygen and substrate. There are substantial fuel stores in the form of carbohydrate and fat in skeletal muscle, and both glucose and free fatty acids from other tissues can be delivered to the muscle via the blood. However, the airborne source of oxygen is remote from the skeletal muscles and with the notable exception of some diving mammals, not much oxygen is stored in the muscles (322). So, fundamental questions for those interested in exercise, especially for more than a few minutes, relate to both how and how much oxygen gets from the air to the exercising muscles (146) via blood flow generated by the cardiovascular system linking the air/lung interface with the contracting muscles (501).

### II. THE RANGE OF OXYGEN CONSUMPTION IN HUMANS

Resting oxygen consumption in humans averages 3–4 ml·kg$^{-1}$·min$^{-1}$. This means that in young healthy humans weighing 50–100 kg, somewhere between 0.15 and 0.4 liters of oxygen is being consumed per minute at rest. Most

#### Table 1. Reference $V_{O_2}$ and hemodynamic values at rest and during maximal exercise

<table>
<thead>
<tr>
<th></th>
<th>Reference Man</th>
<th></th>
<th>Reference Woman</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise (maximal)</td>
<td>Rest</td>
<td>Exercise (maximal)</td>
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<tr>
<td>$V_{O_2}$, ml·kg$^{-1}$·min$^{-1}$</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sed</td>
<td>3.0–3.5</td>
<td>&lt;45</td>
<td>−3.0</td>
<td>&lt;35</td>
</tr>
<tr>
<td>Active</td>
<td>−3.5</td>
<td>50–60</td>
<td>−3.5</td>
<td>40–50</td>
</tr>
<tr>
<td>Elite</td>
<td>3.5</td>
<td>70–85</td>
<td>3.5</td>
<td>60–73</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sed</td>
<td>70</td>
<td>−200</td>
<td>70</td>
<td>−200</td>
</tr>
<tr>
<td>Active</td>
<td>60</td>
<td>−200</td>
<td>60</td>
<td>−200</td>
</tr>
<tr>
<td>Elite</td>
<td>50</td>
<td>−200</td>
<td>50</td>
<td>−200</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>−5</td>
<td>−20</td>
<td>−3.5–4</td>
<td>−15</td>
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<tr>
<td>Sed</td>
<td>−5–6</td>
<td>−25</td>
<td>−3.5–4</td>
<td>−20</td>
</tr>
<tr>
<td>Active</td>
<td>−5–6</td>
<td>30–40</td>
<td>−3.5–4</td>
<td>−25</td>
</tr>
<tr>
<td>Elite</td>
<td>−5–6</td>
<td>30–40</td>
<td>−3.5–4</td>
<td>−25</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sed</td>
<td>−65</td>
<td>−100</td>
<td>−55</td>
<td>−70</td>
</tr>
<tr>
<td>Active</td>
<td>−90</td>
<td>−125</td>
<td>−60–70</td>
<td>−100</td>
</tr>
<tr>
<td>Elite</td>
<td>−110</td>
<td>150–200</td>
<td>70</td>
<td>125</td>
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</table>

The above values are estimates and reflect norms established for humans in their 20s before the obesity and inactivity epidemics of the last 20–30 yr (19, 33, 358). Lean body mass has a marked influence on all of these values (see Table 2).
During exercise in young untrained subjects, oxygen consumption can increase 10- to 15-fold and reach maximal values of 30–50 ml·kg⁻¹·min⁻¹. The variability of VO₂max is due to a number of factors such as the body composition of the subjects, level of physical activity, blood volume, hemoglobin mass, stroke volume, and poorly understood “genetic” factors. With intense aerobic exercise training, many healthy young men can achieve a maximal oxygen uptake near 60 ml·kg⁻¹·min⁻¹, provided the training is of sufficient intensity and duration to eliciting a maximal adaptive response and that they become very lean. Of note, this maximal oxygen uptake value is similar to estimates for male hunter gatherers and pastoralists in nonmechanized cultures (102, 382, 499). In elite male endurance athletes, a VO₂max in the 70–85 ml·kg⁻¹·min⁻¹ range is typically reported (361, 405). Early observations of these very high values were made in the 1930s on Donald Lash (the first man to break 9 min for 2 miles, ~3,200 m) and other elite runners by Robinson and colleagues at the Harvard Fatigue Laboratory (380). Values in women are ~10–15% lower than men as a result of having relatively less muscle mass and lower hematocrit and hemoglobin (139, 352, 405). FIGURE 3 shows the estimated distribution of maximal oxygen consumption (VO₂max) for a group of 44,549 males (472) and also the relationship between whole body VO₂max and total body hemoglobin (238).

It should also be pointed out that VO₂max is typically highly reproducible for a given individual assuming there are not major changes in physical activity or body composition (168, 444, 463). However, on average, VO₂max typically declines by ~10% per decade starting at age 30 (65, 188, 227, 362). The beginning of this decline can be delayed by a decade and its rate can be slowed with intense training (203, 362, 383). There are a number of physiological and gas exchange criteria used to assess what constitutes a maximal or peak response to exercise; however, the most compelling is the observation of a plateau in oxygen consumption despite an increased work load (212, 463). FIGURE 4 shows an example of oxygen consumption leveling off in a well-trained, but non-elite cyclist during an incremental maximal exercise test.

A. Summary

Absolute values for oxygen consumption at rest are largely dependent on body size. In healthy subjects, oxygen consumption can rise dramatically during exercise. The maximum value achieved during exercise is termed VO₂max. It is a highly reproducible value and influenced by a number of factors including exercise training history of the individual.

III. CARDIAC OUTPUT AND PERIPHERAL OXYGEN EXTRACTION DURING EXERCISE: HOW THE OXYGEN DELIVERY NEEDED TO MEET MUSCLE’S DEMAND FOR OXYGEN IS GENERATED

A. Cardiac Output and Oxygen Extraction at Rest

According to the Fick principle, oxygen consumption = blood flow × arterial-venous O₂ difference. When this principle is applied to the whole organism, it becomes oxygen...
consumption = cardiac output \times \text{systemic } a\text-VO}_2 \text{ difference. At rest, textbook values in young healthy males weighing around 70 kg are typically } \sim 5 \text{ l/min for cardiac output} \ (40, 431). \text{ This cardiac output is achieved via a combination of a heart rate of } \sim 70 \text{ beats per minute (bpm) and a stroke volume of } \sim 70 \text{ ml/beat. At sea level, hemoglobin values typically average } \sim 14\text{–}15 \text{ g/dl (} \sim 9 \text{ mM)} \text{ in young healthy men, and this hemoglobin is } \sim 98\% \text{ saturated with oxygen. Because the oxygen-carrying capacity of a gram of hemoglobin is } \sim 1.34 \text{ ml (186), each liter of blood pumped by the heart carries } \sim 200 \text{ ml of oxygen. So, } \sim 1 \text{ liter of oxygen leaves the heart each minute in an average-sized healthy young male at rest. These values (see TABLES 1 AND 2) represent what was once referred to “reference man,” which typically means they were obtained in young healthy male undergraduate or medical students who were relatively lean, normally active, and weighed } \sim 70 \text{ kg} \ (19, 33, 338). \text{ These values have likely declined on a population basis with the recent widespread increases in body fat and reductions in physical activity. However, the specific determinants of resting oxygen delivery cited above vary based on the size of the individual, blood pressure, and hemoglobin. For example, resting cardiac output is higher in anemic individuals or after normovolemic hemodilution (244, 503). Nonetheless, the convective transport of oxygen leaving the heart remains relatively constant under most circumstances at rest.}

When measurements of mixed venous oxygen saturation are made in reference man, blood sampled in the pulmonary artery is typically } \sim 75\% \text{ saturated} \ (39, 40, 323). \text{ This means that } 50 \text{ ml of oxygen is extracted from the peripheral circulation for each liter of blood leaving the heart per minute. Thus, when cardiac output is } 5 \text{ l/min, resting oxygen consumption is } \sim 250 \text{ ml/min or } \sim 3.5 \text{ ml·kg}^{-1} \text{·min}^{-1}. \text{ A key concept is that only a small fraction of the available oxygen delivered to the periphery by the arterial blood is in}

<table>
<thead>
<tr>
<th>Table 2. Reference physical characteristic values</th>
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<tr>
<td>Reference Man</td>
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<tr>
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<tr>
<td><strong>Weight, kg</strong></td>
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<tr>
<td>Sed</td>
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<tr>
<td>Active</td>
</tr>
<tr>
<td>Elite</td>
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<tr>
<td><strong>Height, cm</strong></td>
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<tr>
<td><strong>Age, yr</strong></td>
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<tr>
<td><strong>Lean body weight, kg</strong></td>
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Lean body mass has a marked influence on all of the hemodynamic values (see Table 1).
fact consumed. Additionally, oxygen extraction can vary by tissue, and ~70% of available oxygen is extracted in the coronary circulation at rest and only ~20–30% (or less) in the brain, kidney, and splanchnic circulations (44, 45, 86, 137, 265, 395). These patterns of organ-specific oxygen extraction at rest suggest that blood flow might be safely diverted away from tissues like the liver and kidney during exercise. However, blood and blood flow have other functions beyond gas exchange. These include important roles in metabolism and waste elimination along with fluid and electrolyte balance. Perhaps these functions are better supported by blood flow well in excess of that required to deliver the needed oxygen to specific resting tissues.

B. How Do Cardiac Output and Oxygen Extraction Change With Exercise?

During maximum exercise, heart rate increases to values of ~200 bpm in young healthy humans. The classical view is that this increase in heart rate is accomplished by a combination of vagal withdrawal at the onset of exercise (up to a heart rate of ~100 bpm) and increases in sympathetic nerve activity to the heart (379, 492). However, there is evidence from animal models that cardiac sympathetic nerve activity rises with the onset of exercise (246, 480). Additionally, some care needs to be taken when interpreting data from the human studies that use drugs to evaluate this issue because vagal withdrawal can be very fast and potentially occur within one heartbeat. The onset of sympathetic neural activity might also happen quickly, but the effects on heart rate might take several seconds or more to observe due to the more diffuse nature of sympathetic innervation and slower conduction velocity in the sympathetic nervous system compared with vagal control of the sinoatrial (SA) node.

Stroke volume also increases at the onset of exercise due to a complex interplay of factors including increased myocardial contractility and depending on posture (upright vs. supine) how much blood is returned to the central circulation via the skeletal muscle pump which acts to empty the veins in the lower extremities where blood pools due to gravity (40, 41, 274). Likewise, increases in respiration may also serve to improve venous return to the heart (321). In reference man, a stroke volume of ~100 ml/beat would be typical, meaning that maximum cardiac output might reach a value of ~20 l/min. Again, values vary based on body size, body composition, and sex of the subject. In general, cardiac and lung volumes are scaled on the basis of the allometric relationships discussed earlier (FIGURE 2). These relationships are most clearly seen when there are several log differences (10- to 100-fold or greater) in body size between species. However, in elite endurance athletes from disciplines that favor different-sized participants (e.g., small runners vs. large rowers), it is possible to see the impact of scaling on a number of variables related to oxygen uptake (231).

During maximal exercise in an untrained reference man, mixed venous oxygen saturation falls from ~75% at rest to ~25–30%. This means that ~140–150 ml of oxygen is extracted by the peripheral tissues for each liter of cardiac output. FIGURE 5 shows the classic data from the 1950s on oxygen extraction at rest and during exercise from Mitchell et al. (323). With the use of the values outlined above, whole body oxygen consumption would be ~3 l/min or 43 ml·kg⁻¹·min⁻¹ which is similar to the data reported by these investigators. Of note from this paper are the very low values for oxygen saturation (<20% in some subjects) of blood draining the femoral vein during heavy exercise. Venous saturation from the less active arms also fell from ~50 to 25% during treadmill running consistent with the idea that blood flow is redistributed to the contracting muscles during heavy exercise. Under these conditions, oxygen consumption in the less active arms can be supported with reduced total blood flow and more oxygen extraction.

C. Blood Flow Redistribution

Blood flow redistribution also occurs in vascular beds other than the less active skeletal muscles. For example, as a result of sympathetic vasoconstriction, renal and splanchnic
blood flow can both fall to ~25% of resting values during heavy exercise in humans, but oxygen consumption in these tissues is preserved by marked increases in extraction (86, 395, 396). Blood flow to the kidneys at rest is ~1.2 l/min, and the liver receives ~1.6 l/min; this means that two liters of blood flow can be redirected from these vascular beds to the skeletal muscles during heavy exercise. Cerebral blood flow is ~0.75 l/min or 15% of resting cardiac output. This absolute value does not change dramatically during exercise or perhaps increases slightly (21, 180). Coronary blood flow increases three- to fourfold from 0.15–0.20 to 0.5–0.8 l/min during maximum exercise driven primarily by the increased heart rate (137, 236, 254, 296, 351, 482). It is also important to point out that sympathetically mediated blood flow redistribution in visceral organs does not happen in all species. Dogs, for example, can perform prodigious feats of prolonged high-intensity endurance exercise while renal blood flow remains near values observed in resting animals (485).

A key integrative point from the data above is that ~4 l/min or ~80% of cardiac output is directed to the brain, heart, kidneys, and liver in a human at rest. This means, as shown in Figure 6, that ~1 l/min of blood flow, 200 ml of oxygen delivery, and perhaps 50 ml of oxygen consumption are sufficient to support resting metabolism in the other 80–90% of body tissues. The physiological implications and mechanisms responsible for the redistribution of blood flow during exercise will be discussed in several contexts in upcoming sections of this review.

One puzzling element of these responses is that based on the low oxygen extraction across the brain, it might viewed as relatively “over perfused” at rest like the liver and kidney. However, unlike the liver and kidney, the brain is not subject to a marked reduction in blood flow during heavy exercise in humans.

Figure 6 demonstrates a range of values for maximal oxygen uptake in young healthy subjects of both sexes (18). It also includes data from individuals who are not formally trained but are involved in high physical activity, non-mechanized lifestyles such as traditional hunting and gathering or muscle-powered farming. While there are many changes that occur in humans as a result of aging that can influence these values, the primary factor appears to be a reduction in maximal heart rate with age (344, 461, 473).
The effects of aging on changes in stroke volume are confounded by reduced physical activity and coexisting diseases such as hypertension. However, stroke volume can be preserved in physically active otherwise healthy older subjects (203).

**D. What Are the Effects of Endurance Training?**

With endurance exercise training there can be an increase in left ventricular mass and chamber volume without wall thickening, a phenomenon known as eccentric cardiac hypertrophy (326, 447, 483). This adaptation augments stroke volume and thus maximum cardiac output (maximum heart rate does not change much) (10, 144, 274, 414). This increase in stroke volume is also facilitated by training-induced increases in blood volume that include both increases in red cell mass and plasma volume (94, 95). While healthy untrained subjects can increase their stroke volume by ~20% with standard aerobic exercise training programs, at least some individuals have much more robust responses while others are likely less “trainable” (51, 514). Much greater training induced increases in stroke volume may also be possible with more intense and prolonged training (20, 144, 211).

In addition to changes in stroke volume, peripheral oxygen extraction can increase modestly with training. This is due to increased capillary density in the trained skeletal muscles that facilitates very high levels of oxygen extraction across exercising skeletal muscle vascular beds (5, 104, 143, 313, 314).

In parallel with these structural changes in the heart and the increase in skeletal muscle capillarity, there can be up to approximately twofold increases in skeletal muscle mitochondrial content with endurance training (216, 218). In the 1970s, this increase in mitochondrial content was thought to contribute to training-induced increases in \( \text{VO}_{2\text{max}} \). However, subsequent studies in rodents were able to dissociate changes in skeletal muscle mitochondrial content with training and \( \text{VO}_{2\text{max}} \) (113, 217, 218). Parenthetically, skeletal muscle mitochondrial content and how it changes with training are major determinants of submaximal endurance performance. These changes also have important implications for substrate metabolism especially during prolonged exercise in both humans and other species (218). In contrast to the heart and skeletal muscle, in most cases the pulmonary system does not show major adaptive changes to endurance exercise training (184, 320, 406). However, lifetime exposure to high altitude can increase both lung volumes and diffusing capacity (87).

When typical adaptive values in response to prolonged endurance exercise training are considered, a 20% increase in stroke volume and cardiac output along with a 5–10% increase in oxygen extraction would lead to a \( \text{VO}_{2\text{max}} \) value of ~4 l/min in many young healthy male subjects (224). If this was accompanied by a 5–10% loss of body weight, it would appear that a \( \text{VO}_{2\text{max}} \) value up to ~60 ml·kg\(^{-1}\)·min\(^{-1}\) is achievable in many young males. Maximum values ~10–15% lower are possible in young healthy females who are highly trained but not elite endurance athletes. Such a highly trained but nongenius subject is shown in FIGURE 4, and as mentioned earlier, values in this range are similar to measurements and estimates made in hunter gatherer and pastoral populations.

**E. What Are the Values in Elite Athletes?**

Elite male athletes can typically have \( \text{VO}_{2\text{max}} \) values between 70 and 85 ml·kg\(^{-1}\)·min\(^{-1}\) and up to 6 or even 7 l/min (231, 361, 372). Almost all of this, compared with their well-trained but nongenius counterparts, is due to very large stroke volumes. Values of ~200 ml·beat have been reported using invasive techniques in otherwise normal-sized men (146). Thus a maximum cardiac output of 35–40 l/min is possible in elite male endurance athletes. These values are consistent with the idea that some individuals respond impressively to training. When elite endurance athletes retire from training and become inactive, their \( \text{VO}_{2\text{max}} \) drifts downward towards values similar to untrained controls (105, 106, 473).

While it is assumed that genetic factors may explain why some individuals have an impressive ability to increase their stroke volume in response to endurance exercise training, the evidence for a single or limited number of DNA variants explaining this phenomenon has not emerged. There is evidence that a suite of genetic markers can explain a significant portion of the variable increase in \( \text{VO}_{2\text{max}} \) in response to fitness style training (469); however, it is not clear how these markers influence the stroke volume responses to training. Even less information is available concerning genetic factors that might influence physiological adaptations to the type of prolonged intense training performed by elite endurance athletes. Moreover, success in elite endurance athletics, like most human phenotypes, probably represents a combination of environmental exposures and behavioral factors (e.g., training) that operate in concert with a large number of gene variants and other epigenetic factors (287). There are data suggestive that genetic variability in angiotensin converting enzyme (ACE) might explain at least part of the very high stroke volumes and \( \text{VO}_{2\text{max}} \) values seen in elite athletes. However, the evidence is not convincing for common ACE variants. Likewise, gene variants related to mitochondrial function do not explain the very high \( \text{VO}_{2\text{max}} \) values seen in elite endurance athletes (372, 378).

The high values noted above also appear to be scaled for body size when comparisons are made between very large endurance athletes like rowers and smaller competitors like

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558 Physiol Rev • VOL 95 • APRIL 2015 • www.prv.org
EXERCISE HYPEREMIA: A HIERARCHY OF PHYSIOLOGICAL NEEDS

runners. In endurance sports like swimming and rowing, large body size can be advantageous (424). Elite male rowers who are typically 1.9–2.0 m tall and weigh 90–100 kg can have VO₂max values in excess of 7 l/min (339). VO₂max values for elite women are typically ~10–15% lower on a per kilogram basis. Given that elite women are typically smaller than men, a VO₂max value of 5 l/min would be remarkable (158, 226, 238, 339, 421).

An additional concept that underpins this entire discussion is that these high VO₂max values can be achieved during activities like cycling or running that engage perhaps only 50% of whole body skeletal muscle mass. Under most circumstances and in most subject groups, adding arm exercise to leg exercise does not increase VO₂max further. Exceptions to this general rule include rowers and cross-country skiers, who have highly trained arms and legs. In these subjects, adding arm exercise to leg exercise results in a VO₂max that is 5–10% higher than the peak response seen during leg exercise alone (423, 459).

Finally, another important observation in elite male athletes is that some have a tendency to experience arterial hypoxemia (exercise-induced arterial hypoxemia, EIAH) during heavy whole body exercise (122). While EIAH has not been reported in untrained male subjects, it has been reported in untrained female subjects, and it may be more prevalent in elite female endurance athletes (133, 199, 222, 223). This hypoxemia is due to the complex interactions between the very high cardiac outputs detailed above, flow limitation at very high minute ventilations, ventilation perfusion matching, pulmonary diffusing capacity, and physiological shunts through the lung. The predominant mechanism or mechanisms accounting for this desaturation is a matter of ongoing debate in the pulmonary and exercise physiology communities (3, 118, 122, 198, 219, 233, 353, 366, 367). It is also important for the nonexpert to recognize that in male endurance elite athletes, minute ventilations in excess of 150 l/min are frequently seen (8, 493).

F. Summary

Oxygen consumption can increase 10- to 15-fold above values at rest during exercise in healthy young untrained humans with 20-fold or higher increments seen in highly trained elite endurance athletes. These increases in oxygen consumption are driven by a four- to eightfold increase in cardiac output resulting from acute increases in heart rate and stroke volume and in the case of trained subjects (especially elite athletes) structural changes in the left ventricle that increase stroke volume further. The increases in cardiac output are also accompanied by two- to threefold increases in whole body oxygen extraction. Increased whole body extraction is driven by high arterial-venous O₂ differences in the exercising muscles and reduced blood flow to less active skeletal muscle and the renal and splanchnic vascular beds. Increases in capillary density in the trained skeletal muscles also augment oxygen extraction and contribute to the rise in VO₂max with training.

It is also important to note that in certain “athletic” species including dogs and ponies, VO₂max values in excess of 120 ml·kg⁻¹·min⁻¹ are seen with values of 140–150 ml·kg⁻¹·min⁻¹ reported in both foxhounds and thoroughbred horses (30, 332, 364). Incredibly, pronghorn antelopes are thought to have VO₂maxs in excess of 200 ml·kg⁻¹·min⁻¹ based on the fact that they can run 11 km in 10 min (282). All of these athletic species have unusually high heart-to-body weight ratios (502) with scaled stoke volumes ~1.6 times greater than those seen in less athletic animals. They also possess contractile spleens that store red blood cells which are mobilized during exercise to increase hematocrit and thus arterial oxygen carrying capacity (42, 43, 220, 221, 285, 455). Finally, there are reports of a VO₂max of >90 ml·kg⁻¹·min⁻¹ in an Olympic medalist with a genetic mutation that caused him to have very high hematocrit and hemoglobin levels (245).

IV. TOTAL SKELETAL MUSCLE BLOOD FLOW

Because most of the oxygen consumed during exercise is used by the contracting skeletal muscles, we will now focus on maximal or peak skeletal muscle blood flow. To address the topic of maximal or peak skeletal muscle blood flow, we must first understand what fraction of cardiac output is directed to skeletal muscle and then how much skeletal muscle mass is contracting during heavy exercise. This will then set the stage for subsequent discussions about peak or maximum blood flow values and how these values interact with exercising muscle mass to generate the impressive increases in oxygen consumption outlined above. After we discuss the relevant concepts and data, the factors which contribute to the rise in skeletal muscle blood flow during exercise will be the next major topic for discussion.

On the basis of the concepts outlined earlier, if cardiac output was 20 l/min with 0.5 liters directed to the heart, 0.75 liters directed to the brain, and 0.7 liters directed to renal and splanchnic vascular beds, this would permit ~18 l/min of blood flow be directed to skeletal muscle (see FIGURE 6). Parenthetically, blood flow to the skin is minimal unless the cutaneous vascular bed dilates for the purposes of thermoregulation. During severe thermal stress, total skin blood flow can reach 6–8 l/min in healthy young males. This makes exercise in warm (especially humid) environments perhaps the greatest overall challenge to the human cardiovascular system due to a three-way competition between blood pressure regulation and the need for high levels of both muscle and skin blood flow (389).

Thus, if we take the range of cardiac outputs in normal humans to be between 20 and 40 l/min for healthy young...
men, and 15–30 l/min for healthy young women (the upper limits in both sexes reflecting elite endurance athletes), then total muscle blood flow can reach 30–35 l/min in average-sized men who are elite endurance athletes. Hypothetically, even higher values might be possible in very large elite endurance athletes like rowers, with \( V_{\text{O2max}} \) values in excess of 7 l/min (339). **Figure 6** emphasizes these concepts and shows the regional distribution of cardiac output in a hypothetical resting normal young male of \( \sim 70 \) kg and how this changes with maximal exercise. For comparison sake, it also shows similar estimates for a highly trained elite endurance athlete.

Another way to estimate total skeletal muscle blood flow is to assume that almost all of the increase in oxygen consumption caused by exercise is occurring in the contracting skeletal muscles. Additionally, most (\( \sim 90\% \)) of the oxygen delivered to the leg muscles during maximum running or cycling is being extracted. Since oxygen consumption by nonexercising tissues does not increase, and based on the idea that each liter of arterial blood carries 200 ml of oxygen, it then takes \( \sim 6 \) liters of cardiac output for every liter of whole body oxygen consumption (40). If all of the available oxygen were extracted, it would take \( \sim 5 \) liters of skeletal muscle blood flow to generate 1 liter of additional whole body oxygen uptake during exercise. The values can vary depending on factors such as hematocrit and hemoglobin concentration, but estimates of total skeletal muscle blood flow generated on the basis of either cardiac output or increments in oxygen consumption are generally convergent. Both approaches emphasize that during heavy whole body exercise the vast majority of cardiac output goes to contracting muscles.

**V. PEAK VALUES FOR SKELETAL MUSCLE BLOOD FLOW**

Given the values for whole body skeletal muscle blood flow outlined above, the question then becomes what is peak or maximum blood flow per kilogram of contracting muscle? This question is obviously confounded by both the mass of active muscle and perfusion pressure because blood flow to a given vascular bed reflects both. However, in young healthy subjects, and especially in endurance-trained subjects, mean arterial pressure rises only modestly during heavy exercise as a result of the marked vasodilation in the skeletal muscles (92). This means that vasodilation in the contracting muscles far outstrips changes in blood pressure as the major determinant of exercise hyperemia in humans and most species under most circumstances.

**A. Active Muscle Mass**

Before we address the flow- and pressure-related issues, a few ideas about muscle mass are critical. Skeletal muscle typically comprises 40–50% of lean body mass in young humans, with the lower range reflecting women who have relatively less skeletal muscle mass than men (33). This means that for a 70 kg man with roughly 60 kg of lean body mass (see **Tables 1 and 2**), total muscle mass is \( \sim 30 \) kg. For a 55 kg reference woman with \( \sim 40 \) kg of lean body mass, there would be \( \sim 20 \) kg in total muscle mass (these values assume 15 and 25% body fat for reference man and woman, respectively). Along these lines, for running and cycling, a reasonable assumption for contracting skeletal muscle in young men might be 10–15 kg (33–50% of skeletal muscles mass) based on both imaging and anthropometric techniques (370). Additionally, the respiratory muscles are perhaps \( \sim 2 \) kg and highly active during heavy exercise (191).

**B. Mean Arterial Pressure**

A second important point raised earlier is that mean arterial pressure typically remains \( \sim 100 \) mmHg during aerobic whole body exercise and does not rise markedly above resting values in young healthy humans (91). For example, in the study on elite cross country skiers we discuss next, mean arterial pressure during whole body exercise was \( \sim 95 \) mmHg (67, 68). While blood pressure does rise during exercise, the classic baroreceptor resetting studies of Donald and colleagues (315) in dogs show that during heavy exercise the operating point rises by about 15–20 mmHg. This means that the rise in pressure can be \(<20\%\) while cardiac output is increasing four- to eightfold. Under these circumstances, the vast majority of cardiac output is going to the contracting skeletal muscles and the major factor accounting for this rise in flow is vasodilation. However, depending on the mode of exercise and subject group, a rise in blood pressure of 30–40% during dynamic exercise is not uncommon (6, 376, 422). In this case, the pressor response would amplify the increase in flow caused by the vasodilation by an amount proportional to the increase in pressure.

However, pulse pressure can increase dramatically during whole body exercise due to reductions in diastolic pressure caused by peripheral vasodilation in the contracting muscles and increases in systolic pressure caused by large stroke volumes ejected quickly into the aorta (397). This contrasts with the large increases in mean, systolic, and diastolic arterial pressure seen during even small muscle mass static exercise (2, 56) with even larger increases seen during heavy weight lifting (290). In this context, using an arbitrary value for mean arterial pressure of \( \sim 100 \) mmHg during rhythmic exercise will permit us to focus on blood flow, which is typically the measured variable in most experimental paradigms and also the variable most closely linked to oxygen delivery to the contracting muscles.
C. What Do Cardiac Output, Total Muscle Blood Flow, and Active Muscle Mass Tell Us About Peak Muscle Blood Flow?

If blood flow were equally distributed to all 30 kg skeletal muscles in an untrained male with a peak cardiac output of 20 l/min and ~18 l/min of total skeletal muscle blood flow during heavy exercise, muscle blood flow would be ~60 ml·min⁻¹·100 g muscle⁻¹. These values would increase by ~20% in highly trained subjects and might conceivably double in some elite endurance athletes. If 10–15 kg of muscle were active, then skeletal muscle blood flow would be in the range of 120–180 ml·min⁻¹·100 g muscle⁻¹ in young healthy untrained subjects and values 50–100% higher are possible elite athletes (275, 438). Since V̇O₂max per kilogram of lean tissue (as opposed to total body weight) is generally similar in men and women across training and athletic status, these values usually apply to both sexes. Along these lines, measurements of leg blood flow in elite cross-country skiers during whole body exercise that elicited a cardiac output of 30 l/min report values of ~20 l/min or roughly 200 ml·min⁻¹·100 g⁻¹. At the same time blood flow to the upper extremity in these athletes was ~5 l/min (67).

The calculations, estimates, and experimental values from the skiers all relate to large muscle mass or even whole body exercise. Importantly, they are much higher than the traditional values for maximum muscle blood flow obtained using techniques including venous occlusion plethysmography or xenon (¹³³Xe) clearance (88, 187, 241, 368, 457). In this context, perhaps “the” major advance in the field of exercise hyperemia over the last 30 years (since the Shepherd Handbook chapter of 1983, see Ref. 431) has been the observation that much higher skeletal muscle blood flows are possible in humans and other species.

Prior to the 1980s, maximum skeletal muscle blood flow in humans was thought to be in the range of 50–80 ml·min⁻¹·100 g⁻¹. Notably these values were also about twofold lower than those observed (~100–150 ml·min⁻¹·100 g⁻¹) using various electrical stimulation paradigms to evoke muscle contractions in isolated perfused dog hindlimb preparations (24, 131, 225, 448).

D. Discovery of Much Higher Values

In the early and middle 1980s, several groups began to investigate the issue of maximum skeletal muscle blood flow during exercise in rats, dogs, ponies, and also humans (6, 14, 15, 295, 297, 331, 333, 350, 376). The animal studies used radiolabeled microsphere injections during treadmill running, and the human studies used continuous thermodilution (and later Doppler ultrasound; Ref. 500) during single leg kicking exercise to isolate blood flow to the contracting quadriceps muscles. This means that the animal studies were whole body while the human study focused on a limited mass (2–3 kg) of active muscle. This is an important point because compared with dogs and ponies, humans have relatively small hearts and limited peak or maximum cardiac output.

In both humans and animals, the revision of ideas about peak blood flow was due in part to technical advances. However, there was evidence in the 1970s for high peak muscle blood flow (200 ml·min⁻¹·100 g⁻¹) in the diaphragm muscles of the heat stressed panting greyhound (191). Indicator dilution techniques were used to measure leg blood flow in humans in the 1960s and 70s during large muscle mass exercise, making it hard to assess maximum flow in a limited mass of active muscle (235, 248, 495). A key issue for the animal studies was ensuring that there was adequate mixing and distribution of the radiolabeled microspheres so that the quantity of microspheres embedded in the tissues during exercise reflected the blood flow. For the human studies, a relatively small mass of active muscle that can perform rhythmic exercise needed to be identified. For thermodilution to work, the arterial inflow and venous outflow to the muscle had to have straightforward vascular anatomy that limited potential contamination from other vascular beds. Additionally, these vessels needed to be easily accessible for catheter placement.

TABLE 3 shows values expressed as milliliters of blood flow per minute per 100 g of muscle from a number of human and animal studies showing high values for skeletal muscle blood flow (6, 14, 15, 295, 297, 331, 333, 350, 376). FIGURE 7 shows the data from three early studies that led to the revision of ideas about peak blood flow values in contracting skeletal muscles during exercise (6, 15, 333). The data in TABLE 3 and FIGURE 7 show that values in the range of 200–300 ml·min⁻¹·100 g⁻¹ are possible. The key point is that values are two- to fourfold higher than the previously widely accepted “peak” values of 50–100 ml·min⁻¹·100 g⁻¹. They are also substantially higher than values observed in isolated dog hindlimb preparations. It should be noted that there can also be large regional differences in peak blood flow associated with muscle fiber type in rodents (15, 269, 291, 334). Fiber type is highly compartmentalized in these animals so that in specific areas of a given muscle the fiber type composition is relatively homogeneous. However, in humans, most skeletal muscle has a “mixed” or mosaic pattern so regional differences are probably less pronounced (14, 15, 278).

These very high muscle blood flows are typically associated with only modest increases in blood pressure from rest. Additionally, the highest values in selected muscle groups are on the order of 350 ml·min⁻¹·100 g⁻¹, and flows of ~385 ml·min⁻¹·100 g⁻¹ have been reported in elite cyclists during one-leg kicking (47, 377). Comparable flows have reported in the respiratory muscles of ponies during heavy
One caveat about the human measurements is that perfusion pressure in the lower extremities might be higher than systemic perfusion pressure. This is because the skeletal muscles are below heart level and gravity can augment perfusion pressure. This augmented perfusion pressure, in conjunction with the skeletal muscle pump, which would keep venous pressure extremely low, could contribute to the high blood flows seen in humans during leg kicking (267). Studies in normal humans, patients with valvular insufficiency, and patients with a congenital absence of venous valves all support this interpretation (41, 359, 360, 454). These studies indicate that the muscle pump operates to increase the perfusion pressure gradient across a dependent exercising limb by keeping ve-

<table>
<thead>
<tr>
<th>Author</th>
<th>Species</th>
<th>Exercise Mode</th>
<th>Muscle Group(s)</th>
<th>Blood Flow, ml·min⁻¹·100 g⁻¹</th>
</tr>
</thead>
</table>
| Armstrong and Laughlin, 1983; Ref. 14 | Sprague-Dawley rats | Treadmill running (speed = 60 m/min) | Knee extensors | Vastus intermedius 396 ± 36  
Vastus medialis 284 ± 42  
Vastus lateralis 92 ± 39  
Red 389 ± 50  
Middle 224 ± 32  
White 86 ± 18  
Rectus femoris 18 ± 12  
Red 312 ± 38  
White 166 ± 16 |
| Armstrong and Laughlin, 1985; Ref. 15 | Sprague-Dawley rats | Treadmill running (speed = 105 m/min) | Knee extensors | Vastus intermedius 495 ± 73  
Vastus medialis 325 ± 47  
Vastus lateralis 98 ± 24  
Red 495 ± 66  
Middle 293 ± 50  
White 102 ± 24  
Rectus femoris 18 ± 12  
Red 363 ± 47  
White 173 ± 23 |
| Musch et al., 1987; Ref. 333 | Exercise-trained foxhounds | Treadmill running (maximal) | Gracilis 252 ± 22 |
| Musch et al., 1987; Ref. 331 | Untrained mongrel dogs | Treadmill running (maximal) | Gracilis 206 ± 12  
Gastrocnemius 255 ± 17  
Semimembranosus 330 ± 26  
Semitendinosus 128 ± 14 |
| Parks and Manohar, 1983; Ref. 350 | Ponies | Treadmill running (32 km/h) | Diaphragm −215 ± 20 |
| Manohar, 1986; Ref. 293 | Ponies | Treadmill running (32 km/h) | Diaphragm 265 ± 36  
Gluteus medius 253 ± 36  
Biceps femoris 233 ± 29  
Triceps brachii 227 ± 26 |
| Manohar, 1990; Ref. 295 | Ponies | Treadmill running (32 km/h at a 7% grade) | Diaphragm −325 ± 25 |
| Andersen and Saltin, 1985; Ref. 6 | Humans | Single leg kicking (maximal; avg 54W) | Knee extensors 247 ± 18 |
| Richardson et al., 1995; Ref. 376 | Exercise-trained (cyclists) humans | Single leg kicking (maximal; avg 95W) | Knee extensors 386 ± 26 |

Values are means ± SE.
nous pressure low. It also facilitates venous return and cardiac filling (41).

E. Why Were Values for Peak Blood Flow Before the 1980s so Low?

Given the fact that detailed measurements of oxygen consumption, cardiac output, and deep venous oxygen saturation were available in athletes by the later 1950s and during the 1960s, it is interesting to consider why the accepted values for peak or maximum skeletal muscle blood flow were so low for so long. There was also excellent VO₂ and hemodynamic data on dogs running at high speed (485). In retrospect, estimates of the mass of contracting muscle consuming the oxygen along with the amount of blood flow and extraction required to support this level of oxygen consumption should have been possible. Such estimates would have raised serious questions regarding the values obtained using venous occlusion plethysmography in the forearm and calf or ¹³³Xe washout in other muscles.

The low peak muscle blood flows measured using venous occlusion plethysmography have several explanations (241). First, the whole forearm or calf volume is the tissue denominator and the limbs include fat, bone, and skin as well as muscle. Second, for plethysmography to work, the limb needs to be above heart level. Additionally, during high flow states, venous congestion can increase very quickly during plethysmography and reduce perfusion pressure and flow. In the case of the leg, this has the effect of lowering perfusion pressure compared with the upright posture. Third, the measurements are made during brief pauses in contraction so any contribution of the muscle pump acting locally on the microcirculation to increase flow is lost (however, any impedance to flow caused by the contractions would also be minimized) (478). In the case of the calf, the muscle pump also minimizes venous pressure and ensures that any gravitational augmentation of arterial pressure that occurs in the upright posture can be fully expressed (359, 360). If these mechanisms each led to a 50% underestimation of peak muscle blood flow and they interacted, they could provide at least a partial explanation for the discrepancy between the older and more recent observations. For example, peak calf blood flow between 60 and 80 ml·min⁻¹·100 g⁻¹ after ischemic exercise was reported by Snell et al. (445) in untrained men and endurance athletes, respectively. If adjusted for the factors just outlined, these observations would translate to estimates of flow on the order of ~200 ml·min⁻¹·100 g⁻¹. These estimates are still relatively low, but closer to the more recent values measured with thermodilution, by Doppler ultrasound, and in the case of animal microspheres.

Like venous occlusion plethysmography, there are issues associated with the ¹³³Xe washout technique (88, 92, 187). In this technique, radioactive xenon is injected into a tissue and the rate of washout from the tissue is proportional to the blood flow. The time resolution of this technique is
slow, the relationship between the external radiation counter and the xenon can be variable, and a host of assumptions about the tissue distribution of the label and washout are required. While it is easy to criticize this technique in retrospect, it provided key insights into cerebral blood flow and ventilation perfusion matching that were also applied diagnostically prior to the advent of other imaging techniques (266, 319, 520).

It is also interesting to note that peak values for muscle blood flow made using in situ dog hindlimb preparations with electrical stimulation protocols designed to elicit “maximal” responses are on the order of 100–150 ml·min⁻¹·100 g⁻¹ (225). This is in spite of the fact that the vast majority of blood flow in the dog hindlimb during contractions or exercise is directed to skeletal muscle. This raises questions about the role of normal exercise (vs. electrically stimulated contractions) in evoking a coordinated pattern of mechanical forces that augment skeletal muscle perfusion. Importantly, tetanic contractions that normally evoke “maximal” blood flow responses in preparations that are prevasodilated with adenosine and sodium nitroprusside actually lower hindlimb blood flow (131). Additionally, the values observed (~170 ml·min⁻¹·100 g⁻¹) remain lower than those seen with microspheres during voluntary exercise as summarized in Table 3. The reasons for this “lower peak flow” during pharmacological vasodilation are not clear, but perhaps relate to a washout of dilating “lower peak flow” during pharmacological vasodilation. Importantly, tetanic contractions that normally evoke “maximal” blood flow responses in preparations that are prevasodilated with adenosine and sodium nitroprusside actually lower hindlimb blood flow (131). Additionally, the values observed (~170 ml·min⁻¹·100 g⁻¹) remain lower than those seen with microspheres during voluntary exercise as summarized in Table 3. The reasons for this “lower peak flow” during pharmacological vasodilation are not clear, but perhaps relate to a washout of dilating factors and loss of coordinated flow regulation at the level of the microcirculation. There could also be alterations in how the muscle pump affects flow during concurrent administration of vasodilating drugs. Finally, the contractions themselves might impede flow by compressing the intramuscular arterioles and venules (9, 28, 280, 470).

**F. Is There a Maximum Value for Skeletal Muscle Blood Flow?**

The surprising magnitude of the blood flow values described in the 1980s led to questions about the upper limits for skeletal muscle blood flow. In this context, blood flow to cardiac muscle in the left ventricle can equal ~500 ml·min⁻¹·100 g⁻¹ in equines during heavy exercise (12, 296, 298, 351) with values of 300–400 ml·min⁻¹·100 g⁻¹ seen in other species including humans (150, 204, 264, 519). Estimates of skin blood flow equal to 6–8 l/min distributed in perhaps 2 kg of skin in heated humans would also seem to rival the per 100 g values seen in skeletal and cardiac muscle (389). When additional vasodilator stimuli (either drugs or hypoxia) are superimposed on heavy exercise, under some circumstances there can be further vasodilation. For example, addition of hypoxia during one-leg kicking in healthy untrained young male subjects augmented skeletal muscle blood flow from ~270 to 300 ml·min⁻¹·100 g⁻¹. This ~10% increase in muscle blood flow demonstrated that significant further vasodilation was possible in this subject group (399). In contrast, Manohar (297) infused adenosine into skeletal muscle vascular beds of ponies performing heavy exercise and found no additional increase in blood flow. Of note, in humans studies, with the exception of ATP (181, 329), infusions of high doses of potent vasodilators in the femoral artery at rest typically evoke peak blood flow responses somewhat lower than those seen during heavy exercise (330, 371).

**G. Summary**

Oxygen consumption can increase above resting values 10- to 15-fold during exercise in normal healthy young humans.

This peak value for oxygen uptake can increase 20–50% in most subjects as a result of prolonged intense exercise training and can be 20-fold or greater above resting in elite endurance athletes.

During exercise, each liter of oxygen consumption is typically associated with ~5–6 l of cardiac output. This increase in cardiac output is a result of an increase in heart rate and stroke volume.

The primary effects of endurance exercise training relate to increases in cardiac output driven by an augmented stroke volume due to left ventricular hypertrophy and increases in blood volume. Elite athletes have remarkably high stroke volumes and large blood volumes (94, 95, 414). Cardiac output values of 40 l/min have been seen in elite male endurance athletes (146).

There can be an increase in capillary density in the vascular bed of the trained muscles which can further augment oxygen delivery and extraction. This is especially important during large muscle mass exercise when oxygen extraction can be 80–90%. During small muscle mass exercise including both handgripping and one-leg kicking deep venous saturation during heavy exercise remains at about 30% meaning that only 70% of the available oxygen is extracted. These high values for venous saturation have been interpreted to reflect either “luxury perfusion” for a given oxygen consumption or admixture of venous blood from noncontracting tissue in the limb including skin. In this context, older evidence suggests that deep venous samples from the forearm are relatively uncorrupted by skin blood flow (27, 93).

Based on a number of calculations and also derived from data collected primarily in the 1980s, our understanding of the actual upper limits of skeletal muscle blood flow has increased. Values on the order of 300–400 ml·min⁻¹·100 g⁻¹ are possible. These higher values were discovered due to advances in blood flow measurement techniques and insightful experimental designs.
VI. THE AUTONOMIC NERVOUS SYSTEM: BLOOD PRESSURE VERSUS BLOOD FLOW TO CONTRACTING SKELETAL MUSCLES

We now make the case that blood flow to the contracting muscles is normally restrained by the sympathetic nervous system during heavy large muscle mass or whole body exercise for the purposes of regulating arterial pressure (120, 343, 398). This has been characterized by Rowell (392) as what might be called the “sleeping giant hypothesis.” This characterization reflects the idea that the vast ability of skeletal muscle to vasodilate can potentially outstrip the ability of the heart to generate an adequate cardiac output and maintain a “reasonable” (~100 mmHg) mean arterial pressure. Such a pressure is required to maintain blood flow to other organs including the brain. When blood pressure is not maintained during exercise as in cases of autonomic failure, blood pressure can fall low enough within a minute of exercise to evoke loss of consciousness due to cerebral hypoperfusion (301).

A. Blood Pressure Is Maintained in Cross-Country Skiers

During the review of systemic oxygen consumption, cardiac output, and values for peak skeletal muscle blood flow, one key discrepancy emerged. Values for skeletal muscle blood flow in quadrupeds, including dogs and ponies that are considered “athletic” animals, are higher than values for skeletal muscle blood flow seen during large muscle mass or whole body exercise in humans. However, they are similar to the values seen in humans during one-leg knee extension exercise. This suggests that blood flow to contracting human muscles is restrained during large muscle mass or whole body exercise. This is true even in elite human athletes with very high cardiac outputs. As shown in FIGURE 8, if blood flow to the arms and legs during whole body skiing had been similar to the values seen during either arm or leg only skiing, then mean arterial pressure would have fallen to ~75 mmHg versus the observed ~95 mmHg assuming no change in cardiac output. The observation that blood pressure did not fall in the skiers can be explained by restraint of blood flow to the contracting muscles under these circumstances. This discussion provides one line of evidence that there can be competition among systemic blood pressure regulation, cardiac output, and the demand by contracting skeletal muscles for blood flow during heavy large muscle mass or whole body exercise in humans (68).

B. Blood Pressure Falls During Exercise in Patients With Autonomic Failure

An early key observation with bearing on the concept that the sympathetic nervous system restrains blood flow to maintain arterial pressure is that arterial pressure falls during exercise in humans with autonomic nervous system failure (301). FIGURE 9 shows the blood pressure responses in a patient studied in the early 1960s who had undergone thoracolumbar sympathectomy to treat malignant hypertension. At that time and for a few decades before the advent of effective drug therapy for hypertension, various forms of surgical sympathectomy were used to treat severe hypertension. These procedures were frequently effective in lowering blood pressure, but orthostatic hypotension was a common side effect (301, 508). Even when this subject shown in FIGURE 9 exercised in the head-down position to maximize venous return and stroke volume, blood pressure still fell during exercise. This particular patient had the normal ability to increase heart rate with exercise because vagal and sympathetic innervation to the heart were intact. However, the blood pressure responses clearly show that unrestrained vasodilation in skeletal muscle outstripped the ability of cardiac output to keep up and generate adequate perfusion pressure for the level of exercise.

C. Peak Cardiac Output and Peak Muscle Blood Flow Are Mismatched

Additional evidence for sympathetic restraint of blood flow to contracting muscles during large muscle mass or whole...
body exercise in humans is simply based on calculations (301, 346, 422). If peak cardiac output is 20 l/min in young healthy untrained men and perhaps 15 l/min in young healthy untrained women, this means that only \( \frac{1}{10} \) of skeletal muscle would be able to be maximally vasodilated in the men and perhaps 4 kg in women before arterial pressure would fall to values of \(<100\, \text{mmHg}\). Along these lines, it is likely that more muscle mass is contracting during large muscle mass exercise like running and cycling in humans.

D. Arm Exercise Added to Cycling Can Reduce Leg Blood Flow

When arm exercise of sufficient intensity is superimposed on ongoing leg exercise, there is some evidence that leg blood flow declines so that cardiac output is “conserved” when total blood flow demand by the exercising arms is increased (422). Likewise, maneuvers that increase the work of breathing and thus the demand for blood flow by the respiratory muscles have been shown to cause reductions in leg blood flow during heavy exercise (197). However, as noted earlier, the effects of adding arm exercise to ongoing leg exercise can be complex and contradictory. This is likely the result of differences in the study protocols and the extent to which the subjects had both highly trained arms and legs (67, 413, 422).

E. Additional Evidence for Sympathetic Restraint of Muscle Blood Flow

There are other lines of evidence consistent with the idea that the sympathetic nervous system normally restrains blood flow to contracting skeletal muscles. Highlights include the following observations: 1) when \( \alpha \)-adrenergic blocking drugs are infused into the vascular beds of contracting skeletal muscles blood flow has been reported to increase in some studies (61, 193, 512). 2) When afferent baroreceptor traffic is increased via either carotid neck suction in humans or electrical stimulation of the carotid sinus nerve in animals during exercise (thus sending a false signal that arterial pressure has increased), there can be a reflex reduction in sympathetic outflow and blood flow to contracting muscles can increase (458, 489). 3) Skeletal muscle blood flow during small muscle mass exercise in healthy older men is generally similar to that seen in younger male subjects (134, 230). During larger muscle mass exercise, muscle blood flow is typically lower in older subjects (32, 134, 271, 365). The idea is that peak cardiac output is reduced with aging and thus more sympathetic restraint of blood flow to contracting skeletal muscles is required to maintain arterial pressure. 4) There are also excellent studies demonstrating this principle from both human patients and experimental animal models of congestive heart failure (195, 348, 369, 407, 460, 468).

F. Small Changes in Flow: Impact on Arterial Pressure

Another key concept stemming from the fact that the vast majority of cardiac output is directed toward skeletal muscle during exercise is that small changes in skeletal muscle blood flow can have a critical impact on arterial pressure. If 80% of cardiac output is directed toward skeletal muscle in a subject with a mean blood pressure of 100 mmHg, vaso-
constriction that restraints skeletal muscle blood flow by 10% will increase mean arterial pressure by ~8%. A 20% reduction will increase mean arterial pressure by 16%. These estimates are supported by the data on skeletal muscle blood flow and calculated mean arterial pressure in the cross-country skiers discussed above. It is also important to remember that in the discussions of peak skeletal muscle blood flow during small muscle mass exercise in humans venous saturation from blood draining these muscles typically remains ~30% saturated. This saturation value is substantially higher than the ~10% venous oxygen saturations seen during heavy large muscle mass or whole body exercise. Because skeletal muscle mitochondria can operate at a very low PO2 (174), this suggests there is a significant margin of safety that allows extraction to increase without threatening oxygen consumption by the contracting skeletal muscles. Thus reducing blood flow to contracting muscle by ~20% to regulate arterial pressure can also explain the very low deep venous saturations in the blood-draining contracting skeletal muscles during heavy large muscle mass or whole body exercise in humans (67, 323, 369).

There are a number of caveats to what might be described as the luxury perfusion hypothesis. First, while skeletal muscle oxygen consumption might not be threatened during large muscle mass exercise by low mitochondrial PO2, maneuvers that cause small increases in blood flow or oxygen delivery can improve performance. Second, deep venous O2 saturation does not provide a detailed picture of conditions in the mitochondria of contracting muscles and how adequate oxygenation is deep in the muscle. However, our major point is that any “overperfusion” seen during small muscle mass exercise provides a margin of “excess” flow that can be constricted without too much compromise during large muscle mass exercise. This then “frees up” blood flow for a larger mass of active muscles and also facilitates the maintenance of arterial blood pressure. So, while the performance of one muscle might not be optimal, the collective perfusion of all of the active muscles during large muscle mass exercise might be optimized given the overall limitation of cardiac output on muscle blood flow and oxygen delivery that we have emphasized.

G. Baroreflex Restraint of Blood Flow to Regulate Arterial Pressure

The carotid neck suction and carotid sinus nerve stimulation data introduced above are consistent with the idea that arterial baroreflexes are ultimately responsible for mediating the competing demands between the contracting skeletal muscles for more blood flow with the need to regulate systemic arterial pressure during exercise. This interpretation is consistent with observations about blood pressure falling during exercise in patients with autonomic failure. Thus it is reasonable to introduce the concept of baroreflex resetting during exercise. The arterial baroreflexes are stretch-sensitive afferent receptor systems located primarily in the carotid sinus and aortic arch. These receptors respond to mechanical deformation. They are stimulated by stretch (classically caused by a rise in arterial pressure) and suppress sympathetic activity and activate vagally mediated bradycardia as part of the reflex blood pressure-lowering responses to the afferent signals (237). However, during exercise, blood pressure, sympathetic activity, and heart rate all increase.

For many years, exercise-related increases in blood pressure and heart rate were primarily attributed to baroreceptor inactivation during exercise. In other words, the baroreceptors were “turned off,” and blood pressure and heart rate were permitted to rise to meet the physiological challenges associated with exercise (237). In the 1960s and 1970s, studies in both humans and animals challenged this concept and instead showed that the baroreceptors were reset so that blood pressure and heart rate continued to be regulated, but at a slightly higher pressure during exercise (38, 39, 315, 489, 496, 497). This is shown graphically in FIGURE 10. Along these lines, Ogoh et al. (345), in an extremely clever experiment, used carotid neck suction to alter carotid baroreflex afferent input during exercise at heart rates of 90, 120, and 150 bpm. They showed that as heart rate increased, blood pressure was regulated less by changes in heart rate and cardiac output with more reliance on changes in vascular tone. Again, because so much blood flow is directed to skeletal muscle during heavy exercise, these observations indicate that skeletal muscle is a major

![FIGURE 10. Demonstration in chronically instrumented dogs of baroreceptor resetting during exercise. This record was generated in animals that had undergone isolation of the carotid sinuses, permitting pressure in the carotid sinus to be controlled independently of arterial pressure. The input was carotid sinus pressure (x-axis); the output was systemic pressure measured in the whole animal (y-axis). During exercise, baroreceptor regulation of heart rate was reset to defend a higher arterial pressure, but the stimulus response curve to a given change in pressure was similar. Exercise was performed while running on a treadmill at 5.5 km/h up either a 7 or 21% grade. (Adapted from Joyner (237).)](http://physrev.physiology.org/)}
target for vasoconstriction and thus blood pressure regulation during heavy exercise in humans.

**H. Summary**

We have presented a number of lines of evidence that the sympathetic nervous system normally acts to restrain blood flow to contracting skeletal muscle during large muscle mass or whole body exercise in humans. Key observations include 1) the lower blood flow values observed during large muscle mass or whole body exercise in humans relative to quadrupeds, especially athletic animals with large hearts. 2) The challenges to venous return and cerebral blood flow associated with the upright posture in humans versus the horizontal position in most quadrupeds. 3) The observation that blood pressure falls during supine or head down exercise in patients with autonomic failure. 4) Adding arm exercise to ongoing leg exercise can reduce blood flow to the leg muscles under certain circumstances in some subject groups. 5) In conditions like aging or disease states like congestive heart failure, blood flow to exercising muscles is restrained by the sympathetic nervous system to maintain blood pressure in the face of limited systemic cardiac output. 6) Observations showing that there is ongoing baroreceptor restraint of blood flow to contracting muscles during exercise in both humans and animals. The lines of evidence are also supported by calculations and modeling that use well-accepted blood flow, cardiac output, and blood pressure data. Having established that skeletal muscle blood flow can be very high and under some circumstances threaten arterial pressure, we now consider the mechanisms operating at the level of the contracting muscles that can cause blood flow to be so high.

**VII. LOCAL BLOOD FLOW RESPONSES TO MUSCLE CONTRACTION**

We have worked our way down from concepts related to oxygen transport, cardiac output, skeletal muscle blood flow, and blood pressure regulation and now begin to discuss the blood flow responses to contraction across the vascular bed of a single muscle or perhaps a limb. **Figure 11** shows one of the earliest examples of the blood responses to contraction from Gaskell in 1877 (172). This record is from an in situ study of blood flow across the hindlimb of a dog.
during electrically stimulated muscle contractions. Blood flow was measured by collecting the venous effluent draining muscles electrically stimulated to contract. Adjacent to this tracing is a recent record from our lab of brachial artery blood flow after a single brief forearm contraction in a conscious human.

The blood flow responses shown in these two measurements made more than 130 years apart are strikingly similar, and from these records several things become clear. First, during contraction blood flow may stop temporarily when the contracting muscles compress the microcirculation and obstruct flow. Second, upon release of the contraction, there is a rapid increase in blood flow. Third, the flow then falls quickly and returns to baseline. This pattern demonstrates that the rise in flow in response to a brief contraction can be both large and fast. The increase in flow also occurs without a major increase in perfusion pressure, indicating that the response is generated within the skeletal muscle. It is also consistent with the idea that vasodilation in contracting muscle is the main local phenomenon driving the blood flow responses to exercise. The one problem with this interpretation is that vasodilation might take 5 s to occur (183, 300). However, the increase in flow is essentially immediate and seen after contractions lasting <1 s (324, 488).

As we work through the mechanisms in the contracting muscle that might contribute to exercise hyperemia, we will consider their ability to evoke both rapid and prolonged increases in blood flow, the extent to which these increases are caused by skeletal muscle vasodilation, and also the magnitude of the hyperemic response they can generate. Along these lines, Gaskell (172, 173) and Shepherd (431) identified broad classes of vasodilator mechanisms that might explain the rise in flow including substances released by nerves, substances carried in the blood, or substances released from the skeletal muscles. The major additions to these three factors since the original observations include the potential mechanical effects of contraction on blood flow both in terms of causing vasodilation and also augmenting perfusion pressure in skeletal muscles (131). Importantly, beginning in the 1980s, the role of the endothelium as a major site of vascular control emerged. It is also interesting to note that the observations of Gaskell in the 1870s and the primary role for vasodilation that we and others before us have favored were anticipated in the late 1700s by the Scottish surgeon Hunter who observed that “blood goes to where it is needed” (392). This simple statement also highlights the fundamental idea that metabolic demand and blood flow to contracting skeletal muscles is matched closely under most circumstances.

A. Site of the Vasodilation

Before we examine the mechanisms causing vasodilation in skeletal muscle, it is important to review where this dilation is occurring. The basic architecture of the skeletal muscle vasculature is well known (31, 356). The key point to remember is that compared with exercise, resting skeletal muscle is vasoconstricted. This means we have to identify the location in the microcirculation where most of this vasoconstriction is to coherently discuss where the vasodilation occurs. In this context, the “typical” skeletal muscle is perfused by a feed artery branching off a major conduit artery. There are then four to six branch orders before the terminal arterioles give rise to capillaries where the vast majority (but not all) of the gas exchange takes place in the skeletal muscles (356, 357). When the microcirculation is visualized using imaging and video techniques in a contracting skeletal muscle, there is marked dilation in all elements of the arteriolar tree, with the most pronounced dilation seen in the smallest arterioles (487, 488). Recent evidence also suggests that in many preparations up to ~80% of capillaries are perfused at rest, challenging the older idea that capillary recruitment is a major phenomenon contributing to exercise hyperemia and gas exchange in contracting skeletal muscles (363).

Additionally, when measurements of pressure are made in these very small blood vessels, blood pressure in the feed arteries is similar to that observed in the conduit arteries (~100 mmHg), and then falls to values of ~50–75 mmHg or lower in the most distal elements of the arteriolar tree (115, 132, 169). Pressures of 25–40 mmHg are typically seen in the capillaries. Importantly, a major pressure drop is observed in the arterioles as they descend in size from ~50 to 10 μm. This is consistent with the idea that these vessels are the chief sites of vascular resistance in resting skeletal muscle. However, these concepts are not uniform, and there are observations of pressure drops and hence resistance in the feed arteries of skeletal muscle. These vessels have also been shown to vasodilate in response to contractions (507, 513). Additionally, in some microvascular preparations, there can be a significant pressure drop in the feed arteries before entering the arteriolar network. Finally, with muscle contractions, the smallest arterioles that vasodilate most vigorously are relatively resistant to sympathetically mediated vasoconstriction (132, 487).

While large-conduit arteries such as the femoral or brachial arteries can vasodilate during exercise, this dilation is not functionally significant for the regulation of blood flow in exercising muscles (464). In the coronary circulation, there can be marked anatomic stenosis of large arteries of ~70% before the stenosis limits the ability of downstream vasodilation to cause large increases in blood flow (71, 137, 138). To study parallel events in exercising skeletal muscle, we inflated an intra-arterial balloon in the brachial artery of healthy subjects. During these experiments, we were struck by the magnitude of balloon inflation (~80% of brachial artery cross sectional area on visual inspection) needed to acutely reduce perfusion pressure and blood flow to con-
tracting forearm vessels. However, a combination of downstream vasodilation and collateral circulation around the elbow permitted the blood flow responses to submaximal forearm exercise to recover rapidly (FIGURE 12). At steady state, they were remarkably normal (74, 75, 78, 79, 85).

B. Conducted Vasodilation

Another important feature of the vasodilator response to muscle contractions is that these responses can be conducted upstream in the microcirculation (136, 161, 425, 426, 428). In other words, vasodilation that starts in the smallest arterioles closest to the capillaries in the contracting muscles can ascend to the larger elements of the arteriolar network including the feed arteries. This mechanism is dependent on an intact endothelium and appears to be an active process that includes Ca²⁺/H¹⁺ and electrical signaling along the endothelium and between the smooth muscle cells and endothelial cells (151, 152, 427, 429, 506). This includes cell-to-cell communication between both homocellular gap junctions between cells of similar type and heterocellular gap junctions that facilitate communication between cell types (410). For example, endothelial and vascular smooth muscle cells. From a functional perspective, studies in animal models demonstrate that conducted (e.g., ascending) vasodilation can be blunted in conditions like aging that are associated with reduced blood flow responses to exercise in some models (34, 228). These responses are also subject to modulation by the sympathetic nervous system in ways that might contribute to both the regulation of arterial pressure and the matching of blood flow and metabolism in vivo (22, 200, 201).

C. Properties of Dilating Substances

There are a number of essential criteria that any vasodilating substance must possess to explain all or part of the local effects of contraction on skeletal muscle blood flow (431). TABLE 4 is updated from the 1983 Handbook of Physiology chapter by Shepherd and outlines the relevant properties. 1) A substance or its precursor should be present in skeletal muscles (or perhaps the nearby nerves, blood, or blood vessels). 2) The substances should have access to the muscle resistance vessels because this is where the critical vasodilation occurs. 3) The concentration of substances in the interstitial fluid or endothelium must be sufficient to cause vasodilation, and the concentration should be proportional to the skeletal muscle contractile activity. 4) Endogenous administration of the substance should be capable of causing prolonged and marked vasodilation without major sensations in humans. Exercise hyperemia can last for hours, is not “painful,” and generally does not evoke other sensations, so this is an essential property. 5) Pharmacological agents or other physiological maneuvers which modify the blood flow responses to exercise should also modify the vasodilator responses to any putative dilator substance given exogenously.

Along the lines of the updated Shepherd criteria listed in TABLE 4, it should be noted that basic ideas about both the mechanisms contributing to exercise hyperemia and the basic properties of these mechanisms have not changed much over many years. One major new discovery over the last 35 or so years has been the role of the vascular endothelium as a key site of blood flow regulation (170). The influence of this discovery and the many findings flowing from it are especially remarkable given the widespread prior belief that
the vascular endothelium was primarily a barrier (170, 171). Additionally, in some quarters of the scientific community, it was widely believed that insights from physiological investigations would be limited in the era of molecular biology and reductionism (239).

**D. Speed of the Vasodilation**

This basic pattern of blood flow response to a single muscle contraction shown in **FIGURE 11** demonstrates that the rise in blood flow in response to contraction can be both substantial and fast. The immediacy of the blood flow response has led to debate. The argument is that any dilator mechanism might take at least 5 s to be observed (183, 300). For example, this time frame seems reasonable for substances released by nerves that would be required to bind to receptors on vascular smooth muscle and then cause a series of intracellular events leading to vasodilation. Likewise, substances released by contracting muscles would have to diffuse out of the muscle fibers, avoid degradation or metabolism to survive in the interstitial space, and then activate either receptors on or second messenger systems in the vascular smooth muscle. The argument is that each step involved in either neural or metabolic vasodilation is associated with time delays precluding a major role for these mechanisms in the immediate rise in blood flow following skeletal muscle contractions (436). Evidence to support these concepts includes observations in the microcirculation that a 5- to 20-s delay after the onset of contraction is required to observe vasodilation (183, 300). These data are frequently cited as indirect evidence that the extremely rapid rise in flow almost certainly has to be mediated by the mechanical effects of muscle contraction on the skeletal muscle microcirculation.

More recently, it has been argued that vasodilation can occur almost immediately and that the mechanical effects of contraction only generate a trivial amount of blood flow (412, 443, 478). Other powerful evidence against a major role for mechanical factors dominating the early rise in muscle blood flow with contractions is shown in the **left panel of Figure 1**. It demonstrates that even a very brief contraction elicits a rise in flow that is graded with the strength of contraction. If the dilation were strictly mechanical, then it might be unrelated to the strength of contraction. Importantly, recent observations clearly show that there can be dilation within 1 s in the microcirculation (324, 488). Thus, since there is an increase in blood flow without an appreciable increase in perfusion pressure, the evidence for rapid vasodilation in the skeletal muscle microcirculation is strong and the question is what mechanisms explain this phenomenon and are they fast enough.

**E. Rapid Neurally Mediated Vasodilation**

The theory that there can be neurally mediated vasodilation in skeletal muscle is an old one with two potential sources of neural input. The first is dilation via activation of autonomic vasodilator nerves in skeletal muscle, and the second is vasodilation evoked by motor nerves. Neurally mediated dilation is attractive because it might explain the immediate rise in flow with exercise and, in the case of motor nerves, the matching of blood flow and contractile activity. In many species either behavioral stimuli in conscious animals or electrical stimulation of selected brain areas in anesthetized preparations can evoke a “defense reaction” (1, 96, 159, 213, 307, 308). This is a feed-forward adaptation that includes a rise in heart rate and blood pressure along with an increase in skeletal muscle blood flow that might “prepare” the animal for fight or flight. In awake animals instrumented to measure muscle blood flow on a beat-to-beat basis, there can also be a large increase in limb blood flow when the animals are anticipating exercise (485).

In the defense response sympathetic dilator nerves innervating the skeletal muscle are activated while sympathetic vasoconstriction is occurring elsewhere in the body (96, 160, 162, 484). Recent work by Matsukowa and colleagues

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**Table 4. Criteria for vasodilator substances**

<table>
<thead>
<tr>
<th>Criteria for Vasodilator Substances</th>
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<tr>
<td>1. The substance or substances though to cause vasodilation should be present in the tissue or tissues thought to release them. These tissues could include skeletal muscle, vascular smooth muscle, the vascular endothelium, blood, or nerves.</td>
</tr>
<tr>
<td>2. The substance or substances should have access to the muscle resistance vessels.</td>
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<tr>
<td>3. The concentration of the substance in the interstitial fluid or at the vascular endothelium should be sufficient to cause dilation in a concentration-dependent manner that is related to contractile activity.</td>
</tr>
<tr>
<td>4. Exogenous administration of the substance or substances should be capable of causing prolonged dilation without sensations in humans.</td>
</tr>
<tr>
<td>5. Pharmacological agents or physiological maneuvers that alter the blood flow responses to exercise should have similar effects on the vasodilator responses to any putative substances given exogenously.</td>
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These concepts were adapted from Shepherd (431). The major additions in these criteria since the original criteria of Shepherd include the discovery of the vascular endothelium as a key site of vascular control.
(261, 262, 306) in conscious cats trained to weight lift showed that sympathetic vasodilator fibers can evoke increases in blood flow at the onset of contractions. There is also a history of human studies showing modest levels of forearm vasodilation in a resting limb when contractions are performed with the contralateral hand or other muscles. In some studies dilation in the resting forearm can be blocked by brachial artery administration of atropine (409). In this context, dilation in resting limbs during exercise has been interpreted by a number of investigators as demonstrating neurally mediated vasodilation at the onset of contraction in human muscles (147–149, 402, 409). However, others have argued that the dilation is due to small and difficult to detect unintended contractions in apparently resting limbs. Along these lines, when there is no electrical activity detected in the “resting” limbs, there is no vasodilation (103).

Neurally mediated skeletal muscle vasodilation has been ascribed to histamine, acetylcholine, and also nitric oxide. There is also some evidence suggesting it can be a β₂-mediated vasodilator response to increased circulating epinephrine. In animals, the muscle blood flow responses seen during the defense reaction are sensitive to atropine and can be abolished by sympathectomy. There is also histological evidence for sympathetic cholinergic nerves to limb skeletal muscle in many species (185). More recently, it has been shown that the vasodilator response during the defense reaction or behavioral stress in a number of species can be blocked or attenuated by the administration of nitric oxide (NO) synthase inhibitors (261, 262). This raises the possibility of acetylcholine from sympathetic nerves causing NO release from adjacent vascular endothelium. Other possibilities include a population of nitroxidergic dilator nerves or the release of NO as a cotransmitter from the sympathetic cholinergic nerves (116, 309).

A pattern of hemodynamic responses similar to the defense reaction may be seen in humans exposed to experimental emotional stress (381). When the stress is severe, impressive increases in muscle blood flow are possible. In the late 1950s, prior to the advent of modern ethical review, Blair et al. (46), in one of the most notable human physiology studies ever conducted, instrumented medical students to measure forearm blood flow responses to emotional stress. In some subjects they placed a brachial artery catheter to locally infuse drugs and investigate the mechanisms contributing to vasodilator responses in the forearm. They also graphically described their experimental strategy for inducing emotional stress:

“For the present purposes we were interested in obtaining large responses rather than in the character and reproducibility of the emotional stimuli, and various stimuli were used. Before the experiments the subjects were told about the proposed measurements and injections, but they were not told that they would be emotionally stressed, since surprise was often an important feature of the stress. After the experiments a full explanation was given and the subjects were asked not to divulge this to other subjects.

Periods of emotional stress lasting 2–3 min were produced by the following stimuli. 1) The subject was told that he would shortly be examined orally in physiology or that he would be tested in mental arithmetic. He was then kept in suspense for 2–3 min before being told that the test would not be applied, and that he could relax. 2) Some of the medical students were given a grueling oral examination in physiology, and were severely criticized each time they gave wrong answers and sometimes when they gave correct answers. 3) Some subjects were tested in mental arithmetic. This has been found by several investigators to be a convenient emotional stimulus, capable of causing a considerable cardiovascular disturbance. . . . 4) The subject was asked to worry himself by thinking of unpleasant things. 5) In some of the experiments on the normal subjects a needle was inserted into the brachial artery for the recording of arterial pressure or the infusion of atropine. In other experiments, when arterial puncture was not necessary, a needle was inserted subcutaneously, and the subject was led to believe that this was in an artery. The insertion of the needle itself caused stress and an increase in forearm blood flow in some subjects. In each case time was allowed for the forearm blood flow to revert to resting level for several minutes. The subject was then deliberately frightened in the following way. The operators pretended that blood was leaking around the intra-arterial needle, that a hematoma was forming, and that there was a considerable loss of blood. By their conversation and demeanor they tried to indicate to the subject that they were worried and alarmed, and were thinking of abandoning the experiment. About half the subjects were hoaxed successfully; these became alarmed and some even complained of pain in the arm and throbbing in the head. After a few minutes the subject was reassured and consoled, and the real purpose of the hoax was briefly explained. In every case anxiety was promptly relieved. Other subjects, some of whom were able to look at their arm and see for themselves that all was well, were not deluded by the acting and were not frightened. This particular stimulus, which is later referred to as ‘severe stress’ could, of course, be used only once for each subject.”

In response to the stressors described above, examples of 10-fold or greater increases in forearm blood flow were seen, and under some circumstances, the vasodilation could be blunted by atropine (see left panel FIGURE 13) or also nerve block. The dilation was also blunted or absent in the forearms of subjects who had undergone surgical sympathectomy to treat a variety of conditions. However, there have been competing nonneural explanations for this response in humans over the years, including a primary role for circulating epinephrine released from the adrenal me-
nulla during emotional stress. Epinephrine evokes skeletal muscle vasodilation via $\beta_2$-adrenergic receptors that are located on both the vascular endothelium where they evoke NO release and on vascular smooth muscle where they activate cAMP-mediated dilator pathways (486). Consistent with these observations, the forearm vasodilator responses to emotional stress are blunted or absent in subjects who have undergone regional or systemic $\alpha$-adrenergic blockade (167, 176). Other studies in patients who had undergone upper extremity nerve blocks or sympathectomy sometimes demonstrated a normal forearm vasodilator response during mental stress (185, 215, 281). Finally, in some studies, the limb vasodilator responses to mental stress have been associated with acute sympathetic withdrawal, but such responses have been observed inconsistently (72, 192).

In more recent studies our laboratory showed that brachial artery administration of the NO synthase (NOS) inhibitor N$^G$-monomethyl-L-arginine (L-NMMA) blunted the dilator response in the human forearm to mental stress. The magnitude of this blunting was similar to or slightly greater than the effects brachial artery atropine (126). We initially postulated that acetylcholine from sympathetic cholinergic nerves caused release of NO from the vascular endothelium. In this context, at least some of the dilation evoked by activation of $\beta_2$-adrenergic receptors also has an endothelial component that can be blunted by NOS inhibition (145, 486).

However, in a series of subsequent studies using nerve blocks along with other sympathoexcitatory stimuli, we began to doubt the existence of sympathetic vasodilator nerves in human skeletal muscle (125, 374). We now believe that the rise in blood pressure along with circulating epinephrine accounts for the forearm dilator response to mental stress (240). Our interpretation is that blood pressure response causes mechanical distension of the vascular endothelium and also activation of local cholinergic mechanisms that both cause the release of NO. These factors act in concert with the $\beta_2$-mediated vasodilation caused by circulating epinephrine which can also have an NO-mediated component (302). While there has been strong histochemical evidence for the existence of sympathetic vasodilator fibers in the skeletal muscles of a number of species, such evidence is lacking humans (484). Additionally, either acute or chronic sympathectomy does not appreciably alter the rise in blood flow seen following a brief contraction or more prolonged periods of exercise in young adults (101). Likewise, the initial rise is muscle blood flow at the beginning of exercise is unaffected in acutely sympathectomized rats (354). Finally, in humans and other species, intra-arterial administration of atropine has little or no impact on the rise in muscle blood flow to either a single contraction or more prolonged periods of exercise (13, 54, 60, 441). All of these observations argue against a major role in humans for sympathetic vasodilator nerves in exercise hyperemia.

Conversely, there is evidence both for and against basal sympathetic activity constraining the initial vasodilation in...
contracting human muscle. We have previously demonstrated that acute increases in sympathetic activity (via lower body negative pressure) reduces the blood flow and vasodilator responses to a single muscle contraction in young adults, whereas it has no effect in older adults who presumably already have elevated basal levels of sympathetic activity (76). On the other hand, \(\beta\)-adrenergic blockade augments the blood flow and vasodilator responses following a single muscle contraction in older adults (76).

**F. Acetylcholine Spillover From Skeletal Muscle**

Another potential neural mechanism that can evoke rapid vasodilation in skeletal muscle centers on the idea that acetylcholine spills over from motor nerves and evokes vasodilation in blood vessels near those motor nerves (505). This is an attractive hypothesis because it would closely match blood flow with contractile activity. However, there are several problems with this hypothesis when it is extended to preparations beyond the microcirculation. First, as noted above, administration of atropine has little effect on the blood flow responses to contraction. Second, when the forearm muscles of humans are selectively paralyzed with neuromuscular blocking drugs in a way that permits them to fire and release their acetylcholine but not evoke contractions, marked vasodilation is not seen (140). These observations show that acetylcholine spillover from motor nerves is probably not a major contributor to exercise hyperemia in human skeletal muscle.

**G. The Muscle Pump**

The next major factor that might explain the rapid rise in blood flow seen in [Figure 11](#) is the muscle pump (477). The general concept is that contraction compresses blood vessels (especially veins) in skeletal muscle and relaxation either causes suction or tethers the blood vessels open in a way that permits blood flow to rise dramatically. Any significant suction would effectively augment perfusion pressure. This mechanism is in addition to the role of the muscle pump in functionally augmenting perfusion pressure in the legs during upright exercise by emptying the veins in the lower extremity (267, 360, 430, 431, 434, 454). This keeps venous pressure very low and increases the perfusion pressure (mean arterial pressure minus mean venous pressure) to the dependent limb. Consistent with this interpretation is the observation that peak oxygen uptake is \(~7\%\) higher in the upright versus supine position during cycling in humans (123). There is also evidence that individuals with venous incompetence have altered leg blood flow responses to exercise in the upright posture (335, 336).

Sherriff and Van Bibber (437) used a creative approach to demonstrate the potential for energy to be imparted by the contracting muscles on blood and the ability of this energy to generate flow. They bypassed the heart and surgically constructed an auto-pumping circuit of contracting skeletal muscles in pigs. With this preparation ([Figure 14](#)), a blood flow of \(~100\ mL/min\) could be generated and sustained by the muscle pump compared with values of \(~450\ mL/min\) when blood flow was being delivered by the heart. While total flow from the circuit was modest, direct comparisons with the normal heart-perfused preparation are difficult because of differences in both venous and arterial pressure.

To test the contribution of the isolated muscle pump in humans, Tschakovsky et al. (478) developed a cuff system that rhythmically squeezed the forearm while they measured brachial artery blood flow. The compression pattern and pressures generated by the external cuff were designed to mimic the pressures generated by the contracting muscles. As shown in [Figure 15](#), when the forearm was at or above heart level, this rhythmic “pumping” of the forearm caused little increase in brachial artery blood flow. In contrast, when the arm was below heart level, there were modest increases in blood flow with rhythmic cuff pumping of the forearm. This is consistent with the idea that full but not empty veins can contribute to the hyperemic responses to exercise.
When various maneuvers like unloaded cycling or leg kicking, very light exercise, or measurements of the decay in blood flow immediately after exercise are examined, the relative contribution of the muscle pump can be variable (289, 439). During upright exercise, the rapid reduction in venous pressure can account for 67% of the rise in femoral blood flow seen during the first 10 s of cycling at a low power output (516). However, during more prolonged heavy exercise, the contribution of the muscle pump is more modest and accounts for only a small fraction of the flow, and during heavy exercise, the net effect of higher muscle forces impeding blood flow might offset the flow-promoting effects of the muscle pump (289).

Taken together, these observations suggest that skeletal muscle pump can facilitate exercise hyperemia and that the main contribution is to the immediate rise in skeletal muscle blood flow seen at the onset of exercise. As noted above, the skeletal muscle pump is clearly critical for the systemic hemodynamic responses in humans exercising while upright.

An important caveat related to how much flow the muscle pump can generate is that blood flow values above 150 ml·min$^{-1}$·100 g$^{-1}$ are rarely reported in studies using the isolated dog gastrocnemius plantaris preparation (23, 24, 225). This observation may reflect experimental conditions including how the arterial inflow to the muscle is isolated. However, with careful optimization of all experimental variables, blood flows of 200 ml·min$^{-1}$·100 g$^{-1}$ are possible (452; B. Gladden, personal communication). These values are still substantially lower than those reported by Musch and colleagues using microspheres in running dogs (331, 333). They are also lower than the peak flow of \sim 300 ml·min$^{-1}$·100 g$^{-1}$ (or higher) seen in various species including humans (47, 376). Could the “additional” flow seen in vivo compared with the in situ results be due to the muscle pump? In this context, when voluntary exercise is superimposed on maximum pharmacological vasodilation in conscious dogs, there is no further increase in blood flow. At one level, this is another observation that argues against a major role for the muscle pump in exercise hyperemia, but it could also reflect the flow-impeding effects muscle contraction (194).

In several sections of this review, we have commented on the idea that in addition to their effects on veins, the forces generated by skeletal muscle contraction can impede blood flow to the muscle by compressing other elements of the circulation. One final caveat on this topic comes from an applied observation in competitive cyclists who appear to prefer faster pedaling frequencies than might be predicted based on measurements of oxygen consumption alone. The speculation is that more frequent and lower force contractions at a given power output interrupt blood flow less than slightly longer and higher force contractions at slower pedaling rates (190).

H. Chemical Vasodilation: General Comments

The previous sections have discounted the role of neurally mediated vasodilation and the muscle pump in exercise hyperemia. Thus, by default, we have arrived at the conclusion that the primary mechanism responsible for exercise hyperemia must be vasodilation in the microcirculation caused by chemical factors (TABLE 4). These could be released from the contracting muscles or the nearby endothelium, or perhaps carried in the blood. Before we discuss the many potential mechanisms that might cause chemical vasodilation, several important concepts outlined by Shepherd (431) need to be reviewed.

1) Any chemical factor or factors that initiate the vasodilation (or for that matter, blood flow in general) in contracting skeletal muscles during exercise may not be the same factors that sustain it. Prolonged intense exercise can occur in many species including humans. Therefore, skeletal muscle blood flow must be able to achieve very high levels for prolonged periods of time.

2) There is likely significant redundancy in chemical vasodilating factors. This makes studying these factors very difficult because pharmacological approaches that “block” a putative vasodilator substance, thus revealing its contribution, might be masked by an increased contribution from...
another chemical vasodilator. For example, if substance X is antagonized and the contribution of substance X to exercise hyperemia is eliminated, there might be a buildup of other dilating factors sufficient to either keep the blood flow response relatively normal or restore it after a brief fall in flow. So when blocking compounds are administered (before or during contractions), the temporal resolution of the flow measurements is a potentially important element of experimental design that requires careful consideration. Additionally, a drug given before exercise might not reach the vessels subject to dilation during the contractions, and redundant factors that might compensate for a missing dilator substance could be engaged right away. Likewise, the effects of a blocking drug given during contractions might be missed if blood flow measurements are discontinuous and any temporary reduction in flow is compensated for by another vasodilator mechanism prior to the next measurement of blood flow.

3) Many (in fact most) putative vasodilating substances also stimulate the vascular endothelium to release NO. Thus it is sometimes difficult to know whether the substance in question is contributing directly to the exercise hyperemia, or indirectly via stimulation of NO released from the vascular endothelium, or both. These general considerations can make the design and interpretation of experiments that attempt to “pharmacodissect” exercise hyperemia challenging. Human studies are further limited by the availability of approved pharmacological tools and safety concerns. While more drugs are available for use in animals, their specificity of action is subject to question.

In addition to these factors, muscle contractions can cause a brief compression and cessation of arterial inflow to the skeletal muscle. Additionally, even brief periods of ischemia lasting only a few seconds are typically sufficient to initiate a reactive hyperemia response (256). So, depending on how the contractions compress the skeletal muscle blood vessels, an element of reactive hyperemia might also be involved in exercise hyperemia.

Finally, there is an almost existential question about the continuing search for a single dilating substance that explains the vast majority of the exercise hyperemia response. Is it possible to design an experiment that will permit such a substance to be identified? Are there many examples of single mechanisms dominating important physiological responses? Are most critical physiological responses subject to redundant control so that a margin of safety exists in case one or more mechanism is absent or dysfunctional? While we and others have argued the search for a single dilator is likely to be futile, the evaluation of each new metabolic substance or mechanism that might contribute to exercise hyperemia is frequently framed in the context that it might be the “missing” dominant vasodilator substance (243).

I. Rapid Chemical Vasodilation

Numerous in vivo experiments have demonstrated that there is an immediate (within 1–2 s) increase in flow following a brief muscle contraction (54, 76, 85, 101, 249, 253, 337, 476, 478). Recent evidence from both human and animal models suggests that K+ channels in the vascular smooth muscle play an important role in this immediate dilation. Armstrong et al. (11) originally demonstrated that the initial vasodilation in the hamster cremaster muscle in response to muscle contractions was attenuated when 1) release of K+ from voltage-dependent K+ channels in skeletal muscle were inhibited, 2) inwardly rectifying K+ (KIR) channels in smooth muscle were blocked, or 3) Na+-K+ pump in smooth muscle was inhibited. More recently, inhibition of K+-mediated vascular hyperpolarization in the human forearm effectively attenuates the peak and total vasodilator response to various intensities of single muscle contractions (107).

Emerging evidence in young humans also suggests a potential role of NO in contraction-induced rapid vasodilation (54, 85, 107). NOS inhibition alone (85), in combination with muscarinic receptor blockade (54), or cyclooxygenase inhibition (107) significantly reduces the peak and total postcontraction vasodilation. It is important to note that muscarinic receptor blockade (54) or cyclooxygenase inhibition (442) alone has little to no effect on the rapid vasodilator response to muscle contractions. Lastly, as shown in FIGURE 16, inhibition of NO and prostaglandin synthesis in combination with administration of substances that block or inhibit K+-mediated vascular hyperpolarization nearly abolishes the immediate vasodilation following a single muscle contraction (107).

The immediate vasodilator responses are also facilitated by a temporary loss of sympathetic tone in the contracting muscles, and during whole body exercise a brief reduction in sympathetic outflow (242, 354). This latter effect might occur as blood is translocated from the periphery and activates both cardiopulmonary and arterial baroreflexes which in turn cause a brief reflex reduction in sympathetic outflow to muscle (70). Conversely, increases in sympathetic outflow can limit the rapid vasodilator responses to forearm contractions in humans (76, 119), and stimulation of α-adrenergic receptors with norepinephrine in the microvascular resistance networks of mice blunts rapid-onset vasodilation and restricts blood flow following a single contraction (228).

J. Blood Flow and Metabolism Matching During Ongoing Exercise

As noted repeatedly in this review, skeletal muscle oxygen consumption and blood flow appear to be tightly linked. This relationship suggests that some signal or signals pro-
proportional to the metabolic demand of the contractions are the primary drivers of skeletal muscle vasodilation. In this context, two major ideas related to flow and metabolism matching have predominated. The first is that some factor or factors is released by the contracting muscles and linked to muscle activity. An example might be K$^+$ associated with skeletal muscle repolarization. The second is that some metabolite(s) is released from the contracting skeletal muscles in proportion to metabolic activity that might match blood flow and metabolism. Historically, much interest has focused on adenosine.

K. Substances Released by the Contracting Skeletal Muscles

1. Potassium and osmolarity

Potassium ions and changes in osmolarity associated with muscle contraction have been proposed as potential mediators of exercise hyperemia and, as noted above, appear important to the immediate vasodilation seen at the onset of contractions. These mechanisms might fulfill the general criteria that their concentration is linked to contractile activity in a graded way, but experiments over many years have cast doubt over their role as major contributors to ongoing exercise hyperemia. In the case of K$^+$, it is clear that the concentration can rise sufficiently (>10 mM) to evoke marked dilation via activation of K$_{IR}$ channels and Na$^+$-K$^+$-ATPase with hyperpolarization of affected cells (64, 232). However, exogenous administration of potassium does not cause marked dilation, and it is painful in humans. In a notable experiment, potassium depletion in dogs did affect the vasodilation seen at the onset of contractions. However, it did not disrupt the relationship between oxygen consumption and blood flow during more prolonged bouts of contraction even though the ability of the skeletal muscle to produce force in the potassium-depleted animals was reduced (202). These observations argue against an obligatory role for K$^+$ in the sustained vasodilation seen during exercise.

Like K$^+$, the concentrations of phosphorus and also the osmolarity around the resistance vessels in the contracting muscles can increase. However, these increases are transient, and while they might contribute to vasodilation at the onset of contractions, they are probably not essential to sustain it. Additionally, the range of changes in potassium and osmolarity are probably not great enough to explain the range of blood flow increases seen in contracting muscles during exercise (316, 317, 431, 446). Similar issues apply to other electrolytes (26).

Early studies on metabolites that might cause vasodilation focused on the possibility that lactate or lactic acid might be the metabolic vasodilator (214). However, mild and moderate exercise are not associated with much if any lactic acid release from contracting muscles, so it is difficult to see how either lactate ion or H$^+$ might be obligatory. Additionally, exogenous administration of lactate does not cause appreciable dilation (247). Finally, patients with McArdle’s disease (myophosphorylase deficiency) do not produce lactic acid even in response to heavy exercise (189, 276, 277). These patients also show a hyperdynamic circulatory response to exercise, indicating that their vasodilator responses to exercise are excessive in the absence of lactic acid production. These observations highlight the evidence against a major role for lactate or lactic acid in the sustained vasodilation seen during exercise.

L. Adenosine

The most commonly discussed potential vasodilator substances released by contracting skeletal muscle include the adenine nucleotides adenosine and also ADP and ATP. Along these lines, the so-called adenosine hypothesis is a milestone in thinking about how cardiac muscle contractile activity is linked to blood flow (37), and has been adapted for skeletal muscle (299). In this hypothesis, a mismatch between flow and metabolism leads to the buildup and release of adenosine as either high energy stores in the muscle are depleted or there is increased ATP turnover in the contracting muscles. This then leads to a rise in skeletal muscle blood flow proportional to the contractile activity and metabolic demand.
The adenosine hypothesis and its offspring have generated a
host of ideas and experimental evidence on exercise hyper-
emia. However, it is difficult to test because adenosine has a
very short half-life in blood, obtaining accurate measure-
ments of its interstitial concentration is very challenging, and
values in blood when they are obtained may or may not
reflect concentrations in the interstitial space (29). While
some progress has been made measuring concentrations of
vasoactive substances including adenosine in the interstitial
fluid using microdialysis, there are concerns with this tech-
nique (208). 1) The time resolution of microdialysis mea-
surements is slow, meaning that very brief changes in the
concentration of one or more putative vasodilating sub-
stances would be difficult to detect. 2) Muscle damage with
catheter insertion might contaminate the microdialysate. 3) Many
putative vasodilating substances have exceedingly short half-lives, and this is usually related to sampling sub-
stances directly or some breakdown product of them needs
to be considered. In this context, care needs to be taken
when interpreting data from microdialysis studies. How-
ever, in many cases it is the best data available at this time.

There are four additional caveats concerning a role for
adenosine in exercise hyperemia in humans. 1) While exog-
eneous administration of adenosine can evoke marked vaso-
dilation in the leg, the dilation is less than that seen during
heavy knee extension exercise, so the argument is that if
adenosine is a major factor in exercise hyperemia it must do
so in conjunction with other factors (330). 2) There are
responders and nonresponders to exogenous adenosine ad-
ministration, and both groups have marked hyperemic (and
vasodilator) responses to exercise (303–305). 3) In the re-
sponders, adenosine-mediated vasodilation can be signif-
icantly blunted by administration of NOS inhibitors; how-
ever, exercise hyperemia is not (304). 4) Administration
of compounds that block adenosine deaminase do not cause
a major increase in blood flow to contracting muscles (303).

There are also parallel observations from a number of ani-
mal studies on these issues. For example, addition of adeno-
sine deaminase which should enhance the breakdown of
adenosine does not reduce blood flow in running rats (257).

In a particularly insightful experiment, Hester et al. (210)
performed a series of contractions in an isolated canine
skeletal muscle preparation before and during the infusion
of high doses of adenosine over 3 h. FIGURE 17 shows that
while adenosine alone could produce marked vasodilation,
this vasodilation waned with time. This finding indicates
that the skeletal muscle blood vessels had become desensi-
tized to its vasodilator effects. However, when the muscle
was stimulated to contract after the vasodilator responses
to adenosine were absent, the hyperemic responses to con-
traction were similar to pre-adenosine infusion values (210).

The observations related to adenosine noted above suggest
that either adenosine is not normally participating in skel-
etal muscle vasodilation during exercise or it is not “oblig-
atory.” They also highlight a number of the general prob-
lems associated with identifying a single major diluting sub-
stance that accounts for most of the vasodilator responses
seen in contracting muscles during exercise. One area where
evidence for the participation of adenosine in the regulation
of blood flow to contracting muscles is stronger is when
there is reduced oxygen delivery to contracting muscles via
a restriction of arterial inflow (75, 255, 260). This is also the
case for adenosine in the regulation of coronary blood flow
(272). Additionally, in pigs during heavy exercise, adminis-
tration of an adenosine deaminase blocker lowers blood
pressure during heavy exercise (268). This observation sug-
ests that adenosine is being released from the muscle and
that in this model skeletal muscle is “underperfused.” If so,
it might be contributing to the regulation of blood flow in
the contracting skeletal muscles. However, based on a syn-
thesis of results highlighted above, it is difficult to make a case that adenosine is obligatory for exercise hyperemia under most circumstances. Consistent with these ideas, we have shown that adenosine plays a key role in regulating skeletal muscle blood flow responses to acute hypoperfusion (75).

One important question about adenosine, especially when comparing small and large muscle mass exercise, is the relatively high levels of saturation seen in the venous effluent during small muscle mass exercise. As noted earlier, this suggests that the muscle might be overperfused and that adenosine release might not be occurring. However, during heavy large muscle mass or whole body exercise, when almost all of the oxygen is being extracted across the active muscle, is the muscle “underperfused” and does adenosine contribute to the vasodilator responses?

M. ATP

During the first wave of enthusiasm for adenosine as a vasodilator substance linked to exercise hyperemia in the 1960s and early 1970s, the possibility that either ADP or ATP was the major vasodilating metabolite released by the contracting muscles also emerged (163–165). Many of the issues associated with determining adenosine concentrations in or near contracting skeletal muscles also apply to ADP and ATP. Like adenosine, they can cause marked skeletal muscle vasodilation, and like adenosine, they would directly link metabolism and blood flow. Finally, there are a number of potential sources of ATP and sites of action that include both vasodilator and vasoconstrictor responses (283).

One particularly attractive property of ATP is that it can evoke levels of vasodilation seen in human limbs during heavy exercise when given exogenously (181, 327). To date, it is the only exogenously administered vasodilator with this property. However, the role of NO release as a contributor to ATP-mediated vasodilation is controversial with some studies reporting that NO release is not involved in ATP-mediated vasodilation in human limbs and other studies showing a contribution (109, 327, 384, 440). If NO is a major part of the ATP-mediated vasodilator response, then the question “why NO release does not cause a bigger decrement in exercise hyperemia?” applies to ATP as well as to adenosine. Thus the main arguments in favor of ATP as a key mediator of skeletal muscle vasodilation during exercise are the magnitude of the flow it can evoke and also its ability to interfere with sympathetic vasoconstriction (403). However, many of the general concerns related to adenosine and exercise hyperemia also apply to ATP and ADP. Finally, we will reexamine the contribution of ATP during the subsequent discussion of new ideas about blood-borne factors that might contribute to skeletal muscle vasodilation during exercise, because there is more than one source of its release (283).

N. Substances Released From the Endothelium

The discovery in the 1980s that skeletal muscle blood flow was roughly an order of magnitude greater than previously thought was a major milestone in exercise hyperemia. However, the emergence of the vascular endothelium as a site of vasomotor control had even more widespread implications. Prior to that time it was assumed that the vascular endothelium served primarily a barrier function, separating the blood from the tissues. Additionally, the discovery of endothelial dysfunction as a major risk factor for cardiovascular disease has had important implications for the pathophysiology of a number of diseases (53, 114, 170, 171, 207). Perhaps even more fundamentally, the emergence of NO and a new class of gas transmitter/signaling mechanisms was of even more importance. In this context, it is interesting to note that the fundamental observations on the role of the vascular endothelium as a major site of vascular control was made using classic organ bath studies using physiological and pharmacological approaches as opposed to reductionist molecular techniques (170).

It is also interesting to speculate about the discovery of the vasoactive properties of the endothelium in retrospect. It had been known for many years that arterial infusions of acetylcholine could cause dilation in vivo but not the relaxation of vessel strips or rings. Based on the assumption that the strips and rings provide more insight into the basic behavior of blood vessels, the in vivo response was seen as paradoxical, and efforts to explain it were made (170). One idea was that the acetylcholine temporarily interfered with sympathetic neurotransmission and thus caused acetylcholine-mediated vasodilation (433). However, the increases in flow with temporary loss of sympathetic tone are modest compared with acetylcholine-mediated vasodilation. In view of this history, it is tempting to ask what might have happened if the question had instead been “what is wrong” with the responses observed in vitro? Attempting to reconcile an in vivo observation with in vitro findings is a fundamentally different intellectual proposition than attempting to reconcile the in vitro findings with results from an intact animal or human. If the latter perspective had been more widespread, would the discovery of the endothelium as a site of vascular control come earlier? How many other phenomena are being missed or poorly explained in an effort to reconcile observations from whole animals with ever more granular reductionist preparations? At what point for any given problem might reversing the order of the attempted reconciliation raise new perspectives or questions and lead to additional insight?

With the emergence of the vascular endothelium as a site of blood flow regulation, three important questions emerged. First, what substances are released by the vascular endothelium that might contribute to the regulation of skeletal muscle blood flow? Second, do these factors contribute to exer-
exercise hyperemia? Third, how might other putative vasodilator substances interact with the vascular endothelium? These general topics have been touched on briefly above as needed to discuss other potential vasodilating mechanisms covered earlier highlighting the integrated nature of the response.

The main vasodilating substances released by the vascular endothelium are NO and prostaglandins. Depending on the model used, blockade of endothelial NOS with arginine analogs can reduce skeletal muscle blood flow on the order of 10–30% (141, 417, 419). In most human studies, the upper limit appears to be ≈20%. Inhibition of prostaglandin synthesis leads to smaller reductions in flow than NOS inhibition (328, 419, 442). Additionally, at least some of the vasodilation associated with prostaglandins is due to prostaglandin-mediated NO release (330, 340, 373, 411), further complicating the interpretation of many pharmacological studies. During double blockade, with few exceptions, reductions in blood flow on the order of 20% or less are seen and typically not greater than the reduction seen with NOS inhibition alone (330, 417).

Along these lines, aging can be associated with reduced endothelial function (420) and the effects of NOS inhibition on the blood flow responses in contracting muscles are generally less in older versus younger humans (84, 111, 416). This suggests a blunted contribution of NO to exercise hyperemia in older humans, but the marked dilator responses seen in the contracting muscles of older subjects again highlights the modest role and nonobligatory role of NO in exercise hyperemia. Another fundamental issue in evaluating the role of NO is the extent to which changes in muscle blood flow reflect reductions in blood flow to the resting muscles. In many studies, the increase above resting or baseline during exercise after administration of NOS inhibitors remains similar to control conditions.

The situation during whole body exercise is also complicated by the systemic effects of NOS inhibition on blood pressure and cardiovascular reflexes. In humans, leg blood flow during a whole body eNOS inhibition during cycle ergometer exercise is relatively constant, but vascular resistance is higher because blood pressure is higher (166). The rise in blood pressure with NOS inhibition also leads to a reflex reduction in sympathetic activity, clouding the interpretation of blood flow and vasodilator responses because the loss of an endothelial vasodilator signal might be obscured by the loss of a sympathetic vasoconstriction due to baroreceptor-mediated sympathetic withdrawal (89).

In dogs exercising after ganglionic blockade to eliminate systemic vasoconstrictor activity, NOS inhibition causes a ~30% reduction in blood flow to contracting skeletal muscles (435). In addition to these observations in humans and chronically instrumented animals performing voluntary exercise, there is also evidence from a number of sources suggesting that endothelial NO contributes deferentially to the regulation of exercise hyperemia and different fiber types (98). Under some circumstances, fast-twitch skeletal muscle is more dependent on NO-mediated vasodilation than slow-twitch skeletal muscle (100). There are also observations suggesting the opposite pattern of involvement for NO, and this has to do with the exercise intensity and whether the NOS inhibitor was given before or during exercise (334). However, the relevance of these findings to humans is unclear because, unlike rodents that have highly compartmentalized skeletal muscle containing predominantly fast, slow, or intermediate fiber types, human skeletal muscle is mixed (14, 15, 278). However, an important finding from these studies is that blockade of neuronal NOS can influence the blood flow response to exercise, indicating that in addition to the vascular endothelium, NO might also be released by the contracting skeletal muscles (97, 99, 102).

The other major issue with NO-mediated vasodilation is that as noted several places above at least some element of the vasodilator responses to many substances (adenosine, ATP, β2-receptor agonists, and prostaglandins) have a major NO component. So, the question for any putative dilator substance thought to play a major role in exercise hyperemia is that, if substance X is a major contributor to exercise hyperemia, why doesn’t inhibition of endothelial responses have a bigger impact on exercise hyperemia? For some substances, this question is specific to NOS, whereas for other substances it is specific to combined inhibition of both NO- and PG-mediated effects. Finally, there is emerging evidence that NO interacts with superoxide to generate what has been characterized as a “bang-bang” vasodilator mechanism (177, 178). The extent to which this mechanism might contribute to exercise hyperemia is unclear.

O. Blood-Borne Vasodilator Substances

Two obvious blood-borne vasodilator candidates are oxygen and CO2. Studies conducted over many years have thoroughly evaluated both CO2 and hypoxia per se as vasodilator factors, and while both can cause small increases in blood flow, the magnitude of the dilation they evoke pales compared with that seen with exercise. It is also not easy to determine how changes in their partial pressure might be directly related to changes in flow over a wide range of blood flow values. We and others have systematically manipulated oxygen delivery to contracting muscles using hypoxia, several forms of hyperoxia, and inflation of balloons in the brachial artery to reduce perfusion pressure. In general, changes in arterial oxygen content evoke either increases (hypoxia) or decreases (hyperoxia) in blood flow with the net effect of maintaining constant oxygen delivery to the contracting muscles (73, 80–83, 182, 399, 504, 509, 510). A similar compensatory vasodilator response is seen...
when oxygen delivery is reduced by lowering perfusion pressure via balloon inflation to the contracting muscles (74, 75, 77–79).

However, other experimental approaches to induce hypoperfusion in contracting muscles have produced conflicting results with regards to flow restoration. Partial flow restoration or compensation has been reported to occur when external positive pressure is used to reduce blood flow in the contracting muscles of the arm and leg (112, 400). In both of these studies the partial flow restoration was attributed to an augmented systemic pressor response. Conversely, minimal flow recovery was observed when local forearm perfusion pressure was acutely reduced via positional changes (i.e., forearm above heart level) (498). A lack of flow restoration with positional perfusion lowering is further supported by the idea that muscle force production is reduced and fatigue can be increased by reductions in perfusion pressure (517, 518). Taken together, the magnitude of flow restoration or compensation and mechanisms involved appear to be dependent on the experimental approach used to induce hypoperfusion in contracting skeletal muscle.

In a number of studies we have evaluated metabolic, endothelial, and neural mechanisms that contribute to compensatory vasodilation. These include the contribution of vasodilators like NO and adenosine and interactions between sympathetic vasoconstriction and metabolic vasodilation. In general, our findings demonstrate that NO contributes to sympathetic vasoconstriction and metabolic vasodilation. These include the contribution of vasodilators like NO and adenosine and interactions between sympathetic vasoconstriction and metabolic vasodilation. These include the contribution of vasodilators like NO and adenosine and interactions between sympathetic vasoconstriction and metabolic vasodilation.

Arguments against it include the previously mentioned observation that at least some portion of the dilator response to exogenous ATP administration has an endothelial component that is at the upper end of that seen for exercise. Additionally, there is some evidence that the ATP release is defective in RBCs from patients with cystic fibrosis (449); however, patients with cystic fibrosis have a relatively normal blood flow response to forearm handgripping (418). Finally, ATP release from RBCs might also be blunted or absent in healthy older patients (250) and in diabetics (451), and in both groups contraction can still evoke marked increases in blood flow.

It is also interesting to note that when arterial oxygen content is increased ~25–30% during exercise in hyperbaric hyperoxia, the blood flow responses are reduced by a similar amount (80, 81). The mechanisms of this blunting and relative vasoconstriction are currently poorly understood, but an enhanced α-adrenergic vasoconstriction does not explain the majority of the large reductions in blood flow during exercise in hyperbaric hyperoxia (81). Preliminary data from our laboratory suggest that oxidative stress associated with the hyperoxia inactivating a key dilator substance like NO is not involved. Overall, these findings are another example of the tight linkage between oxygen demand and delivery seen during exercise under most circumstances. They also reinforce the challenge of identifying a dominant factor responsible for the changes in blood flow and vasodilator responses in contracting muscles evoked by a specific intervention. In contrast to the vasoconstriction observed during forearm exercise noted above with hyperbaric hyperoxia, experimentally increasing oxygen delivery to contracting forearm muscles by elevating mean arterial and perfusion pressure does not lead to compensatory vasoconstriction and normalization of blood flow (475).

While oxygen and CO₂ per se are not major blood-borne factors that directly cause vasodilation in the active muscles, two new concepts have emerged related to blood-borne substances and vasodilation. One idea is that ATP is released from deoxygenating red blood cells (35, 179, 229) and that this release evokes vasodilation in areas of the skeletal muscle that are consuming oxygen. ATP can also be released via mechanical deformation of red blood cells (108, 449, 450). In both cases, this mechanism would meet a number of criteria associated with so-called “blood flow metabolism matching.” Importantly, as discussed above, ATP has a number of properties that “mimic” the vasodilator responses associated with exercise including the ability to generate a large increase in skeletal muscle blood flow and also to interfere with sympathetic vasodilation from the contracting skeletal muscles. However, at this time, the primary evidence that ATP released from RBCs is perhaps the major cause of exercise hyperemia is primarily indirect or correlational.

Similar to the ATP-RBC interactions noted, there are also several potential sites of interaction between NO, hemoglobin, and red blood cells. These interactions occur in a way that might also permit NO to be stored in the form of S-nitrosohemoglobin and then released during deoxygenation of hemoglobin to facilitate the matching of blood flow with metabolic demand (124, 453). However, NOS inhibition via local infusions can reduce blood flow modestly consistent with the idea that endothelial (or perhaps skeletal muscle) sources of NO are the main contributors during exercise, particularly under hypoxic conditions (82, 110). This interpretation seems reasonable since local infusions of small amounts of NOS inhibitors should not disrupt the red blood cell-mediated NO metabolism or the recently identi-
The distribution of NO from other sources including the RBC. For endothelial sources of NO, they do not rule out a compensation. However, while these observations show a role of compensatory vasodilation would have been maintained despite NOS inhibition. Directly or indirectly (via reduction to NO), the compensatory response (135, 175, 471). If nitrite were responsible, either from human forearm studies. In general, efforts to block the pathway of interest. The individual responses seen in the larger experiment were variable, highlighting the possibility that there might be significant individual variability in the pathways normally recruited to evoke exercise hyperemia. [Adapted from Schrage et al. (415).]

FIGURE 19. Individual record showing the critical importance of time resolution and redundant vasodilator pathways in evaluating blood flow responses to pharmacological blockade in contracting skeletal muscles. In this forearm handgripping study (rhythmic contractions performed at 10% of maximal voluntary contraction for 20 min), addition of the KATP channel blocker glibenclamide after combined blockade of nitric oxide and prostaglandin synthesis (L-NAME + Ketorolac) caused an impressive but temporary reduction in blood flow to contracting forearm muscles. This was followed by a compensatory hyperemic response and return to steady-state values. One possible interpretation is that the blood flow response to contractions became more dependent on KATP channels during blockade of nitric oxide and prostaglandin synthesis. Thus it fell dramatically when glibenclamide was administered. This fall in flow then caused a mismatch between oxygen delivery and metabolism in the contracting muscles that evoked adenosine release. This caused a brief hyperemic response above the normal blood flow value associated with contractions and then a return toward the steady-state value seen before any intervention. These observations emphasize the need for rapid time course measurements of flow (beat-to-beat) when pharmacological blocking agents were given during contractions. Otherwise, it might be possible to miss effects of the drug on the pathway of interest. The individual responses seen in the larger experiment were variable, highlighting the possibility that there might be significant individual variability in the pathways normally recruited to evoke exercise hyperemia. [Adapted from Schrage et al. (415).]
While adenosine does not appear obligatory in the vasodilator response seen in exercise, a role for adenosine in regulating vascular tone shows that when blood flow is reduced using this approach, a role for adenosine in regulating vascular tone becomes more critical when blood flow to the contracting muscles is restricted.

The other possibility is that some un- or ill-defined and undiscovered vasodilator substance might explain a large percentage of the exercise hyperemia response. Based on the fact that the vascular biology world was generally surprised at the emergence of the vascular endothelium as a major site of vascular regulation and the observation that it explained a number of unexplained vasodilator responses, the possibility of additional vasodilating mechanisms should not be discounted. However, based on the repeated demonstrations of redundancy to date, the idea that there is a missing factor that might explain most or all of the vasodilator responses to exercise should be viewed with caution.

### VIII. METABOLIC VERSUS SYMPATHETIC CONTROL OF BLOOD FLOW IN SKELETAL MUSCLES

#### A. Functional Sympatholysis

As part of our discussion on the human hemodynamic responses to whole body exercise, we pointed out that under some circumstances it is possible for the marked vasodilation in the contracting muscles to potentially “threaten” blood pressure regulation and highlighted the competition between skeletal muscle vasodilation and systemic blood pressure regulation. These themes have run throughout this review. Now we turn our attention to how the factors that cause vasodilation in skeletal muscle interact with the sympathetic nervous system to ultimately regulate both skeletal muscle blood flow and mean arterial pressure during exercise in humans.
B. Contraction Blunts Sympathetic Vasodilation

While Figure 9 clearly shows the impact of metabolic vasodilation in contracting skeletal muscles on the blood pressure responses to exercise in the absence of sympathetic vasosconstriction, what happens to skeletal muscle blood flow when the sympathetic nervous system is activated? In another foundational study conducted in the early 1960s, hindlimb skeletal muscles in the dog were pump perfused at varying flow rates at rest and during contractions. Thus flow was controlled at fixed levels in contrast to the usual hindlimb preparation that permits blood flow to rise in response to contractions. Figure 21 shows that at rest, carotid occlusion, a maneuver that stimulates sympathetic outflow to the muscle, caused an increase in pressure in the perfusion circuit consistent with the interpretation that there was vasodilation in the hindlimb (375).

During contraction, blood pressure was lower at a given rate of flow consistent with the interpretation that contraction induced vasodilation in the muscles. Importantly, there was also no increase in pressure in the circuit when the sympathetic nervous system was stimulated by carotid occlusion. This lack of a rise in perfusion pressure demonstrated that the ability of the sympathetic nerves to evoke vasoconstriction in contracting skeletal muscles was either blunted or eliminated by contractions. This phenomenon was termed “functional sympatholysis” (375).

The term functional sympatholysis has been the matter of some debate because some investigators believe that implicit in this term is the absolute elimination of all sympathetic control of blood flow to contracting skeletal muscle. There are also arguments about whether or not the magnitude of any blunting is dependent on whether vascular resistance or vascular conductance is used as the primary outcome variable (393).

This debate also emphasizes the general problem of how to compare blood flow and hemodynamic responses at vastly differing levels of blood flow prior to an intervention, in this case activation of the sympathetic nerves. For example, if blood flow to a resting skeletal muscle has a hypothetical arbitrary value of 50 units and sympathetic activation reduces the blood flow to 25 units, is the magnitude of vasodilation the same or different if the blood flow during contraction is 500 arbitrary units and sympathetic activation reduces the blood flow to 475 units? The answer to this question can depend on the analysis used. In terms of absolute flow, perhaps constriction is the same. In terms of percent reduction in flow, the constriction during exercise is lower assuming arterial pressure is similar under both circumstances. Differences in the answer will also be obtained if resistance versus conductance is used. However, the fundamental observations in Figures 9 and 21 show apparently divergent results indicating that at least some sympathetic control of blood flow to contracting muscles is essential during whole body exercise in humans to maintain the arterial pressure, but at the same time under some circumstances sympathetic control of blood flow can be completely eliminated in contracting muscles. Is it possible to reconcile these findings?

In an attempt to resolve this confusion we performed a series of experiments using brachial artery administration of tyramine to evoke norepinephrine release from the perivascular nerves in the forearm (479). Tyramine was used to avoid a number of issues associated with brachial artery administration of norepinephrine including stimulation of luminal and nonjunctional adrenergic receptors. We then had subjects perform rhythmic handgrip exercise at varying intensities and infused the tyramine to see if the vasodilation was the same or different than that observed at rest. As part of our experimental strategy, we used brachial artery infusions of sodium nitroprusside and adenosine to serve as high flow controls and adjusted the doses of tyramine to account for the higher flows. This approach was done to ensure the concentration of the tyramine was not diluted by higher brachial artery blood flows during either exercise or the drug infusions. Using this approach we
were able to generate dose-response curves to tyramine that caused graded reductions up to ~70% of forearm blood flow during the drug induced high flow control experiments. In contrast, the effects of tyramine on blood flow during contractions were markedly attenuated, but not eliminated, during exercise intensities that closely matched the blood flow increases caused by the drug infusions. For example, tyramine infusions caused reductions in blood flow of ~10–15% during heavy rhythmic handgrip exercise (81, 128, 130, 385, 386, 479). These findings are summarized and illustrated in FIGURE 22.

There are two important points from these experimental results. First, our experimental strategy bypassed many of the data analysis issues related to baseline flow and provided clear evidence that the sympathetic nerves evoked vasoconstriction in contracting skeletal muscles is blunted in humans. Second, we also demonstrated that this blunting was not absolute and that at least some adrenergic vasoconstriction was possible in contracting skeletal muscles during heavy exercise. These points now provide a springboard for further discussions on sympatholysis.

Many of the metabolic vasodilating substances discussed previously have been shown in one preparation or another to reduce norepinephrine release from the sympathetic nerves innervating blood vessels (prejunctional sympatholytic) or interfere with vasoconstriction (postjunctional sympatholyis) evoked by either sympathetic nerve stimulation or administration of α-adrenergic agonists (490, 491). In addition, pH may also play an important role in this response.

In a series of beautifully executed studies, Faber and colleagues evaluated the interaction of local metabolic environment in skeletal muscle on α1- and α2-mediated vasoconstriction in rat skeletal muscles (7, 153, 154, 341, 347). In these muscles, postjunctional α1 receptors predominate in larger arterioles while postjunctional α2 receptors predominate in the smaller arteriolar elements of the microcirculation. Most importantly, reductions in pH interfere with α2 mediated postjunctional vasoconstriction but α1-mediated vasoconstrictor responses are intact (311, 312, 462). Parenthetically, there is also substantial and generally underappreciated postjunctional α2 tone in humans that accounts for perhaps 50% of overall adrenergic tone at rest (127), and a similar fraction is also seen in dogs (284).

In support of these observations, VanTeeffelen and Segal (487) evaluated the ability of sympathetic nerve stimulation to cause vasoconstriction in different sized arterioles during several levels of contraction in hamster skeletal muscles. Consistent with the ideas from the Faber group, they demonstrated as shown in FIGURE 23 that contraction caused almost complete sympatholysis in the smallest arterioles with diameters of ~10–20 μm. The ability of the sympathetic nerves to evoke vasoconstriction upstream in the first and second-order arterioles and feed arteries with diameters between ~30 and 80 μm was preserved during contractions. In addition to this retained sympathetic control during contractions upstream in the arteriolar tree, sympathetic nerve stimulation also appears to eliminate or attenuate conducted vasodilator responses (200, 263, 429). Together, these findings demonstrate a significant sympatholytic effect in the smallest blood vessels, but with the possibility for substantial sympathetic control of vascular resistance upstream. From a hemodynamic perspective, this is important because it implies that the chief site of vascular control tends to drift upward towards larger vessels in vasodilated tissues.

Conceptually, these findings in the microcirculation also reinforce the systemic hemodynamic observations we have emphasized. They are consistent with the idea that at least some sympathetic control of blood flow to contracting muscles is required to maintain a mean arterial pressure of at least 90–100 mmHg during large muscle mass exercise. First, constriction in larger elements of feed arteries and proximal arterioles might be sufficient to provide the overall level of vasoconstriction needed to generate or ensure this blood pressure. Second, vasodilation in the most metabolically stressed areas of the microcirculation would be relatively preserved because the α2 receptors located in the

FIGURE 22. The effects of tyramine infusion on brachial artery vasodilator responses at rest and during rhythmic forearm exercise (20 contractions/min for 8 min). Tyramine is the prototypical indirectly acting sympathomimetic amine that causes release of norepinephrine from the sympathetic nerves. At rest and during both moderate (6.4 kg) and heavy exercise (12.1 kg), increasing doses of tyramine (2, 4, and 8 μg·dl forearm volume −1 min −1) caused dose-dependent vasoconstriction. This constriction was blunted by moderate exercise and attenuated more during heavy exercise. The tyramine infusions were adjusted to account for differences in blood flow to ensure a similar concentration under each condition. Importantly, when brachial artery flow was raised with either sodium nitroprusside or adenosine in the absence of exercise, there was no blunting of the constrictor responses (data not shown). The results highlighted in this figure show that contractions blunt sympathetic vasodilator responses in humans but that some constrictor tone is still present. This tone is critical to restrain blood flow to the contracting muscles for the purposes of blood pressure regulation during large muscle mass or whole body exercise. [Adapted from Tschaikovsky et al. (479).]

FIGURE 23. A hierarchy of physiological needs. The effects of tyramine infusion on brachial artery vasodilator responses at rest and during rhythmic forearm exercise (20 contractions/min for 8 min). Tyramine is the prototypical indirectly acting sympathomimetic amine that causes release of norepinephrine from the sympathetic nerves. At rest and during both moderate (6.4 kg) and heavy exercise (12.1 kg), increasing doses of tyramine (2, 4, and 8 μg·dl forearm volume −1 min −1) caused dose-dependent vasoconstriction. This constriction was blunted by moderate exercise and attenuated more during heavy exercise. The tyramine infusions were adjusted to account for differences in blood flow to ensure a similar concentration under each condition. Importantly, when brachial artery flow was raised with either sodium nitroprusside or adenosine in the absence of exercise, there was no blunting of the constrictor responses (data not shown). The results highlighted in this figure show that contractions blunt sympathetic vasodilator responses in humans but that some constrictor tone is still present. This tone is critical to restrain blood flow to the contracting muscles for the purposes of blood pressure regulation during large muscle mass or whole body exercise. [Adapted from Tschaikovsky et al. (479).]
smallest arterioles lose their ability to evoke vasoconstriction during exercise. Third, while total blood flow to a given muscle might be reduced by perhaps 10–20%, a differential pattern of vasoconstriction within the muscle might also have the effect of matching blood flow and metabolism across the vascular bed by preferentially reducing flow to areas of the muscle under less metabolic stress. Such a pattern of constriction might also explain the increases in oxygen extraction seen during large muscle mass exercise compared with small muscle mass exercise.

This interpretation and working hypothesis is also consistent with the early ideas promulgated by Strandell and Shepherd (457) who showed continued sympathetic control of blood flow to contracting muscles was possible. Consistent with this hypothesis, it is interesting to note that infusions of vasodilating substances into the limbs of humans performing heavy exercise do not improve oxygen consumption. In fact, vasodilator infusions during heavy exercise seem to disrupt the matching of blood flow and metabolism that might result from the interactions of metabolic vasodilation and sympathetic vasoconstriction described above (69, 288, 401). Our interpretation of these observations is that when total limb flow is already very high and parts of the muscle are maximally dilated, infusions of exogenous vasodilators would dilate regions with little demand for oxygen and blood flow. Under these circumstances, this would cause a classic “steal syndrome” with the drugs causing dilation in parts of the limb that are relatively constricted and not consuming much oxygen thus diverting or “stealing” flow from areas of the contracting muscle where demand is high.

Thus it appears possible to reconcile the interactions between metabolic vasodilating factors and sympathetic vasoconstriction in contracting skeletal muscles both at the local level, and in terms of the need to regulate mean arterial pressure during heavy exercise. This conclusion is also supported by observations that sympathetic control of exercise hyperemia is relatively preserved in aging where it might be critical to restrain vasodilation more compared with young subjects during heavy exercise when maximum cardiac output is limited (130, 259, 349).

There are several other features of sympatholysis that warrant discussion. First, in rodent models, sympatholysis appears to be more pronounced in contracting highly glycolytic versus highly oxidative skeletal muscle fibers (466).
Again, the relevance of this observation to humans is not clear, because humans have mixed skeletal muscle versus the highly compartmentalized skeletal muscle of rodents. Second, as is the case with the mixture of skeletal muscle fibers in human muscles versus the more compartmentalized muscle in rodents, the effects of contraction on \( \alpha \)-mediated responses might not be as pronounced in humans and vasoconstriction caused by both receptor subtypes appears to be blunted by exercise (385). Third, as is the case for metabolic vasodilatation in general, there has also been a search for the substance principally responsible for sympatholysis. In animal models and some human studies, NO has emerged as a mediator of sympatholysis, and there is evidence to both support and reject a role for it (90, 128, 129, 155, 467, 479). However, administration of exogenous nitrovasodilators does not cause sympatholysis (81, 386). To date, exogenous administration of ATP does mimic the sympatholytic effects of contraction on sympathetic vasoconstriction (252, 387, 388), and this is also one of the primary arguments favoring ATP as a major player in exercise hyperemia. Fourth, in conditions like hypertension, aging, and perhaps congestive heart failure, there is evidence that sympatholysis is attenuated (130, 156, 251, 494). In other words, the blood vessels in contracting muscles under these conditions remain subject to substantial sympathetic control. This has the potential to reduce skeletal muscle blood flow and perhaps limit exercise capacity in individuals with these conditions.

In addition to norepinephrine, it is also possible that cotransmitters including ATP and neuropeptide Y (NPY) released from the sympathetic nerves also can evoke vasoconstriction in contracting muscles. The idea is that as sympathetic nerve firing rates increase, more ATP and NPY are released from the sympathetic nerve and then bind on postjunctional P2X and Y1 receptors where they can evoke vasoconstriction. Studies that have tested this hypothesis in dogs support some role for those mechanisms (57–59, 62), but the primary competition between vasodilation and vasoconstriction in contracting muscle during exercise is likely one between the vasodilator mechanisms and norepinephrine.

There are also interactions between metabolic vasodilation and \( \alpha \)-adrenergic vasoconstriction that influence the blood flow responses to hypoxia, hyperoxia, and hyperperfusion. As discussed earlier, muscle blood flow is augmented during exercise under hypoxic conditions. This augmentation occurs despite an increase in sympathetic vasoconstrictor activity directed at the skeletal muscle (196), which is capable of restraining the increase in blood flow to the contracting muscle during hypoxia (456, 509). So there is competition between hypoxic dilation and sympathetic constriction and evidence that hypoxia can attenuate vasoconstrictor responses to sympathetic nerve activation and exogenous norepinephrine in resting skeletal muscle of animals and humans (48, 205, 206). However, we have found that the increased blood flow during hypoxic exercise (relative to normoxic conditions) is due to enhanced vasodilator mechanisms as opposed to reduced postjunctional \( \alpha \)-adrenergic vasoconstrictor responsiveness (e.g., sympatholysis) (510). In contrast, the magnitude of vasodilation in hypoperfused contracting muscle is also under some degree of sympathetic vasoconstrictor restraint, as \( \alpha \)-adrenergic blockade unmasks a greater flow recovery (74).

C. Summary

The functional sympatholysis narrative has emerged as a classic example of how local and systemic responses work together to optimize physiological function (see Figure 24). Retained vasoconstriction in larger blood vessels permits total muscle blood flow to remain under some sympathetic control while sympatholysis especially in the smallest arterioles ensures that the available flow is distributed to the most metabolically stressed areas of the active muscles. Together, these mechanisms permit arterial blood pressure to be maintained while maximizing the extraction of oxygen across the exercising skeletal muscle during conditions when 80–90% of cardiac output is directed to contracting skeletal muscles. These observations also explain the very high levels of systemic oxygen extraction outlined at the outset of this review and demonstrated in Figure 5.

IX. INTEGRATION, PERSPECTIVES, AND KEY QUESTIONS

There can be vast increases in blood flow to contracting skeletal muscles during exercise in humans and other species. These increases in skeletal muscle blood flow are essential to meet the demands of the contracting skeletal muscle for oxygen, and for exercise to be prolonged. On a systemic level, the key determinant of these overall responses is the generation of a cardiac output as a result of the increases in heart rate and stroke volume that can both meet the demands for oxygen by the contracting muscles and perfusion pressure by other organs. In humans, these demands are also met by the diversion of blood flow away from less active skeletal muscle and other tissues so that the vast majority of cardiac output is directed toward the exercising skeletal muscles. These responses and adaptations are at their most impressive in elite highly trained endurance athletes.

At the same time these systemic hemodynamic and gas exchange events are occurring, there is a competition at the level of the contracting skeletal muscles between mechanisms that cause local vasodilation and reflex sympathetic vasoconstrictor mechanisms that maintain systemic arterial pressure. Vasodilating factors operating within the skeletal muscle limit sympathetic vasoconstriction in the arterioles.
closest to the contracting skeletal muscles while permitting continued vasoconstriction upstream. This interplay between dilator and constrictor mechanisms improves the extraction of oxygen across the muscle and provides enough vascular tone in the skeletal muscles so the arterial blood pressure does not fall or increases modestly. When this balance is lost, as in autonomic failure, blood pressure falls during large muscle mass exercise. When it is excessive, there can be a hypertensive response to exercise, limited skeletal muscle blood flow, and exercise intolerance (494).

Importantly, while neural and mechanical factors might contribute modestly to the rise in skeletal muscle blood flow, during exercise the main driver is vasodilation in the active muscles by a combination of chemical or metabolic factors that remain obscure. To date, no single factor has been shown to account for much more than 20–30% of the vasodilator responses to ongoing exercise in experimental conditions that favor a key role for that substance. Attempts to block one or more dilating factor alone or in combination either before or during contractions are typically ineffective in identifying a single or even several major factors that could explain the majority of vasodilator responses we have discussed.

Does this mean there are key mechanisms similar to the endothelial-derived factors discovered in the 1980s, yet to be discovered that might explain the vasodilator responses to exercise? Are the number of potential vasodilating substances simply so numerous that blockade of one or more of them will evoke alterations in the concentration of other factors to generate a relatively intact response? Are studies in either isolated human muscles or contracting muscles in animal models fundamentally flawed because unlike whole body exercise, oxygen extraction across the vascular bed even during heavy exercise is incomplete and blood flow is relatively “luxuriant”? Are the current experimental tools, especially the pharmacological agents, simply inadequate to fully explore what is likely happening in the interstitial space at the interface between the contracting muscles and resistance vessels? Do genetically modified animals offer a solution or will lifelong alterations of a key pathway or mechanism merely evoke compensatory phenotypic plasticity in other pathways so that the overall response remains intact? Finally, have we engaged in futile effort to reconcile complex responses with observations made in simpler systems versus using simple systems to understand complex responses? In either case, the experimental approaches and
data may be similar, but perhaps the intellectual perspective and thus the conclusions different.

At the end of this review we clearly know, as Hunter stated in the 1700s (392), that blood goes where it is needed, and this principle certainly applies to contracting skeletal muscles during exercise in humans and other species. However, beyond this simple principle, how much do we really know? The vasodilating substances from one or more sources acting in combination under various circumstances to cause exercise hyperemia remain elusive. However, before we become too focused on what has not been learned in the last 30 or so years, perhaps we should review what has been learned in that time.

Blood flow to contracting muscles can be much higher than previously imagined.

The vascular endothelium is a major site of vascular regulation.

We can assert, with some confidence, that neurally mediated vasodilation and the mechanical effects of the muscle on the blood vessels do not drive the vast majority of blood flow to contracting skeletal muscles during exercise.

The interactions of the autonomic nervous system, sympathetic vasoconstriction, and metabolic vasodilation have been explored, and during large muscle mass rhythmic exercise in humans, the sympathetic nerves can cause some vasoconstriction in the active muscles. While this constriction is attenuated compared with rest, it is critical to maintain arterial blood pressure. Additionally, the distribution of the retained vasoconstrictor tone within the contracting muscles seems to operate in a manner that optimizes or maximizes oxygen extraction within the muscles.

Progress about the factors including K⁺-mediated mechanisms in conjunction with endothelial factors appear to play a major role in initiating the vasodilation at the onset of contractions have been made. Additionally, blood-borne sources of ATP and NO that might sustain vasodilation during exercise have been proposed and are being explored. Understanding the contribution of the factors that initiate the vasodilation and the blood-borne substances that contribute to vasodilation as exercise continues would seem like an especially ripe area for further research because older studies suggest that K⁺-mediated mechanisms are not obligatory for vasodilation and exercise hyperemia during prolonged periods of rhythmic contractions.

For almost all of the mechanisms and interactions outlined above, insight into how they are altered in diseases like heart failure and hypertension along with conditions like aging have been made. In these cases the contribution of endothelial factors and functional sympatholysis to exercise hyperemia are blunted. These observations may explain some of the peripheral factors associated with exercise intolerance in these groups and also have therapeutic implications (91, 468, 494).

The conclusion in the early 1980s was that the topic of muscle blood flow contained “a wealth of hidden information for those with the ability to find it” (431). The summary above clearly shows the fruits of the research conducted since that time. Thus the conclusion from the early 1980s might be modified to read that the topic of exercise hyperemia contains a wealth of integrative challenges for those with the curiosity, creativity, and ability to explore them.

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No conflicts of interest, financial or otherwise, are declared by the authors.
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