Withstanding the flow

*Human cardiovascular control during postural challenges*

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Chapter 10

GENERAL DISCUSSION
This thesis evaluates cardiovascular autonomic control during orthostatic challenges under both healthy and pathologic conditions. The effect of orthostatic stress on both systemic and regional blood circulation were studied. In addition, the role of autonomic cardiovascular control mechanisms that secure optimal blood flow to the vital organs, specifically the brain, was evaluated. Insight is given in the orthostatic transfer of blood volume to the lower extremities and the importance of autonomic cardiovascular reflexes in health and disease.

The first cardiovascular effect upon moving from the horizontal to the erect position is a displacement of blood from the central blood vessels to the lower extremities. In order to recognize a suboptimal central blood volume, which is essential for sufficient venous return to the heart, first the normal blood volume, i.e. normovolemia, should be defined. We defined normovolemia as the level of blood volume at the plateau of the Frank-Starling curve, where central blood volume does not limit cardiac stroke volume. In healthy humans this is reached in the supine position, which implies that central blood volume is not optimal in the upright posture. To compensate for this suboptimal level of central blood volume autonomic cardiovascular mechanisms, specifically the baroreflex and cerebral autoregulation, are activated to ensure sufficient blood flow to the brain and other vital organs.

The time course of the blood volume displacement from the thoracic compartment to the lower extremities is of interest for the comprehension of orthostatic cardiovascular physiology. We demonstrated that the rapid blood volume increase in the legs after moving to the upright position is followed by a more gradual increase of blood volume. This contrasts with the earlier assumption that the prolonged orthostatic increase in leg circumference is mainly due to the transfer of fluid from the intra- to the extravascular compartment. Traditional studies on orthostatic volume shifts were mainly performed using strain gauge plethysmography that quantifies changes in limb circumference. The advantage of the method we used, NIRS, is that it detects changes in hemoglobin tissue concentration that reflect changes in intravascular blood volume solely. Our findings contribute to the understanding of orthostatic blood pooling and may eventually support a further understanding of the pathophysiology of orthostatic hypotension. These findings point to a prolonged accumulation of blood volume in the intravascular compartment and this knowledge could be helpful in the development of therapies for orthostatic hypotension, for instance, by limiting this intravascular volume accumulation.

As the blood volume shifts to the lower parts of the body upon transferring to the upright position autonomic cardiovascular reflexes compensate for the decrease in cardiac preload in order to secure sufficient blood flow to the vital organs. One of the most important autonomic reflexes under these circumstances is the baroreflex. With unloading of the arterial baroreceptors diminishing activity of the parasympathetic efferent arm of the baroreflex induces an increase in heart rate in order to enhance cardiac output, whereas the sympathetic arm induces vasoconstriction resulting in an increase in blood pressure. The reaction of the baroreflex for a given change in blood pressure, expressed as baroreflex sensitivity, is not constant. Both internal and external conditions modulate baroreflex sensitivity, particularly those associated with stimulation of the sympathetic nervous system. With activation of the sympathetic nervous system baroreflex sensitivity is inhibited, while pharmacologic blockade of adrenergic β-receptors enhances the sensitivity
of the baroreflex. The sympathetic nervous system is activated, among other things, by psychological stress and heart disease. Combined these two conditions, as well as a low baroreflex sensitivity, are associated with increased risk for cardiac arrhythmias. On the other hand, β-blockers decreases this risk in patients with ischemic heart disease. Whether β-blockers also reduce the risk for cardiac arrhythmias during psychological stress is yet unknown. We demonstrated that the baroreflex sensitivity during psychological stress is increased by β-adrenergic blockade. Moving to the upright position also activates the sympathetic nervous system and accordingly we observed that the cardiovascular response to standing is affected by psychological stress. Our findings support a simultaneous increase in parasympathetic activity during psychological stress that results in an attenuated heart rate response to standing. When part of the sympathetic activation is blocked by β-blockade the stress induced increase in parasympathetic activation becomes obvious as we observed that heart rate in the upright position was lower during than after the psychological stress. Possibly, the parasympathetic activation during psychological may contribute to the risk for reflex syncope during psychological stress.

As mentioned, sympathetic activation and reduced baroreflex sensitivity are also common in patients with heart disease. Blockade of adrenergic β-receptors improves outcome in these patients. The clinical effectivity of therapy with β-blockers is however dependent on the selectivity of these drugs, to either the β1-receptor alone or combined with the β2-receptor. In addition, genetic variations in the β2-receptor influence the response to non-selective β-blockers. Subjects with the Gly16/Glu27 haplotype are relatively resistant to agonist mediated β2-receptor desensitization compared to subjects with the Arg16/Gln27 haplotype. We found that in chronic heart failure patients with the Gly16/Glu27 haplotype the non-selective β-blocker carvedilol, as compared with the β1-selective blocker metoprolol, improved baroreflex sensitivity, whereas this effect of β-blocker selectivity was not found in patients with the Arg16/Gln27 haplotype. This finding supports that genetic profiling of patients and individualized treatment may lead to improved clinical outcomes.

This thesis ends with two studies on the cerebrovascular regulation during gravitational stress. In the end sufficient cerebral perfusion is the foremost requisite for maintaining consciousness specifically and life in general. The systemic cardiovascular reflexes are on their own probably insufficient to secure adequate blood flow to the brain in the upright position. Additional regulation of cerebral blood flow supports adequate perfusion of the brain during fluctuations in cerebral perfusion pressure as during changes in posture. Cerebral autoregulation secures relatively stable cerebral blood flow despite variations in perfusion pressure. Notwithstanding cerebral autoregulation blood flow to the brain slightly decreases when the head position is being transferred above heart level, as occurs with standing. The upright decrease in arterial carbon dioxide partial pressure that induces cerebral vasoconstriction would be a solid explanation for the reduction in cerebral blood flow when standing. By clamping end-tidal carbon dioxide we demonstrated that the postural reduction in arterial carbon dioxide explained the reduction in cerebral blood flow during the first minute after standing only. In other words, the persistent decrease in cerebral blood flow after the first minute of standing is not clarified by a reduction in arterial carbon dioxide. The reduction in cardiac output and the increase in sympathetic nervous activity with standing are factors that likely play an important role in the postural cerebral blood flow decrease.
While the postural reduction in cerebral perfusion seems harmless in healthy individuals these variations may not be tolerated when cerebral perfusion is already compromised, like in ischemic stroke. This is emphasised by the fact that cerebral autoregulation is impaired after ischemic stroke.\textsuperscript{40-42} Very early mobilization of ischemic had a negative effect on outcome in ischemic stroke patients,\textsuperscript{520} although whether cerebral hypoperfusion played a role in this finding is yet undetermined. On the other hand, impaired autoregulation is associated with an increased risk for the development of cerebral edema and hemorrhagic transformation,\textsuperscript{48} and care should be taken to avoid cerebral hyperperfusion. At group-level no effect on clinical outcome was found in stroke patients with the head-of-bed in either the horizontal or elevated position.\textsuperscript{521} The effect of head-of-bed position on cerebral perfusion in acute ischemic stroke patients seems however quite variable among patients,\textsuperscript{43-47} questioning a generalized approach for positioning and mobilization. We observed that the cerebrovascular response to head-of-bed position depends on the performance of cerebral autoregulation in patients with acute ischemic stroke. This may imply that individualized recommendations on positioning and mobilization, according to cerebral autoregulation performance, may be more appropriate after ischemic stroke.

In conclusion, several aspects of the physiology and pathophysiology of the cardiovascular response to posture change were evaluated in this thesis. Insight is gained in the postural redistribution of central and peripheral blood volume, sympathetic modulation of the baroreflex and finally the orthostatic influence on cerebral perfusion. Together these findings add to the understanding of the gravitational effect on human blood circulation and the autonomic reflexes we possess the prevent consequent hypoperfusion of vital organs. This knowledge can contribute to the development of strategies to treat conditions in which the gravitational effects on blood circulation can no longer be averted, as in systemic or cerebral autonomic failure. Insight in the (patho-)physiology of the individual patient seems essential for the further development of patient tailored therapies and personalised medicine.