Withstanding the flow
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Chapter 1

GENERAL INTRODUCTION AND OUTLINE
Before *Homo sapiens* explored the world in the upright posture our very early ancestors, and still most animals today, moved on four legs with all vital organs at more or less the same horizontal level. With adopting the erect posture the opportunity was provided to develop fine motor skills of the hands and anatomical changes of the head and neck were essential for the increase in brain volume and the development of speech. Without proper counter-regulatory mechanisms, this evolution would have introduced the hazard of a decrease in blood pressure and of inadequate blood flow to the brain in the upright position. In the upright body position gravity drives part of the total blood volume from the upper to the lower body parts. As a consequence, the amount of blood returning to the heart (venous return) decreases. This thesis reports our studies on the physiology of autonomic cardiovascular regulation that secures blood flow, particularly to the brain, during orthostatic stress. The general hypothesis is that blood flow to the vital organs in the upright position depends on intact function of cardio- and cerebrovascular autonomic reflexes. Dysfunction of these cardiovascular autonomic reflexes are characteristic for several pathologic conditions. In order to understand the regulation of the blood circulation under these pathologic conditions, normal function should be elucidated first.

**Human blood volume and its displacement during orthostatic stress**

Since the heart cannot pump out what it does not receive, the output of the heart (cardiac output) depends on the available blood volume that returns to the heart via the venous blood vessels (venous return). Clinically, a decline in blood volume is mainly evaluated by monitoring heart rate and arterial pressure. However, arterial pressure is not a reliable index of the intravascular volume as it is a regulated variable that is maintained during, e.g. hemorrhage until blood loss exceeds about one litre. In order to recognize an abnormal blood volume, first normal blood volume (normovolemia) should be defined. A definition for normovolemia is however lacking with the consequence that deviations from normovolemia are often not recognized until blood volume reaches an extreme value that requires immediate intervention. With a clear definition of normovolemia hyper-, but particularly hypovolemia can be recognized in an early stage and action can be taken to avert further deterioration. In *Chapter 4* normovolemia is defined form the relation between venous return and cardiac stroke volume according to Frank-Starling’s “Law of the Heart”.

Assumption of the upright position initiates a gravitational displacement of blood to dependent regions of the body and a fall in venous return. Approximately 300-800 ml of blood volume is shifted from the chest to lower parts of the body. Knowledge of the dynamics of the postural blood volume shift to the lower body parts is essential for understanding its effects on central blood volume. Current assumption is that a rapid shift of blood volume fills the capacitance blood vessels in the legs upon changing to the upright position. A subsequent increase in leg volume is thought to result from translocation of fluid from the intra- to the extravascular compartment. The exact time course and contribution of the intravascular compartment of the leg in the upright position is however unclear. This is of importance since the intravascular volume is more easily recruited than the extravascular fluid for amplification of central blood volume and hence venous return, for example by passive leg raising or leg crossing to prevent collaps in vasovagal presyncope. In *Chapter 5* we studied the time course of the accumulation of (intravascular) blood volume in the leg upon standing.
SYMPATHETIC MODULATION OF THE BAROREFLEX

With progressively decreasing cardiac preload the baroreflex is activated to compensate for the subsequent decrease in cardiac stroke volume and resulting lower blood pressure. The sensitivity of the baroreflex is a reflection of sympathico-vagal balance and can be expressed by the heart rate response to a given change in blood pressure. A major modulator of baroreflex sensitivity is the sympathetic nervous system that is activated under hazardous conditions that require a ‘fight-or-flight’ or stress response. The cardiovascular adaptation to psychological stress seems physiological, but may trigger cardiac arrhythmias in the presence of heart disease. Both blocking sympathetic activation and increased baroreflex function have beneficial effects on outcome in patients with cardiovascular disease probably by preventing these cardiac arrhythmias. Whether blocking the sympathetic activation by psychological stress prevents the inhibition of baroreflex function is unknown. In Chapter 6 the hypothesis that partially blocking the activation of the sympathetic nervous system prevents the inhibition of baroreflex function is tested in healthy individuals under psychological stress.

Another condition in which sympathetic overactivity plays a fundamental role is in heart failure. High levels of sympathetic activity attenuate baroreflex function, which is independently associated with increased mortality in these patients. On the other hand, blockade of sympathetic β-receptors improves baroreflex sensitivity in these patients. The clinical effect of a single β-blocker may, however, have various responses among patients that cannot solely be explained by the pharmacological selectivity to the β1- or β2-receptor in these patients. Genetic variations in the β2-receptor associated with agonist-mediated desensitization could play an important role. In Chapter 7 we studied the combined effect of β-blocker selectivity and two genetic polymorphisms of the β2-receptor on baroreflex sensitivity in chronic heart failure patients.

CEREBROVASCULAR CONTROL DURING GRAVITATIONAL STRESS IN HEALTH AND DISEASE

An important modulator of cerebral blood flow independent of cerebral autoregulation is carbon dioxide partial pressure ($P_{CO_2}$) with a low $P_{CO_2}$ reducing cerebral blood flow by cerebral vasoconstriction. The postural decline in cerebral blood flow is therefore commonly attributed to the concomitant reduction in $P_{CO_2}$ by an increase in pulmonary minute ventilation. To study the contribution of the orthostatic reduction of $P_{CO_2}$ on the response of cerebral blood flow we clamped $P_{CO_2}$ to the supine value in Chapter 8 and evaluated whether this affected the postural decline in cerebral blood flow.

Together with the systemic autonomic regulation to secure central hemodynamics, cerebral autoregulation is an organ-specific mechanism aimed at the stabilization of blood flow to the brain despite fluctuations in cerebral perfusion pressure. Cerebral autoregulation may become affected into various degrees in the acute phase after ischemic stroke posing the already underperfused brain to harmful fluctuations in blood flow, for instance due to an orthostatic decrease in perfusion pressure. Horizontal head-of-bed position has been suggested as a simple intervention to optimize cerebral blood perfusion in these patients, while considerable heterogeneity of the cerebrovascular response to head-of-bed
manipulation is observed among patients. On the other hand, dysfunction of cerebral autoregulation after stroke is associated with an increased risk for development of cerebral edema and hemorrhagic transformation. Hence, the safe upper limit for cerebral perfusion pressure may be easily exceed with head-of-bed lowering without the interference of functional autoregulation. In Chapter 9 we studied whether the efficacy of cerebral autoregulation after acute ischemic stroke relates to the cerebrovascular response to head-of-bed lowering, of potential importance for individualized positioning and early mobilization of patients in the acute phase of ischemic stroke.