Contributions of muscle sympathetic nerve activity and potent vasoconstrictors for blood flow redistribution during dynamic heavy exercise in humans

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Abstract

Blood flow circulation must be redistributed in the human body at the onset of dynamic exercise to deliver an appropriate amount of oxygen to exercising muscles. Muscle sympathetic nerve activity (MSNA) has been recognized as a major regulator of blood flow redistribution. However, recent research has indicated that there are some potent substances that affect peripheral blood flow circulation in humans. This review focuses on the physiological significance of functional sympatholysis, which can occur in exercising muscles, and the role of some potent vasoconstrictors in determining how blood flow in humans is redistributed during heavy exercise.

It is expected that, during heavy exercise that requires marked blood flow redistribution (i.e. endurance sports), the maximal blood flow is enhanced as a function of the individual's maximal cardiac output ($\dot{Q}_{max}$) by chronic exercise. This will contribute to overall muscle performance.

Keywords: Blood flow redistribution, muscle sympathetic nerve activity (MSNA), functional sympatholysis, vasoconstriction, vasodilation

1. Introduction

Oxygen consumption by skeletal muscles at rest is less than that of the splanchnic organs that are essential to the maintenance of the human body such as the heart, brain, and lungs. On the other hand, oxygen consumption by skeletal muscles increases abruptly at the onset of exercise (Rowell 1993). Blood flow adjustment is expected to occur during continuous dynamic muscle contractions in concert with a marked increase in the oxygen demand of the exercising muscles. During such a dynamic muscle contraction, vasodilation must occur within a few seconds to increase blood flow to the exercising muscles if the exercise is continued. (Saltin et al. 1998, Shoemaker and Hughson 1999). This phenomenon is called exercise hyperemia, and it physiologically influences rapid oxygen delivery to exercising muscles, removes metabolites from exercising muscles, and transfers increased muscle temperature.

The main physiological significance of the blood flow adjustment during heavy exercise

is delivery of oxygen to exercising muscles. If exercising muscles can receive the necessary amount of oxygen from arterial capillaries, a blood flow redistribution does not necessarily occur. To adjust the appropriate blood flow at the onset of exercise, cardiac output ($\dot{Q}$) increases along with the demand for oxygen delivery to exercising muscles. However, the maximal cardiac output ($\dot{Q}_{max}$) cannot cover such a huge blood flow demand from exercising muscles during heavy exercise. According to several previous reports, adding a dynamic arm cranking exercise to a dynamic leg exercise did not increase $\dot{Q}_{max}$. Rather, leg blood flow decreased due to an increase in oxygen demand from the respiratory muscles (Harns et al. 1998, Wetter et al. 1999). Due to an increase in the cutaneous blood flow, blood flow to the exercising muscles decreased during heavy exercise that was performed in a hot and humid environment (Bell et al. 1983). The maximal forearm blood flow during rhythmic handgrip exercise was much greater than that observed in cycle ergometer exercise. The maximal blood flow reached 350ml/100g/min when the isolated muscle was artificially perfused (Saltin et al. 1998, Rowell 1993).

Those previous investigations suggest that blood flow redistribution is required to cover the oxygen demand of exercising muscles during heavy exercise. It means that blood flow to the non-exercising muscles and splanchnic organs needs to decrease during heavy exercise. Because of a limitation in measurement of the actual blood flow in the splanchnic organs, especially in the kidney, direct evidence of splanchnic blood flow during exercise in human subjects *in vivo* has been limited (Marraccini et al. 1996, Middlekauff et al. 1997, Osada et al. 1999). Therefore, this review will discuss blood flow redistribution during exercise in human subjects, forcusing particularly on functional sympatholysis of exercising muscles, as well as the factors contributing to vasoconstriction in both non-exercising muscles and splanchnic organs.

2. Neural blood flow control during exercise in humans: Focus on functional sympatholysis

Muscle sympathetic nerve activity (MSNA) increases during static exercise at 20% of the maximal voluntary muscle contraction (MVMC) and during dynamic exercise at 40 or 50% $\dot{V}O_{2max}$ in humans (Saito et al. 1990, Rowell 1993, 1997). Consequently, in exercise over those work intensities, vasoconstriction resulting from MSNA is expected to occur in both exercising and non-exercising muscles, contributing to a decrease in vascular conductance as work intensity increases. If the work intensity continues to increase, so too does MSNA, creating a circulatory imbalance between oxygen demand and supply. In other words, decrease in vascular conductance resulting from MSNA in the exercising muscles totally conflicts with their increased oxygen demand. Therefore, the cessation of MSNA, using some kind of vasodilative metabolite such as lactate, potassium ion, or adenosine, must occur in the exercising muscles. This phenomenon is called functional sympatholysis.

It is conceivable that functional sympatholysis resulting from the cessation of MSNA would inhibit adrenergic alpha receptors in blood vessels. It has been noticed that vasoconstriction resulting from MSNA does not occur selectively in peripheral exercising muscles during exercise because some metabolites work as vasodilators. However, the following information suggests that vaso-

constriction might occur, even in exercising muscles, during heavy exercise (Rowell 1997).

1) Blood flow in the exercising muscles increased when MSNA was blocked (Saltin et al. 1998).
2) Leg blood flow decreased when the baroreceptor (carotid sinus) was stimulated during cycle ergometer exercise at heavy work intensity (Strange et al. 1990).

It is assumed that vasodilation caused by some metabolites and vasoconstriction triggered by MSNA compete with each other in the blood vessels of exercising muscles. The actual muscle blood flow is determined by the integration of this competition. It is reported that this effect is different between muscle fiber types (Thomas et al. 1994, Delp and Laughlin 1998), indicating that the effect of functional sympatholysis in type II muscle fibers is greater than that in type I muscle fibers. It is also reported that its effect is dependent on the work intensity (Thomas et al. 1994, Delp and Laughlin 1998). Concerning those previous investigations, Hansen et al. (1996) reported that the effect of vasoconstriction resulting either from MSNA or a release of norepinephrine from the sympathetic nerve due to functional sympatholysis is different between exercising muscles and non-exercising muscles. A selective blood flow adjustment controlled by MSNA may exist because plasma norepinephrine concentrations in the exercising skeletal muscles were higher than those in the non-exercising muscles (Hansen et al. 1996). However, similar studies have found that MSNA was not significantly different between exercising and non-exercising muscles in human subjects (Callister et al. 1994). Therefore, there is no agreement regarding whether the sympathetic nerve adjusts blood flow selectively in both exercising and non-exercising muscles.

Metabolites accumulated in exercising muscles during heavy exercise, indicating that muscle metaboreflex may counteract the effects of an acceleration of MSNA in exercising muscles. In this context, the physiological significance of muscle metaboreflex must be to increase oxygen delivery to the exercising muscles through vasoconstriction of the non-exercising muscles. However, as described earlier, there are conflicting factors influencing the blood flow to the exercising muscles. If an accelerated MSNA never occurs in exercising muscles at a heavy work rate, arterial blood pressure decreases because the conductance of the exercising muscles greatly increases due to peripheral vasodilation. Therefore, the physiological role of accelerated MSNA during heavy exercise is not only a trigger to induce vasoconstriction in non-exercising muscles but also an important stimulant for maintaining arterial blood pressure in the entire body.

Some investigations opposed those conclusions. For example, Callister et al. (1994) reported that MSNA in a non-exercising limb (arm) during cycle ergometer exercise either did not increase or somewhat decreased when compared to non-exercising limbs. Strange (1999) reported that MSNA in an arm increased when a static handgrip exercise at 20% MVMC was added to a leg exercise (cycle ergometer exercise), although MSNA in the leg did not increase. Shoemaker et al. (1997b) also denied the existence of functional sympatholysis in non-exercising muscles during dynamic exercise. Regarding Strange's report (1999), Kagaya and Homma (1997) reported that blood flow in the arms during dynamic leg exercise did not decrease

when compared to non-exercising limbs. Blood flow in the non-exercising arm during dynamic handgrip exercise at a moderate work intensity increased, although it was not significant (Shoemaker et al. 1997a). Also, blood flow in the non-exercising leg during one-leg dynamic exercise at a moderate work intensity increased significantly (Osada et al. 1999). One consistency throughout those previous studies is that a drastic blood flow redistribution was not observed when the work intensity was moderate or when only a small muscle mass was employed. Thus, during dynamic exercise, vasoconstriction in non-exercising muscles and splanchnic organs is not necessarily induced by blood flow redistribution. Rather, it is hypothesized that, in this situation, blood flow in non-exercising muscles can sometimes decrease. In addition, it appears that sometimes blood flow redistribution does not depend on work intensity, exercise type (static or dynamic), or muscle mass used.

Regardless of the existence of functional sympatholysis, it is unclear whether oxygen delivery to exercising muscles is sufficient during heavy exercise in humans. Further studies are needed.

3. Hormonal blood flow control during exercise in humans: Focus on some potent vasoconstrictors

The exercise-induced decrease in the splanchnic blood flow is mainly due to a reflex-invoked increase in MSNA in resistance blood vessels of the kidneys. This response is caused by the activation of group III and IV sensory afferents in the exercising muscles and central neural mechanisms (Mitchell 1990). Vasoconstriction in the peripheral blood vessels may be induced not only by MSNA, but also by other substances such as neurotransmitters, metabolites, peptides, and hormones.

The mechanism(s) for vasoconstriction in non-exercising muscles and splanchnic organs has mainly been attributed to the central nervous system or an interaction between sympathetic and parasympathetic nerve activity. However, information about hormonal substances affecting peripheral blood flow circulation during exercise is lacking (Rowell 1993). Vasopressin (ADH), angiotensin-2 (ANG2), catecholamines, and serotonin are recognized as vasoconstrictors, but their effect on humans remains unclear. For example, Stebbins and Symons (1995) reported that a selective blockade of ANG2 AT1-receptor caused a significant decrease in the peripheral blood flow in miniswine. Stebbins and Symons (1993) also tested the effects of a selective vasopressin V1-receptor inhibitor on the cardiac output of miniswine, but the results of the study indicated that ADH did not affect blood flow redistribution during exercise. The circulatory system of the miniswine seems to be similar to that of humans, suggesting a similar interpretation would be found in human beings. However, the reaction duration of ANG2 is so short that it is unknown whether ANG2 can actually contribute to vasoconstriction in human kidneys during heavy exercise. Nor is it known to what degree ADH contributes to peripheral blood flow circulation, even when it affects blood flow redistribution.

Recently, it has been reported that adenosine might be one of the potent vasoconstrictors in the kidneys (Marraccini et al. 1996, Middlekauff et al. 1997). It has already been recognized as a vasodilator in exercising muscles (Radegran and Saltin 1998, Hellsten et al. 1998). There is a possibility that one

substance can work as a vasodilator in one region and a vasoconstrictor in another.

Yanagisawa et al. (1988) found a potent vasoconstrictive peptide in cultured pig's aortic endothelial cells and named the peptide endothelin. Endothelin has a strong and long-lasting effect as a vasoconstrictor. Endothelin-1, endothelin-2, and endothelin-3 were discovered as isozymes, and it is known that endothelin-1 has the strongest vasoconstrictive function of all three (Weitzberg et al. 1991). After its discovery, many investigations were performed to examine the clinical effects of endothelin on human beings. Using its long-lasting effects *in vivo*, endothelin synthase inhibitors and selective/non-selective antagonists for endothelin receptors (ET-A and ET-B) have been developed and prescribed to patients with chronic heart disease or hypertension (Benigni and Remuzzi 1999, De Lombaert et al. 2000, Weber et al. 1999a, 1999b).

It is suggested that increased plasma endothelin concentrations in skeletal muscles may influence blood flow redistribution during exercise. For example, the average plasma endothelin-1 concentration after 30-minute cycle ergometer exercise above the ventilatory threshold was significantly higher than that below the ventilatory threshold (Maeda et al. 1994). Plasma endothelin-1 concentrations were also significantly different between non-exercising limbs and exercising limbs (Maeda et al. 1997, Tanabe et al. 2000). Considering those observations, an intravenous infusion of endothelin-1 into a human forearm blood vessel resulted in a significant, long-lasting vasoconstriction of the at-rest splanchnic and renal blood vessels (Pernow et al. 1991, Weitzberg et al. 1991). Those reports suggest that, during heavy dynamic exercise in humans, endothelin may be able to explain the mechanism(s) for reduced blood flow in non-exercising muscles and splanchnic organs. However, there is a lack of information about the blood flow dynamics in those studies because of limitations of blood flow measurement *in vivo* (Maeda et al. 1994, 1997, Tanabe et al. 2000, Pernow et al. 1991, Weitzberg et al. 1991). A significant increase in the expression of endothelin-1 mRNA was observed in the kidneys and left ventricle of chronically trained rats, but not in their lungs. Those findings suggest that endothelin plays an important role in blood flow redistribution during exercise. However, all the previous studies lacked blood flow dynamics measurements (Maeda et al. 1998a, 1998b). Further studies to develop methodology for direct blood flow measurement during exercise in humans are necessary.

Hemodynamic shear stress has been recognized as a trigger for the release of endothelin from cultured pig endothelial cells (Yoshizumi et al. 1989). It was also shown that shear stress enhanced mRNA expression of angiotensin converting enzymes in cultured rat endothelial cells (Gosgnach et al. 2000). It is interesting to point out that shear stress may be a trigger for the release of potent vasoconstrictors such as endothelin and ANG2, and the release of the vasodilator EDRF (nitric oxide). Contrary to the results of Maeda et al. (1994, 1997) and Tanabe et al. (2000), other researchers found that plasma endothelin concentrations in non-exercising limbs did not increase immediately after exhaustive dynamic exercise, although a similar methodology was employed in those studies (Lenz et al. 1998, Richter et al. 1994). There is currently no general agreement how endothelin affects blood flow redistribution during dynamic heavy exercise in humans.

As described earlier, peripheral vasocon-

striction in non-exercising muscles and splanchnic organs that contribute to blood flow redistribution during dynamic heavy exercise has mainly been explained by neural control theory (Rowell 1993). Therefore, explanations concerning peripheral blood flow circulation through the non-exercising regions during exercise will change drastically if it is revealed in future studies that hormonal substances play a role in peripheral vasoconstriction.

4. Conclusion

To conclude, the physiological significance of vasoconstriction in non-exercising muscles and splanchnic organs during dynamic heavy exercise is to redistribute the limited cardiac output and maintain arterial blood pressure. However, mechanisms to explain how the neural and hormonal blood flow controls work together to affect peripheral blood flow circulation during exercise remains unclear.

It is expected that, during heavy exercise that requires marked blood flow redistribution (e.g., cross-country ski, cycling, and long-distance running), maximal blood flow can be enhanced as a function of the $\dot{Q}_{max}$ of maximal stoke volume by chronic exercise, thus contributing to overall muscle performance.

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