ABSTRACT

Oxygen delivery to skeletal muscle is regulated precisely to match the oxygen demand; however, with aging the regulation of oxygen delivery during exercise is impaired. The present thesis investigated mechanisms underlying the age-related impairment in regulation of blood flow and oxygen delivery to contracting skeletal muscle. Two studies, one acute exercise study and one large 8-week training intervention study, were conducted in young (18-28 years) and older (65-80 years) healthy, male subjects. In both studies, pharmacologic potentiation of the formation of cyclic guanosine monophosphate (cGMP) was used as intervention, and skeletal muscle blood flow, oxygen delivery, and functional sympatholysis was examined.

The two studies included 53 healthy, habitually active, male subjects. All subjects participated in an experimental day in which femoral arterial blood flow and blood pressure were assessed and blood sampling were obtained. A total of 30 subjects (15 young and 15 older) participated in the training intervention study and were tested before and after a period of high-intensity interval training. In the acute exercise study and at baseline in the training intervention study, it was demonstrated that potentiation of cGMP signaling increased leg blood flow, leg vascular conductance and leg oxygen uptake during exercise in the older subjects but not in the young. Interestingly, 8 weeks of exercise training abolished this effect of cGMP potentiation in the older subjects. Collectively, this suggest that reduced cGMP signaling contribute to the impaired skeletal muscle blood flow and oxygen delivery in older men and that an enhancement in cGMP signaling is one of the mechanisms underlying the training-induced improvement in the regulation of blood flow and oxygen delivery during exercise in older men.

In order to elucidate if an improved functional sympatholysis contributed to the increased leg blood flow in the older subjects with cGMP potentiation, leg vascular conductance was assessed during exercise with simultaneous femoral infusion of tyramine. No difference was observed between the tyramine-evoked attenuation of vascular conductance in the control situation and with cGMP potentiation; hence, cGMP potentiation was not associated with an improved functional sympatholysis. It was also shown that exercise training improved functional sympatholysis in the young but not in the older subjects, which suggest that improving sympatholytic capacity by training may be a slower process in older than in young men.
In conclusion, this thesis provides new important knowledge related to the regulation of skeletal muscle blood flow in aging. Specifically, it demonstrates that changes in cGMP signaling is an underlying cause of age-related impairments in vascular function but also one of the mechanisms underlying exercise training-induced vascular improvements. Future studies should evaluate to what extent cGMP signaling is central in diseases with impaired blood flow and exercise intolerance, such as diabetes.