Chapter 5

Mechanisms of Increased Cardiac Output and Skeletal Muscle Hyperemia during Exercise

INTRODUCTION

In physiological terms, any activity involving muscular contraction is an exercise. So, it includes not only athletic sports but also routine daily activities, like walking, running to catch a bus, or lifting a heavy bag of groceries, etc. Exercise not only involves neuromuscular coordination but also produces a considerable disturbance of internal environment. As a result, almost all the body systems undergo readjustments. Study of exercise physiology gives an excellent scope to discuss the interplay of different organ systems in the maintenance of constant internal environment.

A Synopsis of Cardiovascular Adjustments during Exercise

During exercise, oxygen consumption of the skeletal muscle increases 20-folds as compared to the resting values. Numerous cardiorespiratory adjustments occur in the body to meet with increased demand of oxygen and nutrients in the exercising muscles (myocardium, respiratory muscles and contracting muscles) and to dissipate heat via cutaneous vasodilation. To sustain the increased metabolic demand of these tissues, increased oxygen and nutrient delivery are accomplished by (i) increased cardiac output, (ii) increased blood flow to the active tissues, (iii) greater microvascular surface area available for exchange in the active tissues, and (iv) greater oxygen extraction from the blood in the active tissues.

The changes include large increases in heart rate and cardiac contractility to increase cardiac output, increased rate and depth of respiration which requires enhanced blood flow to respiratory muscles, vasodilation and increased blood flow in the contracting skeletal muscles, and vasoconstriction in the renal, splanchnic, and inactive skeletal muscle vascular beds (Fig. 5.1). These changes result in the regional redistribution of the cardiac output that allows diversion of greater percentage of cardiac output to the metabolically active tissues. Moreover, increased peripheral resistance in metabolically inactive tissues compensates for markedly decreased peripheral resistance in the metabolically active tissues and helps the blood pressure to be maintained or even increased during exercise. These alterations are coordinated by the sympathetic nervous system, which directs increased sympathetic outflow to the heart, resulting in increased cardiac output, and evokes selective vasoconstriction in peripheral organs (e.g. kidneys, small and large intestines, and non-exercising skeletal muscles). Changes in cutaneous blood flow during

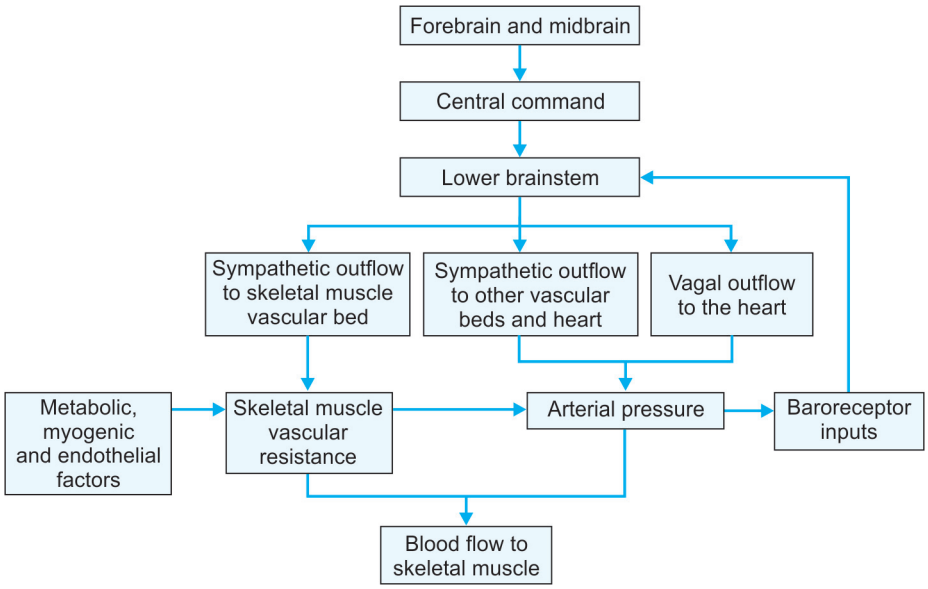

Fig. 5.1: Cardiovascular regulation during exercise

exercise depends on ambient temperature and the rise in body core temperature induced by increased metabolism with exercise, which increases skin blood flow to dissipate heat.[1, 2] Mechanisms of increased cardiac output, increased skeletal muscle blood flow, and changes in splanchnic blood flow shall now be discussed.

I. CARDIAC OUTPUT DURING EXERCISE

An increase in heart rate and force of cardiac contraction leading to increased cardiac output is hallmark of cardiovascular changes during exercise. Exercise induces parasympathetic withdrawal and sympathetic activation, which are a function of exercise intensity and the muscle mass recruited. Parasympathetic withdrawal aims at increasing heart rate (HR), while the engagement of the sympathetic activity aims at increasing HR, at enhancing myocardial contractility to increase stroke volume (SV). In this autonomic modulation at least two neural mechanisms are involved in normal physiological response: One is a central mechanism (central command), while the other is peripheral (exercise pressor reflex).

a. Central Command

The increase in heart rate at the onset of exercise was documented as early as 1913 by the pioneering exercise physiologists, August Krogh and Johnas Lindhard[3] (Fig. 5.2). Based on this rapid response, they concluded "that the mechanism which shall produce the abrupt changes must be a nervous mechanism" and "we think that the evidence is in favor of an irradiation of impulses from the motor cortex" to the cardiovascular center. Later, the irradiation of impulses from the motor cortex to medullary cardiorespiratory centers came to be known as "central command."

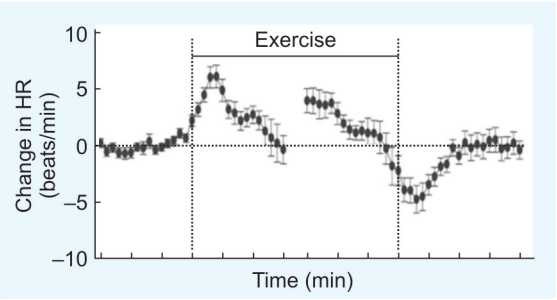

Fig. 5.2: Abrupt changes in the heart rate at the start and the end of exercise

In the central command mechanism, the activation of regions of the brain responsible for motor unit recruitment also activates the cardiovascular control areas located in the medulla. It is thought that central command establishes a basal level of sympathetic activity to the cardiovascular apparatus closely linked to the intensity of the effort.[4]

Nonetheless, an attempt to directly identify the response in sympathetic nerve activity during exercise has been conducted. Ninomiya et al[5] recorded for the first time cardiac and renal sympathetic nerve activity (CSNA and RSNA) during voluntary body movement in freely moving conscious cats and found abrupt increases in the sympathetic outflows prior to the onset of body movement. Tsuchimochi et al[6] observed an exercise–intensity-dependent increase in CSNA at the onset of treadmill exercise in conscious cats. Taken together, central command does not have uniform influence on the sympathoadrenal system at the onset of exercise, but selectively augments sympathetic outflow to specific organs such as heart, kidneys, and skin.

In exercising muscles, it is difficult to separate the central command component from peripheral component. The problem was solved by first observing cardiovascular response to graded loads and observing the response after partial neuromuscular blockade by tubocurarine. Increasing work load in normal subjects resulted proportional increase in CV response. However, in individuals with partial neuromuscular block, even mild load produced large CV response, indicating that the greater effort to lift the load resulted in greater central command (Fig. 5.3). In this experimental condition, the chemical milieu of the contracting muscle is not altered and hence peripheral signals cannot be responsible for cardiovascular response.[7, 8]

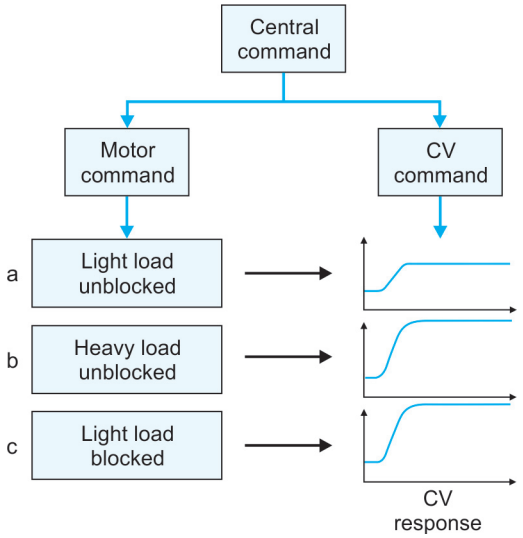

Fig. 5.3: Graded cardiovascular response to increasing workload (a and b). In (c), cardiovascular response is as great with light load in partially blocked person as with heavy load in unblocked individuals

b. Exercise Pressor Reflex

Alam and Smirk, in 1937[9] demonstrated the role of peripheral mechanism(s) in cardiovascular changes during exercise. They recorded blood pressure in human volunteers during and after the end of exercise. They observed increased blood pressure during exercise which rapidly declined after the end of exercise. The experiment was repeated but circulation to the limb was arrested at the end of exercise. In the second group, the blood pressure remained elevated for several minutes even after cessation of exercise. The phenomenon was called "metabolic pressure reflex". Since then a large bulk of evidence has demonstrated that metabolic reflex coming from skeletal muscle evokes cardiovascular adjustments during exercise.

Several substances have been demonstrated to be able to activate the metaboreflex, such as lactic acid, potassium, bradykinin, arachidonic acid products, ATP, deprotonated phosphate, and adenosine. Moreover, studies with ^{31}P nuclear magnetic resonance spectroscopy revealed that the metaboreflex can be activated by decrements in intramuscular pH. These findings are interpreted with the concept that the metaboreflex is activated whenever blood flow to contracting muscles is insufficient to warrant oxygen delivery and/or metabolites washout, there-

by suggesting that this reflex corrects any possible mismatch between blood flow and metabolism in the muscle. However, there is evidence that in humans the metaboreflex can be active even during mild exercise, when there is sufficient O_2 delivery to the muscle. In this situation there is no evident mismatch between muscle flow and metabolism, thereby demonstrating the essential role of the metaboreflex in the normal blood pressure response even for light exercise intensities. Therefore, the metaboreflex might be responsible for a tonically active feedback to the cardiovascular control areas which induce cardiovascular changes whenever the muscle metabolism is activated by muscle contractions, even at mild intensities of effort.[10]

In 1971, Coote et al[11] demonstrated that the muscle pressor reflex could be elicited by ventral root stimulation. Then, McCloskey and Mitchell[12] showed the involvement of group III/IV afferents in this cardiovascular reflex. This component is known as the muscle "metaboreflex." It was later demonstrated that mechanical changes in muscles and tendons can also elicit cardiovascular responses. This component has been termed "mechanoreflex." These two reflexes of muscular origin together constitute the *exercise pressor reflex*. It is well established that these two reflexes have their afferent arm in groups III and IV nerve endings within the muscle, with type III nerve afferents mainly acting as mechanoreceptors and type IV as metaboreceptors. These receptors collect information concerning the mechanical and metabolic conditions of contracting muscles and send this piece of information to cardiovascular controlling centers located in the *medulla*, where the information is integrated and elaborated. Then, cardiovascular medullary centers organize the hemodynamic response to exercise taking into account the mechanical and metabolic status of the working muscle.[13]

II. EXERCISE HYPEREMIA

Exercise hyperemia refers to the increase in skeletal muscle blood flow that occurs during muscular activity. Because this increase in blood flow occurs in response to increased cell metabolism, exercise hyperemia is also referred to as active or functional hyperemia. The term, active or functional hyperemia also applicable to the increase in flow to any organ that experiences an increase in parenchymal cell metabolism.[2]

Initial Versus Later Vasoregulatory Mechanisms in Exercise Hyperemia

Blood flow increasing within one second of the onset of muscular activity is referred to as the *fast vasodilator response*. This is followed by a larger *vasodilation that is sustained* and dependent on the magnitude and duration of exercise. This second vasodilatory phase is thought to result from the production of vasodilator metabolites by the contracting muscle cells that can be modulated by other local vasoregulatory mechanisms. Since it takes some time for active muscles to produce metabolites, which then have to diffuse to nearby arterioles, followed by binding to their receptors and activation of the second messenger signaling mechanisms that cause relaxation of vascular smooth muscle, the fast vasodilator mechanism must result from other processes, which are not exactly clear. Withdrawal of sympathetic tone does not explain this initial vasodilator phase because sympathectomy or treatment with ganglionic blockers does not alter the time to onset of this fast response. Some workers have proposed that muscle pump may be responsible for this early increase in muscle blood flow during exercise.[2]

Mechanisms Responsible for Exercise Hyperemia

Mechanical Factors

Arterial inflow to active skeletal muscle decreases during contractions and increases when the muscle relaxes. In contrast, the venous outflow increases during rhythmic contractions but decreases during muscle relaxation. These mechanical effects of

exercise are due to increased extravascular pressure during rhythmic contractions, which expel blood through the venous system and increase the arteriovenous pressure gradient. This muscle pump mechanism can contribute up to 60% of the hyperemic response, at least under some conditions, and provides an attractive explanation for the observation that going from supine to upright position produces a twofold increase in exercise hyperemia (which is difficult to ascribe to other known mechanisms that contribute to the increased flow). The muscle pump also provides an explanation for the fast vasodilator mechanism.[2]

Role of Sympathetic Innervation in Exercise Hyperemia

Skeletal vessels have extensive adrenergic sympathetic innervation and there is a tonic vasoconstrictor discharge. In many animals, cholinergic sympathetic innervation has also been reported. Possibly, exercise hyperemia may be at least partly be due to decreased vasomotor discharge or increased cholinergic sympathetic discharge:

i. **Activation of cholinergic sympathetic fibers:** Bülbring and Burn[14], in 1935, reported for the first time the existence of sympathetic cholinergic nerve to skeletal muscle contributing to exercise vasodilatation in the cat and dog. It is histologically verified that sympathetic cholinergic nerves innervate blood vessels of skeletal muscle in several species such as the cat, dog, sheep, etc. but there is no histological evidence for the existence of sympathetic cholinergic nerves to skeletal muscle in the monkey and man.[15] Even in the dog possessing the sympathetic cholinergic system, exercise hyperemia of hindlimb contracting muscle is not significantly influenced by surgical sympathectomy or ganglionic or muscarinic blockade. Taken together, it has been currently accepted that the cholinergic sympathetic nervous system is not responsible for exercise hyperemia.

ii. **Withdrawal of sympathetic vasoconstrictor activity or sympatholysis in exercise hyperemia:** During high intensity exercise the adrenergic sympathetic nerve activity is markedly increased to elevate cardiac output and peripheral resistance. It contributes to the control of blood pressure during exercise. It also helps to redistribute the blood flow from inactive muscles as well as splanchnic area to active tissues. In contrast, there is intense vasodilation in the actively contracting muscles. Is this a result of withdrawal of sympathetic activity in the skeletal vessels? Theoretically yes, but there is no known mechanism by which sympathetic discharge to the skeletal vessels can be increased in inactive muscles as well as decreased in active muscles. Nowadays, it is believed that, during exercise, there is increased sympathetic discharge to all the skeletal vessels. In active muscles, effect of increased vasomotor discharge is counteracted by local vasodilator metabolites. This phenomenon is known as functional sympatholysis.[16]

Metabolic Mechanisms in Exercise Hyperemia

Although it is clear that the increased interstitial concentration of vasodilator metabolites derived from active muscle cells plays a major role in producing exercise hyperemia, it does not appear that one single metabolite accounts for metabolic vasodilation of arteriolar vascular smooth muscle. Alterations in the type of contraction (isometric *vs* isotonic) and the mass of muscle involved in the contractile activity may also produce differential release of metabolites.

While a large number of metabolites have been suggested to mediate exercise hyperemia, the most compelling evidence suggests that adenosine, potassium ions, and osmolarity changes may be quite important. In addition, decreases in arteriolar pO_2 (hypoxemia) that may occur in exercise owing to enhanced diffusion of the gas across the walls of these vessels may also contribute to active

hyperemia. The notion that release of ATP from contracting myocytes and by erythrocytes in response to hypoxia and mechanical deformation of red cells as they pass through microvessels of contracting skeletal muscle is also gaining support.[16]

Criteria for Consideration of a Metabolite as a Vasodilator[17]

In 1983, Shepherd[17] laid down the following criteria:

1. The substance should be present in the skeletal muscle.
2. The substance should have access to skeletal resistance vessels.
3. The concentration of the substance should be sufficient to cause vasodilation and concentration should increase in proportion to the increase in muscle activity.
4. Exogenous administration of the substance should produce a prolonged and sustained vasodilation without producing any sensation (pain) to the subject.
5. Pharmacological or physiological maneuvers that alter the blood flow responses to exercise should have similar effects on the vasodilator responses to any putative substance given exogenously.

In line with these criteria, the following metabolites have been considered as chemical mediators responsible for exercise hyperemia:

a. **K^+:** Any muscle action potential leads to release of potassium ions from skeletal muscle cells which, under conditions of high action potential frequency cannot be compensated for by the re-uptake by the sodium potassium ATPase pump or the washout by the bloodstream. As a result, interstitial potassium concentration increases. This is reflected by an enhanced K^+-efflux from working skeletal muscle which occurs early after initiation of exercise.

   Thus K^+ seem to fulfill some of the criteria set by Shepherd.[17] First, K^+ is released during skeletal muscle repolarization. Second, K^+ is released from the contracting muscles in proportion to its metabolic activity. During exercise interstitial K^+ concentrations as high as 10 mM have been reported. But, in dogs, K^+ depletion did not disrupt the relationship between oxygen consumption and blood flow during exercise. Moreover, exogenous administration of K^+ is *very painful* and does not produce sustained vasodilation. In view of these observations, it is unlikely that K^+ plays an obligatory role in exercise hyperemia.[13]

b. **Lactate or H^+:** Early studies on vasodilatory metabolites focused on lactate.[18] With the onset of heavy exercise, there is an increase in interstitial and venous concentrations of lactate. Particularly in the transition from rest to heavy exercise there is a net production of lactic acid by muscle. The increase in lactate formation is not necessarily due to a lack of cellular oxygen. Indeed it has been shown in human muscle under exercise that the lactate efflux is unrelated to cellular pO_2 but increases with increasing oxygen consumption. Though lactate has been shown to act principally as a dilator of vascular smooth muscle, a study in humans demonstrated that interstitial lactate concentration as measured with microdialysis did not correlate with the changes in muscle blood flow at 30–60% of maximal work capacity, thus challenging its role as a major mediator of exercise hyperemia under submaximal exercise.[19]

c. **Adenosine:** In exercising or hypoxic skeletal muscle an enhanced breakdown of adenosine triphosphate (ATP) occurs during the resynthesis of which, adenosine is formed. Part of it can probably be released from skeletal muscle and reach the cells of the arteriolar walls. Exogenous application of adenosine induces strong dilatation.[20] Furthermore, in humans, a strong correlation between leg blood flow during exercise and interstitial adenosine concentrations as measured by microanalysis has been reported.[21] Adenosine receptor antagonist theophylline reduced exercise hyperemia in humans but not in dogs. These discrepancies suggest that

adenosine need not necessarily play an essential role in exercise hyperemia, but rather it may be an important mediator under experimental conditions that involve skeletal muscle hypoxia.

To conclude, muscle-derived interstitial potassium, lactate and adenosine concentrations increase during exercise and all can reach by diffusion into the vascular smooth muscle of adjacent arterioles as well as the pericytes located in the capillary areas. This makes a contribution to exercise hyperemia likely and plausible but it is difficult to quantitate their respective contributions.[20]

d. **Endothelial derived vasodilators:** The main vasodilators released by vascular endothelium are NO and prostaglandins. In 1969, prostaglandins were proposed to be involved in muscle blood flow regulation based on the findings that infusion of prostaglandins into the brachial artery increased blood flow. A role for prostaglandins in exercise hyperemia was later supported by the findings that both plasma and interstitial prostacyclin and prostaglandin E_2 concentrations were increased during muscle contractions in the forearm and leg, respectively. However, infusion of cyclooxygenase (COX) inhibitors to inhibit the formation of prostaglandins, has shown no effect on blood flow at rest or during exercise in the human forearm.

In the late 1980s,Vallance and coworkers blocked NO synthase (NOS) by infusion of NG-monomethyl-L-arginine (L-NMMA) and showed a 50% reduction in resting forearm blood flow. The importance of NO for resting blood flow, blood flow in recovery from exercise, and blood flow during passive movement has since been widely confirmed. During exercise, however, inhibition of NO formation has been shown not to reduce blood flow. Thus, neither NO nor prostanoids appear to be obligatory for exercise hyperemia (Fig. 5.4). However, experiments in which the synthesis of NO and prostanoids have been inhibited simultaneously have demonstrated a clear reduction in blood flow

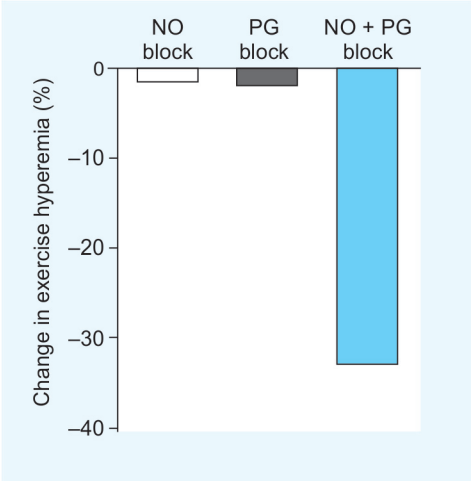

Fig. 5.4: Effect of nitric oxide (NO) and prostaglandins blockade on skeletal muscle hyperemia during exercise

during exercise. The observation that single inhibition of a system has no effect on exercise hyperemia, whereas combined inhibition markedly lowers blood flow suggests that there is a compensatory formation of the other vasodilator so that adequate blood flow is achieved. Direct interactions between the vasodilator systems may explain this redundancy.[22]

Conducted Vasodilation

Arterial circulation in skeletal muscle is typically comprised of feed arteries and branch arterioles including first-, second- and third order terminal arterioles. While distal branch arterioles are embedded in the skeletal muscle, proximal feed arteries are not directly involved in vasomotor regulation involved in exercise hyperemia. However, vasodilation in feed arteries and arterial network outside the skeletal muscle has to coordinate with skeletal vessel hyperemia essential for supplying greater amount of blood to the exercising muscles. The mechanisms responsible for intramuscular vasodilation have been discussed in detail above. So, the mechanism of vasodilation in extramuscular arteries need to be elucidated. In this context, a concept of conducted vasodilation is currently popular.

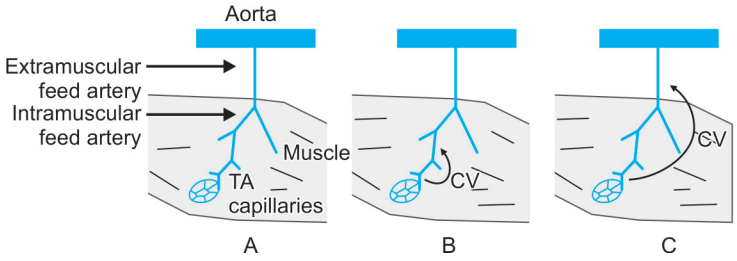

Fig. 5.5A to C: Conducted vasodilation (CV). TA: Terminal arteriole

In this concept, dilatation originating in the microcirculation embedded in the skeletal muscle ascends through gap junctions in the smooth muscle of arterioles to proximal feed arteries (Fig. 5.5). The resulting dilation of feed arteries allows increased blood flow to the muscles.[23]

SPLANCHNIC BLOOD FLOW DURING EXERCISE

At rest, the splanchnic organs receive 20% of the cardiac output, but only consume 10–20% of the available oxygen. To a certain extent, blood may be safely redistributed from the splanchnic organs to the working muscles and skin. The splanchnic vascular bed may therefore act as a reservoir of blood for the increased needs of skeletal muscle during exercise. Sympathetic nervous system (SNS) activity is massively increased in response to exercise. This causes increased splanchnic vascular resistance that may decrease splanchnic blood flow (SBF), despite the massive rise in cardiac output associated with physical exercise. In fact, SBF can decrease by 80% during maximum intensity exercise.[24] The importance of the SNS activity was demonstrated in a study in healthy individuals and patients with spinal cord injury at two levels (high and low). The effects of exercise with an arm-crank test on the portal vein flow and femoral artery, were measured. In normal persons and those with high level spinal cord lesions, a 30% reduction in portal vein flow was observed, but in high spinal cord injury (sympathetic denervation), the portal vein flow remained unchanged.[25]

The effect of exercise on the GI blood flow is dependent on various factors including exercise duration, environmental temperature and prandial state.[26] The effect of exercise duration on SBF was studied by Rehrer et al.[24] A gradual reduction in portal vein flow from 20% after 10 min to 80% after 1 hour of exercise was observed. The reduction in SBF during exercise is more pronounced in high environmental temperatures. Kenney et al[27] compared the effects of exercise in 22°C and 36°C. Exercising in 36°C resulted in an additional 17% decrease in SBF compared with 22°C at the same exercise intensity.

Thus, there is a redistribution of blood flow during exercise and diversion of blood flow from the splanchnic viscera to the working muscles. The mechanism of this redistribution is still unclear. One mechanism would be that the splanchnic vasoconstriction simply reflects generalized increased sympathetic tone during exercise. In working muscles the increase in sympathetic drive could be opposed by the effect of local vasodilator metabolites.

In view of these reports of decreased splanchnic blood flow during exercise, it would be prudent that the exercise is better avoided during the immediate postprandial period. This would be particularly important when the meal is a large one or environmental temperature is high.[28]

References

1. Joyner MJ, Casey DP. Regulation of increased blood flow (hyperemia) to muscles during exercise: A hierarchy of competing physiological needs. Physiol Rev. 2015; 95: 549–601.

2. Korthuis RJ. Skeletal Muscle Circulation. San Rafael (CA): Morgan & Claypool Life Sciences; 2011. Chapter 4, exercise hyperemia and regulation of tissue oxygenation during muscular activity. Available from: https://www.ncbi.nlm.nih.gov/books/NBK57139
3. Krogh A,Lindhard J. The regulation of respiration and circulation during the initial stages of muscular work. J Physiol. 1913; 47,112–36.
4. Matsukawa K, Liang N, Ishii K. Central command: Feed forward control of the system during exercise. Phys Fitness Sports Med. 2012; 1: 573–77.
5. Ninomiya I, Matsukawa K, Nishiura N. Central and baroreflex control of sympathetic nerve activity to the heart and kidney in a daily life of the cat. Clin Exp Hypertens. 1988; 10 Suppl 1: 19–31
6. Tsuchimochi H, Matsukawa K, Komine H, Murata J. Direct measurement of cardiac sympathetic efferent nerve activity during dynamic exercise. Am J Physiol Heart Circ Physiol. 2002; 283: H1896–906.
7. Eldridge, FL, Millhorn, DE, Kiley, JP, et al. Stimulation by central command of locomotion, respiration and circulation during exercise. Respir Physiol 1985; 59**:** 313–27.
8. Turner DL.Cardiovascular and respiratory control mechanisms during exercise: An integrated view. J Exp Biol. 1991; 160: 309–40.
9. Alam M, Smirk FH. Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. J Physiol. 1937; 89: 372–83
10. Crisafulli A, Marongiu E, Ogoh S. Cardiovascular reflexes activity and their interaction during exercise. Biomed Res Int. 2015; 2015: 394183. Published online 2015 Oc18. doi: 10.1155/2015/394183
11. Coote JH, Hilton SM, Perez-Gonzalez JF. The reflex nature of the pressor response to muscular exercise. J Physiol. 1971; 215: 789–804.
12. McCloskey DI, Mitchell JH. Reflex cardiovascular and respiratory responses originating in exercising muscle. J Physiol. 1972; 224: 173–186
13. Adreani CM, Hill JM, Kaufman MP. Responses of groups III and IV muscle afferents to dynamic exercise. Jo Appl Physiol. 1997; 82: 1811–17.
14. Bülbring E, Burn, JH. The sympathetic dilator fibres in the muscles of the cat and dog. J. Physiol (Lond.). 1935; 83, 483–501
15. Bolme P, Fuxe K. Adrenergic and cholinergic nerve terminals in skeletal muscle vessels. Acta Physiol Scand. 1970; 78: 52–59.
16. Hong KS, Kim K. Skeletal muscle contraction-induced vasodilation in the microcirculation. Journal of Exercise Rehabilitation 2017; 13: 502–7.
17. Shepherd JT. Circulation to skeletal muscle. In: *Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow*. Bethesda, MD: Am Physiol Soc. 1983; 3: 319–370.
18. Hilton SM. Experiments on the post-contraction hyperaemia of skeletal muscle. J Physiol 1953; 120: 230–45.
19. Sarelius I, Pohl U. Control of muscle blood flow during exercise: local factors and integrative mechanisms**.** Acta Physiol (Oxf). 2010; 199: 349–65.
20. Lott ME, Hogeman CS, Vickery L, et al. Effects of dynamic exercise on mean blood velocity and muscle interstitial metabolite responses in humans. Am J Physiol Heart Circ Physiol. 2001; 281: H1734–41.
21. Hellsten Y, Maclean D, Radegran G, et al. Adenosine concentrations in the interstitium of resting and contracting human skeletal muscle. Circulation. 1998; 98: 6–8.
22. Hellsten Y, Nyberg M, Jensen LG, et al. Vasodilator interactions in skeletal muscle blood flow regulation. J Physiol. 2012; 590: 6297–305.
23. Bagher P, Segal SS. Regulation of blood flow in the microcirculation: Role of conducted vasodilation. Acta Physiol (Oxf). 2011; 202: 271–284.
24. Rehrer NJ, Smets A, Reynaert H, Goes E, De MK. Effect of exercise on portal vein blood flow in man. Med Sci Sports Exerc. 2001; 33: 1533–7.
25. Thijssen DH, Steendijk S, Hopman MT. Blood redistribution during exercise in subjects with spinal cord injury and controls. Med Sci Sports Exerc. 2009; 41: 1249–54.
26. Steege RWF, Kolkman JJ. Review article: the pathophysiology and management of gastrointestinal symptoms during physical exercise, and the role of splanchnic blood flow. Aliment Pharmacol Ther. 2012; 35:516–28.
27. Kenney WL, Ho CW. Age alters regional distribution of blood flow during moderate-intensity exercise. J Appl Physiol. 1995; 79: 1112–19.
28. Qamar MI, Read AE. Effects of exercise on mesenteric blood flow in man. Gut. 1987; 28: 583–87.