SUMMARY AND CONCLUSION

The precise matching of blood flow, O_2 delivery and metabolism is essential as it ensures that any increase in muscle work is precisely matched by increases in O_2 delivery. Therefore, understanding the control mechanisms of exercise hyperemia is of great biological importance. The present work provides new insight in to vasodilator interactions important for exercise hyperemia and sheds light on mechanisms important for vascular function and regulation of skeletal muscle blood flow in essential hypertension and aging and identifies mechanisms by which physical activity affects vascular function.

Regulation of skeletal muscle blood flow and O_2 uptake in the initial phase of exercise

The majority of studies investigating skeletal muscle blood flow regulation have focused on limb hemodynamics once steady-state is achieved. In this thesis, NO and prostanoids were found to be important for regulation of skeletal muscle blood flow at the onset of moderate- and high-intensity exercise as evidenced by a ~25-50% reduction in leg blood flow with combined inhibition of these vasodilator systems. Despite similar reductions in leg blood flow with pharmacological inhibition of NO and prostanoids in the initial phase of exercise with moderate- and high-intensity exercise, leg O_2 uptake was only reduced during high-intensity exercise. These findings demonstrate that a threshold from which a reduction in blood flow will attenuate the rise in O_2 uptake is evident at less severe reductions in O_2 delivery during high-intensity knee-extensor exercise compared to moderate-intensity exercise engaging a small muscle mass. This is likely to be a consequence of the reduced blood flow and O_2 delivery relative to O_2 utilization during high-intensity exercise.

Vasodilator interactions and implications for exercise hyperemia

Adenosine has been proposed to induce vasodilation by direct stimulation of P1 receptors on smooth muscle cells. In contrast, a lack of additive effect of inhibiting adenosine receptors during

NOS and COX blockade during knee-extensor exercise suggests that adenosine contributes to blood flow regulation in the exercising leg of humans by increasing prostanoid and NO formation. This suggestion was supported by the finding that both plasma and interstitial adenosine stimulate the formation of NO and prostacyclin. Interstitial adenosine is likely to be most important for regulation of exercise hyperemia as the concentration of adenosine in this compartment increase in proportion to blood flow, whereas no change in plasma adenosine concentrations is detected during exercise.

Interstitial ATP has generally been described to be a vasoconstrictor. In the rat gluteus maximus skeletal muscle model, interstitial ATP was found to induce vasodilation at concentrations measured during contractions. The increase in interstitial ATP levels is associated with the magnitude of exercise hyperemia, suggesting that interstitial ATP contributes to blood flow regulation during muscle contractions. Interstitial ATP induces vasodilation by stimulating the formation of NO and prostanoids.

Vascular physiology and essential hypertension

Essential hypertension is associated with increased vascular resistance and this disease state could, therefore, also be associated with reductions in blood flow and O_2 delivery during exercise. This aspect of essential hypertension was confirmed as blood flow and O_2 delivery to leg muscles during knee-extensor exercise were found to be lower in hypertensive than in normotensive subjects. The blunted vascular response to exercise did not appear to be an effect of an impaired capacity of the NO and prostanoid systems to induce vasodilation or due to an inefficient sympatholysis. Plasma levels of ET-1 were found to be higher in hypertensive than in normotensive individuals, indicating that increased ET-1 vasoconstrictor activity may limit leg exercise hyperemia in hypertensive subjects.

Adaptive responses to physical activity in hypertensive subjects

Eight weeks of aerobic exercise training reduced leg blood flow during exercise in the normotensive subjects, whereas blood flow was unaltered in the hypertensive subjects. The unaltered exercise hyperemia in the hypertensive subjects may reflect an improvement in vascular function in parallel with optimized blood flow distribution and/or improved blood-myocyte O_2 transfer. A preserved role of NO and prostanoids for exercise hyperemia and reduced plasma ET-1 levels and potentially ET-1 vasoconstrictor activity are likely mechanisms behind the training-induced effect on vascular function and exercise hyperemia in hypertensive subjects.

Vascular physiology and aging

Despite indications of an impaired blood flow and O_2 delivery in older subjects, acute restoration of NO bioavailability with antioxidant infusion did not increase blood flow to the exercising leg, suggesting that the age-related reduction in leg blood flow is not an effect of decreased NO bioavailability. The lower blood flow could, however, be an effect of impaired modulation of α-adrenergic vasoconstriction in the vascular beds of contracting muscle as blood flow during exercise was reduced during tyramine infusion in the older subjects. This reduced sympatholytic capacity was associated with a lower vasodilator response to ATP infusion and skeletal muscle P2Y2 receptor content.

Adaptive responses to physical activity in aging humans

Lifelong physical activity can preserve functional sympatholysis in the exercising leg which potentially could explain the preserved O_2 delivery and uptake in these subjects. In this context, lifelong physical activity was associated with a preserved vasodilator response to intravascular ATP and increased skeletal muscle P2Y2 receptor levels compared to sedentary subjects. This effect of physical activity may be important for preserving functional sympatholysis with aging.

Essential hypertension, aging and skeletal muscle blood flow regulation

A large body of evidence indicates that alterations which occur in the vessel wall in hypertension are an accelerated form of the changes seen in aging. In agreement, blood flow to contracting leg muscles was found to be lower in essential hypertension and with aging. However, although both subject groups demonstrated higher levels of plasma ET-1, the mechanisms underlying the reduction in exercise hyperemia appear to be different as impaired functional sympatholysis, higher skeletal muscle ET-1 levels and/or a reduced vascular function (as assessed by the vasodilator response to ACh) are likely to contribute to the reduced leg blood flow in older subjects but not in subjects with essential hypertension.

Conclusion

ATP and adenosine stimulate the NO and prostanoid systems in skeletal muscle. These vasodilator interactions may, at least in part, explain the central role of NO and prostanoids in the regulation of exercise hyperemia. Furthermore, blood flow to contracting leg skeletal muscles is reduced both in essential hypertension and with aging. The potential difference in vasoactive system(s) responsible for the reduction in blood flow in the two conditions is in agreement with the suggestion that no single compound can explain exercise hyperemia and indicates that any condition associated with reduced O_2 delivery needs to be investigated independently. Physical activity can attenuate or even counteract the effects of essential hypertension and aging on vascular function and exercise hyperemia.