GENERAL INTRODUCTION

In the 13th century al-Nafis proposed that blood coming from the right chamber of the heart would flow through the vena arteriosa (pulmonary artery) to the lungs, where it would be mingled with air, and then pass through the arteria venosa (pulmonary vein) to reach the left chamber and there form the vital spirit (1). Later, various descriptions of the circulatory system were proposed, but the first doctrine of the complete circulation of blood was introduced by Harvey in 1628 where he described in detail the systemic circulation and properties of blood being pumped to the body by the heart (2). In 1660 Malphigi filled out the missing link in Harvey´s work as he characterized how blood flows from the arteries to the veins through the capillary bed (Figure 1) (3).

Blood flow through skeletal muscle at rest and during contraction, and the mechanisms underlying this regulation, have been subjects of great interest since the early experiments by Sadler in 1869 (4) and Gaskell in 1877 (5) demonstrating an increase in blood flow in response to muscle contraction. Skeletal muscle blood flow and O_2 delivery are closely related to workload and the O_2 demand of the contracting muscles during one-leg knee extensor exercise and submaximal cycling (6-9). Furthermore, perfusion of skeletal muscle can increase from resting values of ~4 to ~250 ml min^{-1} (100 g)$^{-1}$ in untrained humans and ~400 ml min^{-1} (100 g)$^{-1}$ in endurance-trained athletes performing one-leg knee-extensor exercise (6; 10; 11). This precise matching of blood flow and metabolism and enormous vasodilator capacity is essential for physical performance as it ensures that any increase in muscle work is precisely matched by increases in O_2 delivery.

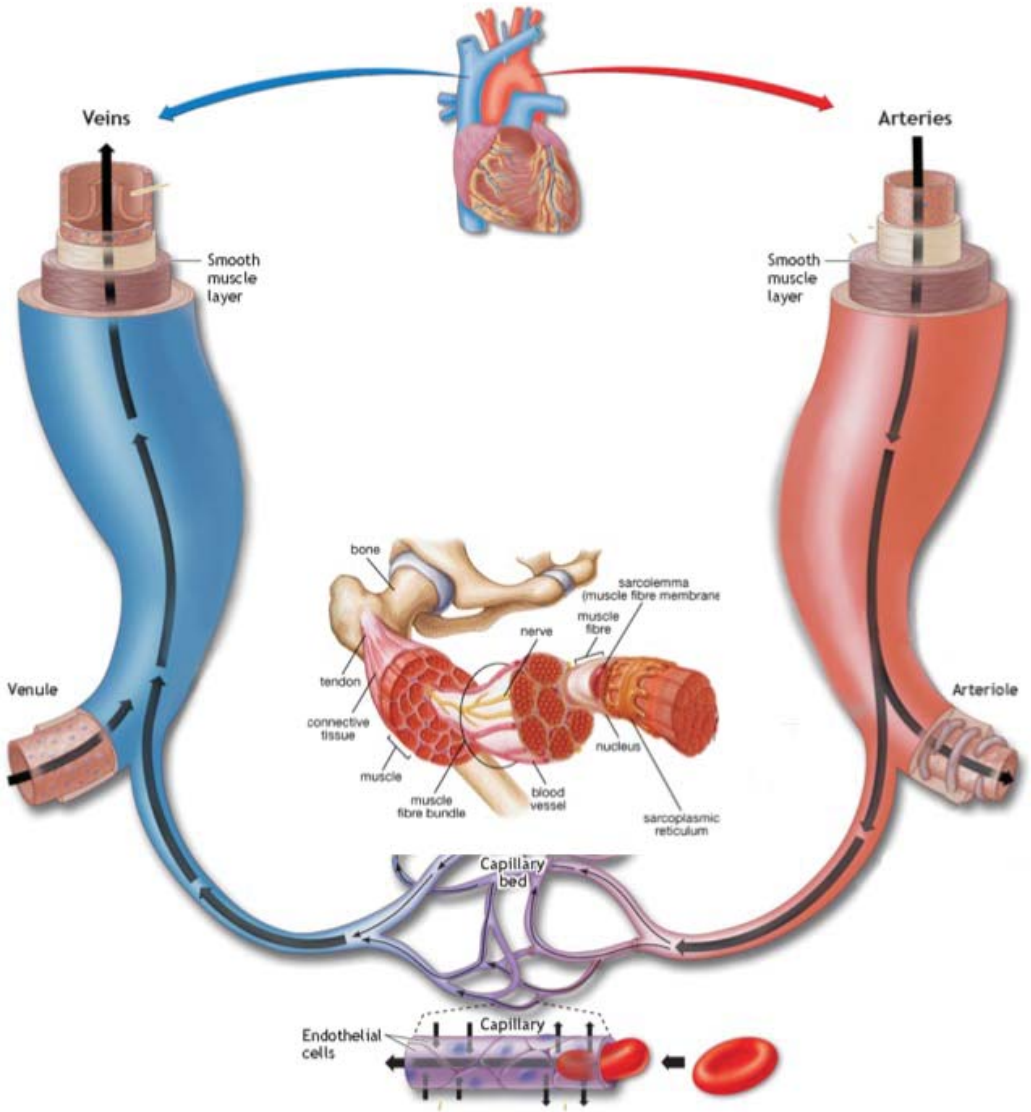

Figure 1. The cardiovascular system.

The close association between workload, skeletal muscle O_2 utilization and magnitude of exercise hyperemia suggest that both mechanical compression of the vascular tree and chemical substance(s) produced in the contracting muscle causes vasodilation as proposed by Gaskell in 1877 (5). In congruence, several vasodilators released from endothelial cells, erythrocytes and skeletal muscle cells during contraction, including ATP, adenosine, nitric oxide (NO) and prostanoids, have now been proposed to be of importance for blood flow regulation (12). Nevertheless, despite the identification of several putative vasodilators, no more than a ~20% reduction of the hyperemic response to exercise has been observed when one single vasoactive system is inhibited in humans (13). The failure to identify one single compound responsible for exercise hyperemia could potentially be explained by redundancy among vasodilators, where a compensatory formation of one vasoactive compound may preserve adequate blood flow when the formation of another is compromised (14; 15). However, simultaneous inhibition of two or three vasodilator systems has only resulted in a reduction of exercise hyperemia by ~30% in humans (15; 16).

With the large increases in vascular conductance to raise blood flow to the contracting muscles, the cardiovascular system has to adjust by increasing cardiac output and by redistributing blood flow to ensure delivery of O_2 to all tissues without compromising arterial pressure. The redistribution of blood flow is, in part, an effect of a contraction-induced activation of the sympathetic nervous system, known as the exercise pressor reflex (17; 18), as the increase in sympathetic drive impairs perfusion of most non-muscular tissues and inactive skeletal muscle tissue (19; 20). These sympathetically-mediated reductions in regional perfusion at or near maximal cardiac output can provide as much as 500-600 ml min^{-1} of additional O_2 to active muscle if all of these reductions are diverted to active muscle (20). Conversely, when muscle sympathetic nervous activity is increased experimentally, the vasoconstrictor effect is blunted or abolished in active muscles (21-27), termed functional sympatholysis (26). Despite this altered responsiveness of the vasculature to sympathetic

nervous activity, withdrawal of sympathetic outflow to contracting skeletal muscle by interruption of sympathetic outflow or antagonism of α-adrenoceptors has been shown to increase blood flow, demonstrating sympathetic restraint of blood flow to active muscles (28-30). There is also growing evidence that ATP in animal skeletal muscle stimulates P2X receptors on vascular smooth muscle cells, which induces vasoconstriction at rest and during exercise (31-33).

In congruence with these observations, it is now generally accepted that the precise matching of blood flow and O_2 utilization is the result of a complex process involving competing vasodilator and vasoconstrictor influences that optimize perfusion of the contracting skeletal muscle (Figure 2) (10; 12; 34; 35).

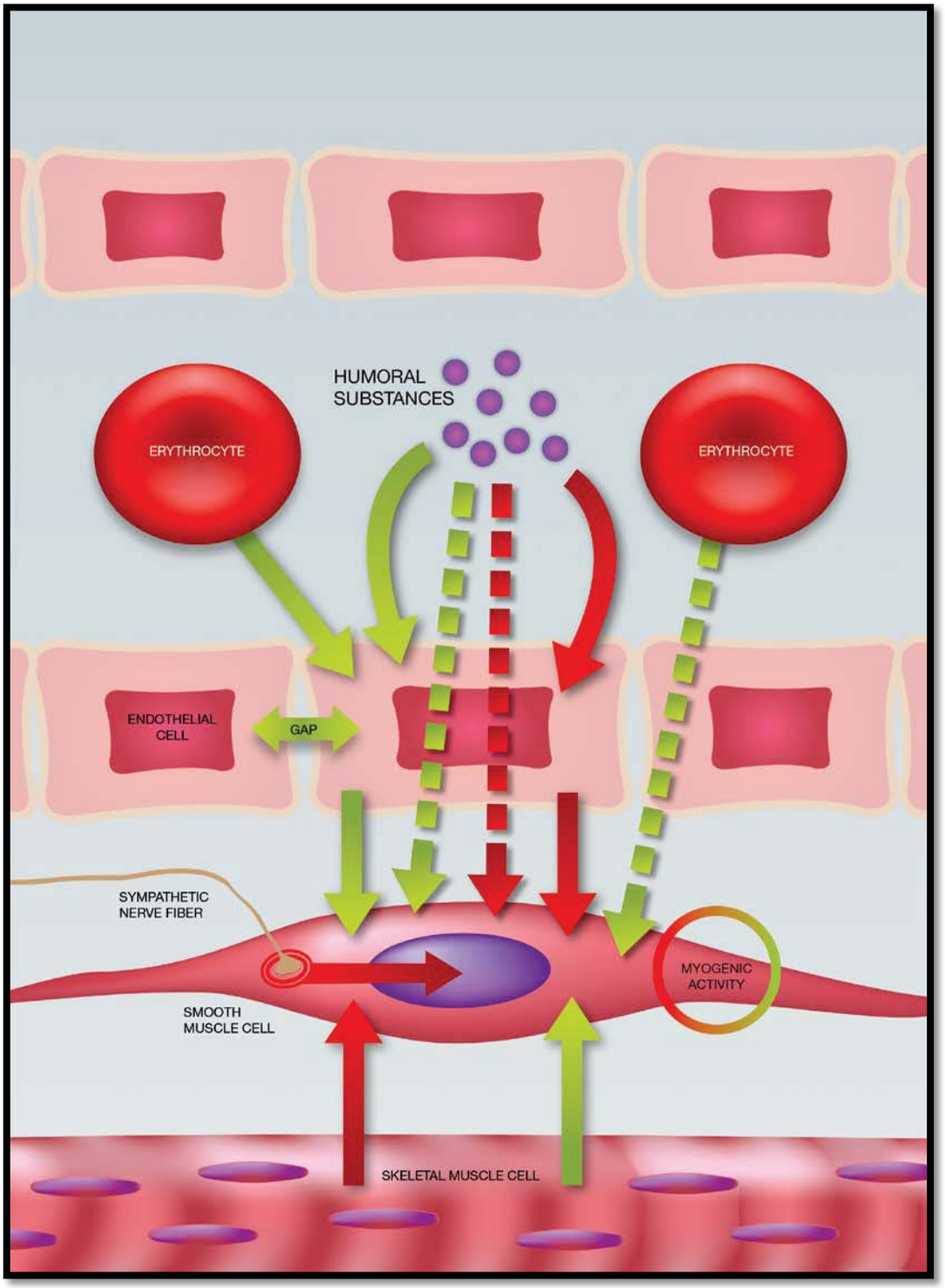

Figure 2. The precise regulation of skeletal muscle blood flow is the result of a complex process involving competing vasodilator (green arrows) and vasoconstrictor (red arrows) influences, which include: 1) central mechanisms involving neural and humoral factors and 2) local mechanisms involving myogenic activity, vasoactive substances released from erythrocytes, endothelial cells and skeletal muscle cells in response to chemical and mechanical stimuli.

Increased peripheral resistance and decreased vasodilation to vasodilator stimuli are well known characteristic features of chronic hypertension (36-38), and as a consequence this disease state may be associated with reductions in blood flow to muscles at rest and during exercise. This potential impairment in O_2 delivery to contracting muscle could lead to tissue ischemia and an impaired ability to perform physical activity. The vascular changes associated with essential hypertension are generally considered to be an accelerated form of the changes seen with aging (36; 39) and there is accumulating evidence in humans that aging is associated with a reduced blood flow response to exercise in both the upper (40) and lower extremities (41-44). As a consequence of these alterations in vascular function, aging and hypertension are useful models in the investigation of mechanisms underlying vascular disorders and basic regulation of skeletal muscle blood flow.

Exercise training has been shown to improve vascular function as assessed by infusion of the endothelium-dependent vasodilator acetylcholine (ACh) (45-47) and to lower blood flow during exercise performed at the same absolute workload (48-51). In contrast to a lower blood flow to contracting muscles with aging, and potentially essential hypertension, that is likely to reflect an impairment in O_2 delivery and microvascular O_2 tension and blood-myocyte O_2 transfer (52), a training-induced lowering of exercise hyperemia is thought to be the result of an optimized blood flow distribution and improved conditions for O_2 diffusion (49; 51; 53). Consequently, exercise can be used to reveal important regulatory systems within the vascular network of skeletal muscle.

The general aims of this thesis were to determine vasodilator interactions important for exercise hyperemia and the effects of essential hypertension, aging, and physical activity on vascular function and the mechanisms underlying skeletal muscle blood flow regulation. To accomplish these aims both human, animal, and cell culture studies were applied.