Cerebral and cardiovascular dynamics in response to orthostatic stress
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Summary

In this thesis several methodological, (patho)physiological and therapeutical aspects of the cardio- and cerebrovascular system during orthostatic stress are addressed. We performed studies in healthy subjects and in patients with sympathetic failure.

Chapter 2: Methods

Chapter 2.1 describes the methodology used in this thesis for the non-invasive assessment of cerebral perfusion. Transcranial Doppler ultrasound was used to determine middle cerebral artery mean blood velocity. Cerebral oxygenation was monitored using near-infrared spectroscopy. For better understanding of the cardiovascular dynamics during orthostatic stress in humans a continuous recording of blood pressure, stroke volume and changes in central blood volume is required because events proceed rapidly. Preferably this is recorded non-invasively because invasive procedures themselves can induce a neurally mediated syncope. In Chapter 2.2 we describe how thoracic impedance can be used as a non-invasive index of changes in central blood volume. Blood pressure can be measured non-invasively by a continuous recording of finger blood pressure. The principle, its ability and limitations to track intra-arterial pressure is described. Application of pulse wave analysis to the arterial finger pressure offers a non-invasive and continuous recording of stroke volume. The Modelflow method computes a flow wave from the arterial pressure wave that delivers cardiac stroke volume. We describe in this chapter the theoretical and physiological background of the Modelflow method. The Modelflow computation of stroke volume is based on a supine model of the arterial hemodynamic characteristics and it was uncertain whether under the condition of orthostatic stress, stroke volume could be derived from the arterial pressure wave. Chapter 2.3 addresses both the non-invasive and invasive applicability of this model approach during orthostatic stress. In ten awake healthy subjects the modelled cardiac stroke volume was computed from the intra-arterial and non-invasive finger pressure measurements. For comparison, a computer-controlled series of four thermodilution determined stroke volumes were averaged during supine, standing, head-down tilt at 20° and head-up tilt at 30° and 70°. The results of this study indicate that orthostasis may lead to an offset in stroke volume derived by Modelflow from intra-arterial pressure. It was demonstrated that stroke volume as obtained by Modelflow from the non-invasively determined finger pressure reflects thermodilution determined stroke volume, with a non-significant offset over the full range of stroke volume changes observed during postural changes and orthostasis.

Chapter 3: Central blood volume, normovolemia and orthostatic stress

In chapter 3.1 a definition of normovolemia in healthy humans is considered when evaluating the body position that provides the heart with enough volume to establish a maximal cardiac output at rest. Activation of cardiovascular reflexes for postural adaptation questions whether,
in healthy humans, the central blood volume is optimised to support the upright position. A functional definition of normovolemia, or an “optimal circulating volume”, that provides the heart with enough central blood volume to establish a maximal cardiac output and mixed venous oxygen saturation at rest was evaluated in nine healthy subjects. Preload to the heart was varied by passively changing the body position from head-up tilt at 70° to head-down tilt at 20° and mixed venous oxygen saturation was compared with simultaneously measured computer controlled thermodilution cardiac output estimates. With varying tilt angle, changes in cardiac output were paralleled by concordant changes in mixed venous oxygen saturation. Cardiac output, and in turn mixed venous oxygen saturation, do not increase from supine rest to head-down tilt, a condition in which central blood volume was assumed to be expanded. Conversely, both cardiac output and mixed venous oxygen saturation decreased during head-up tilt and were lower by 1.3 l·min⁻¹ and 10%, respectively, when fainting was imminent. Thus, in healthy humans normovolemia may be defined as the central blood volume provided with during supine rest, since maximal values for cardiac output and mixed venous oxygen saturation are reached in the horizontal position.

In chapter 3.2 the hypothesis was studied that, even with an intact autonomic nervous system in healthy subjects, changes in stroke volume relate to those in thoracic fluid content rather than to the concomitant changes in central vascular pressures during manipulation of the central blood volume. As an index of central blood volume, central venous pressure, together with pulmonary artery wedge pressure are commonly used. Most often stroke volume or cardiac output is related to central venous pressure, mean pulmonary or pulmonary artery wedge pressures. The implicit assumption is that pressure changes in parallel with the central blood volume but, in some cases, the reverse may be true. Recent studies have questioned the correlation between these estimates of ventricular filling pressures and ventricular end-diastolic volumes/cardiac performance variables. These findings question if central pressures are useful predictors of ventricular pre-load and supports the idea that the function of the heart relates to its volume rather than to its so-called filling pressures. In nine healthy humans we evaluated the interdependence of stroke volume and electrical admittance of thoracic fluid content versus central venous, mean pulmonary artery and wedge pressures. During both head-up tilt at 70° and head-down tilt at 20°, stroke volume of the heart changed with the thoracic fluid content rather than with the central vascular pressures, confirming that the function of the heart relates to its volume rather than to its so-called filling pressures. The implication is that, for the assessment of pre-load to the heart, central vascular pressures can be substituted by an evaluation of the central blood volume by electrical admittance, or ideally, cardiac volume measurement of the heart, e.g. by echocardiography.

Chapter 4: Orthostatic systemic cardiovascular and cerebrovascular control in healthy subjects and patients with sympathetic failure

The postural tachycardia syndrome is characterised by an increase in heart rate by >30 beats/min and symptoms related to the assumption of the upright position including fatigue,
and symptoms indicative for cerebral hypoperfusion as light-headedness or dizziness in the absence of orthostatic hypotension. Chapter 4.1 reports on the cerebrovascular and cardiovascular responses associated with orthostatic intolerance and tachycardia in a 33-year-old woman presenting with an 8-months history of orthostatic dizziness, fatigue, exertional dyspnea and palpitations related to inactivity. The patient was instructed to raise dietary salt intake and to avoid supine resting at daytime, and she engaged in a reconditioning program with leg muscle strengthening exercise. By doing so she regained orthostatic tolerance with standing time unrestricted and after six months she had returned to her former daily-life activities without orthostatic complaints. At re-examination the postural heart rate increase and the reduction in cardiac output and middle cerebral artery mean blood flow velocity had normalized. The symptomatically low middle cerebral artery mean blood flow velocity, she initially presented with, seemed to be related to an excessive postural reduction in cardiac output rather than to a low mean arterial pressure. This suggests that the symptomatic and reversible reduction in cerebrovascular conductance is to be interpreted as being an adaptive response to a critical limitation of systemic blood flow, rather than to a derangement of cerebral autoregulation.

When standing up humans adjust the cardiovascular system to the gravitational displacement of blood to the lower part of the body by increasing systemic vascular resistance through autonomic reflex activity, but patients with sympathetic failure lack this ability to modulate vascular tone in the upright position. Although their capability to maintain cerebral blood flow in response to a reduction in arterial pressure is reported to be preserved, patients with sympathetic failure often develop symptoms such as light-headedness and blurred vision when upright. In chapter 4.2 the hypothesis is tested that in patients with sympathetic failure orthostatic symptoms reflect a reduced cerebral perfusion with an insufficiency of cerebral oxygen supply. We found that the orthostatic reduction in cerebral blood flow velocity and oxygenation is larger in nine patients with sympathetic failure compared to healthy reference subjects. Patients with sympathetic failure who become symptomatic within 5 minutes standing are characterized by a pronounced orthostatic fall in blood pressure, cerebral blood flow velocity and oxygenation manifest within the first 10 s of standing, suggesting that the rapidity of the reduction also contributes to trigger orthostatic symptoms. Patients with sympathetic failure may combat symptomatic orthostatic hypotension by tensing leg muscles as a result of leg crossing. The purpose of the study in chapter 4.3, was to evaluate how orthostatic manoeuvres, like leg crossing, in patients with orthostatic hypotension due to sympathetic failure improve cerebral perfusion. In six patients with sympathetic failure and their age and sex matched controls the acute cerebrovascular effects of leg crossing were studied. Leg crossing appeared a highly reproducible manoeuvre that improved cerebral perfusion and oxygenation in patients with sympathetic failure associated with a relieve of symptoms. The underlying mechanism is a rise in cardiac output, total peripheral resistance and mean arterial pressure. Patients with orthostatic intolerance should therefore be advised to apply leg crossing when they stand up.