Cerebral and cardiovascular dynamics in response to orthostatic stress
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INTRODUCTION
“...It certainly was a bold enterprise of nature to create quadrupeds like man or the giraffe with a predominantly vertical extension, who carry their heads and hearts at a considerable distance above the center of gravity of the body...” (Gauer and Thron, 1965)

The ancients knew already that prolonged exposure to upright posture would eventually lead to unconsciousness and death (227). Death was the consequence of hypotension and cerebral ischemia. Orthostatic hypotension is derived from the Greek “orthos” (“straight” or “upright”) and “statikos” (“standing still”). The brain is the organ most susceptible to ischemia. Its location with respect to the heart when in the upright position also makes it susceptible to the effects of gravity on cerebral perfusion. As soon as cerebral blood flow falls below a critical level for 6-10 seconds, consciousness is lost. (227, 272). Orthostatic hypotension has intrigued scientist over the centuries. Amberson wrote: "When man’s subhuman ancestors dared to rise and walk upon their hind legs, they essayed a physiologic experiment of no mean difficulty" (5). Consequently, in order to withstand its vulnerability to the effects of gravity the human body has been provided with a set of remarkably effective controllers that secure cerebral perfusion and oxygenation under conditions as orthostatic stress.

Adjustments in orthostatic stress in healthy humans

Influence of gravity

When humans stand up from the supine position, the first circulatory event is a gravitational displacement of blood away from the thorax to dependent regions of the body (6, 254, 256, 293). Depending on the type of orthostatic stress (i.e. active standing, head-up tilt or lower body negative pressure) one half to one litre of thoracic blood is transferred to the region below the diaphragm. Orthostatic pooling of venous blood begins immediately, the greater part is transferred within the first 30 seconds and the total transfer is almost complete within 3 minutes. Most of this volume pools in the large deep veins of the upper legs and buttocks. Additionally there is some pooling in the abdominal and pelvic regions (Figure 1) (85, 154,227, 254). Pooling in the splanchnic area during orthostasis (by passive head-up tilt) is maybe more important than previously reported in studies using simulated orthostasis by applying lower body negative pressure (263, 268). The pooled blood is not stagnant; its circulatory transit time through the lower part of the body is increased by changes in the pressure gradient across the vascular bed and by increases in venous volume (220, 225, 256). In addition to this transfer of thoracic blood, central blood volume decreases in the upright posture due to transcapillary filtration of fluid into the interstitial spaces in the dependent parts.
Figure 1. Influence of gravity on intravascular fluid shift (From Rowell). Change of intravascular fluid shift from the supine to the upright body position.

of the body in response to the high capillary pressure with little interstitial counterpressure (256, 293). Continued filtration further reduces the circulating volume, although fluid is gained from tissue above the venous hydrostatic indifference point, which is defined as the axial reference within the column of venous blood where pressure is not altered by postural reorientation (158, 205, 227). In humans the venous hydrostatic indifference point is approximately at diaphragmatic level (227). The transcapillary loss of fluid is considerable and also occurs initially rather fast. During 5 minutes of standing the plasma volume decreases by about 10% (500 ml) and the transcapillary loss of fluid approaches stability after 20-30 minutes with a fall in plasma volume of 15-20% (700 ml), but a steady state is probably not reached (157, 163, 167, 256). As a consequence of gravitationally induced blood pooling and the superimposed decline in plasma volume, the return of venous blood to the heart is reduced and central venous pressure falls from about 5 mmHg in the supine position to nearly 0 mmHg, or even lower, in the upright position (167, 227, 287). This affects the end-diastolic filling volume of the right ventricle, which in turn leads to a reduction in stroke volume via the Frank-Starling relationship that is not compensated by the reflex increase in heart rate resulting in a ~ 20% fall in cardiac output (123, 261, 287, 324).
Neuro- and humerocardiovascular adaptation

Despite the postural fall in cardiac output, mean arterial pressure is preserved by compensatory vasoconstriction of the resistance and capacitance vessels in the splanchnic, musculo(cutaneous) and renal vascular beds (44, 173, 225, 295). The rapid short-term circulatory adjustments to orthostatic stress are mediated exclusively by the neural pathways of the autonomic nervous system. During prolonged orthostatic stress, sympathetic outflow of the autonomic nervous system continues to play a pivotal role. Sustained elevation of efferent sympathetic activity is documented by directly recorded sympathetic nerve activity to skeletal muscle and indirectly by an increased plasma spillover of noradrenaline (38, 61, 107, 122, 323). During prolonged orthostatic stress additional adjustments are mediated by the humoral limb of the neuro-endocrine system (i.e. renin-angiotensin-aldosteron system and vasopressin vasoconstriction) (256, 293). The humoral responses are of importance for cardiovascular adjustments during hypotensive orthostatic stress, but cannot supplant the function of the neural system (226). When the effective circulating blood volume is adequate, defined as the part of the volume within the vascular system effectively perfusing the tissues, renin-angiotensin and vasopressin vasoconstriction is minimally involved in the early steady-state circulatory adjustment (3, 241, 256). Activation of neuro-endocrine mechanisms becomes more important during prolonged orthostasis, particularly in combating imminent arterial hypotension in the volume-depleted state (228, 256, 293). As long as salt intake is normal, blood pressure is maintained during passive head-up tilt also when renin release is pharmacologically inhibited by propranolol or angiotensin formation is prevented by angiotensin-converting enzyme inhibition (176, 231). Under these circumstances, the sympathetic nervous system and vasopressin act in concert to maintain arterial pressure. Thus, the renin-angiotensin system and vasopressin can compensate for each other. Activation of both systems simultaneously appears of importance in the maintenance of orthostatic blood pressure in salt-depleted states (256).

The main sensory receptors involved in orthostatic neural reflex adjustment are the arterial mechanoreceptors (baroreceptors) located in the aortic arch and carotid sinuses and mechanoreceptors located in the heart and lungs (cardiopulmonary receptors) (Figure 2). In the upright position the drop in arterial and cardiac filling pressures is perceived by the carotid sinus and aortic arch baroreceptors and cardiopulmonary receptors and results in an increase in heart rate and vasoconstriction (21, 228).

The gradual increase in diastolic pressure at heart level during postural stress is related to a rise in peripheral vascular resistance, whereas the change in systolic pressure is only small. The net effect is an increase in mean arterial pressure of 5-10 mmHg at heart level in the upright posture. Cardiopulmonary receptors act in concert with arterial baroreceptors to effect the necessary adjustments in sympathetic vasomotor outflow, but are not essential for the cardiovascular adjustments to orthostatic stress (256). The baroreflex-mediated sympathoexcitation can be reinforced by local reflex mechanisms as the venoarteriolar reflex and a myogenic response (58, 95, 256, 295).
Figure 2.
Schematic drawing of the afferent and efferent pathways of the arterial baroreceptor reflex arc. Nerve fibres from the carotid and aortic join the glossopharyngeal nerve and vagus nerve respectively toward the vasomotor centre (VMC) in the brainstem. Nerve fibres from the lungs and the heart (not shown) join the vagus nerve as cardiopulmonary afferents. The baroreflex-mediated sympathoexcitation can be reinforced by local reflex mechanisms as the venoarteriolar reflex and a myogenic response.
Mechanical adjustments to orthostatic stress

A vital defence mechanism against a critical reduction in central blood volume during orthostatic stress is that of muscle activity or the “skeletal muscle pump” (163, 256, 269). In the upright position maintenance of sufficient venous return to the heart is assisted by the circulatory effects of the pumping action of contracting muscles, serving as a second heart (10, 227). If the muscle pump is inactivated, this may result in syncope that even healthy humans experience (133, 163, 266). The static increase in skeletal muscle tone involved opposes pooling of blood in limb veins. Postural sway during quiet standing may compensate for otherwise poor orthostatic tolerance (46). The importance of skeletal muscle activity in opposing gravitational pooling of venous blood is illustrated when applying low levels of isometric leg muscle tension enhancing orthostatic tolerance in both patients with sympathetic failure and persons with recurrent vasovagal (pre-) syncope (Figure 3) (29, 33, 134, 259, 291, 309).

Figure 3.
Leg crossing in standing position in a healthy subject. Note the instantaneous increase in finger arterial blood pressure at the start of leg muscle tension.

These muscle tensing manoeuvres translocate blood pooled below the diaphragm to the chest and thereby partially restore cardiac filling, stroke volume and cardiac output (131, 132, 269, 285, 287). There is evidence that a reduced leg intra-muscular pressure is associated with lower orthostatic tolerance (169). However orthostatic tolerance is not associated directly with leg muscle mass (143). Thus an adequately functioning muscle pump seems to rely more on intra-muscular pressure than on anatomical factors. The “respiratory pump” is another mechanism supporting venous return to the heart. During inspiration, the thoracic pressure lowers and intra-abdominal pressure increases thereby promoting venous return and right atrial filling (172, 227). A sighing respiration often precedes an actual faint and it remains uncertain whether this is of advantage. It has been proposed to assist in preventing syncope by enhancing the respiratory pump and by inducing vasoconstriction in the skin (308). However,
Central blood volume, normovolemia and orthostatic stress

Humans are exposed to a reduced central blood volume when standing, because the first circulatory event is a gravitational displacement of blood away from the thorax to dependent regions of the body (6, 254, 256, 293). Despite this fall in central blood volume, and subsequently cardiac output, mean arterial pressure is preserved by compensatory vasoconstriction of the resistance and capacitance vessels to secure cerebral perfusion and oxygenation under orthostatic stress (225). Identification of the optimal central blood volume under orthostatic stress and how to determine and monitor is therefore of clinical interest. Normovolemia is the normal blood volume of healthy individuals and averages ~75 ml·kg body weight⁻¹ (258). The effective circulating blood volume is assumed to depend mainly on the central blood volume, that is, the amount of blood directly available to the left heart. Transition from the supine to the upright posture has little effect on the blood pressure and orthostasis is proposed as the operating set point for human cardiovascular function (65). However as mentioned earlier, in order to maintain blood pressure to compensate for the fall in central blood and cardiac output during standing, an elevated vascular tone is required (225). The need for activation of cardiovascular reflexes for circulatory adaptation questions whether, in healthy humans, central blood volume is optimised to support the circulation in the upright position.

Physiology is concerned with the regulation of variables such as mean arterial pressure, regional blood flow, vascular resistance and blood volume, whereas clinical practice focuses on the information that such variables provide to guide volume treatment (246). A functional definition of normovolemia would be the ability to provide the heart with appropriate central blood volume, i.e. cardiac preload (55, 120). However, no single variable responds exclusively to a reduced central blood volume and the usual clinical and hemodynamic parameters are not reliable indices of preload to the heart. Also an “optimal” volume is neither defined nor it is an easily measurable entity (28, 210). Hypovolemia may be characterised by a reduced preload to the heart, i.e. with stroke volume and cardiac output becoming dependent on central blood volume. An increase in cardiac output in response to a fluid challenge is taken to imply that a patient is preload responsive (28, 210). Conversely the intravascular volume may be expanded beyond the volume that can provide for a “maximal” cardiac output at rest.

Several methodologies are used to estimate the central blood volume (246). However each
method has its drawbacks. The classical method for the determination of central blood volume is by a dye-dilution estimate of cardiac output with a concomitant determination of transit time (255). A tracer is injected through a central venous catheter and the dilution curve is registered from an artery to calculate cardiac output. Multiplication of cardiac output (l/min) by time (min) derives a volume that represents the amount of blood between the tip of the two catheters. A common assessment of central blood volume is by assessing central venous pressure, together with pulmonary artery wedge pressure (246) thereby examining the Frank-Starling relationship. Starling's law of the heart was established in an animal preparation (261), but it is also accepted widely to apply to the function of the heart in the intact organism. In parallel with the length-tension diagram for skeletal muscles, the “law of the heart” states that stroke volume depends on the diastolic volume (123, 324). However most often stroke volume or cardiac output is related to central venous or pulmonary artery wedge pressures (148, 204). The implicit assumption is that pressure changes in parallel with the central blood volume but, in some cases, the reverse may be true (214). In patients there may be no correlation between stroke volume and central pressures (276). Recent studies have questioned the correlation between these estimates of ventricular filling pressures and ventricular end-diastolic volumes/cardiac performance variables. Healthy subjects demonstrate a lack of correlation between central venous or pulmonary artery wedge pressures and both end-diastolic ventricular volume indices and stroke volume index (137). These findings question whether central pressures are useful predictors of ventricular preload and support the concept that the function of the heart relates to its volume rather than to its so-called filling pressures (73, 246).

Orthostatic hypotension in autonomic failure

Historically, the first reported cases of autonomic failure were described by Bradbury and Eggleston as idiopathic orthostatic hypotension (8, 30). Major symptom of the syndrome are light-headedness, blurring of vision and fainting when upright with immediate recovery of symptoms and blood pressure when supine. A neck ache radiating to the occipital region of the skull and the shoulders (“cloth hanger area”) often precedes the loss of consciousness (20, 293). The postulated mechanism is ischemia in continuously contracting postural muscles. Other symptoms suggesting impaired muscle perfusion are lower back and buttock ache or angina pectoris (20, 293). Orthostatic hypotension is one feature of autonomic failure, the condition is usually associated with other symptoms related to neurological disturbances of organ systems like urinary bladder, sexual function and sweating. Patients with orthostatic hypotension due to autonomic failure are markedly incapacitated to perform daily life activities. Light-headedness forces patients frequently to sit down in order to prevent fainting. Meals, heat and exercise worsen the fall in blood pressure during standing (30, 193, 194, 196, 309). During the day symptoms of orthostatic hypotension may gradually improve (30, 116,
This improvement is related to an increase in upright blood pressure. The underlying mechanism is an increase in stroke volume and cardiac output, with total peripheral resistance unchanged (193). The debilitating early morning orthostatic intolerance is attributed to the nocturnal polyuria observed in patients with autonomic failure (166, 314). Important shifts of fluid volume between the intravascular and extravascular compartments may also be an important contributing factor (193, 292, 315). The primary abnormality in patients with autonomic failure is the reduced capacity to increase total peripheral resistance due to disturbances in sympathetic pathways (14, 44, 97, 164). In addition the fall in cardiac output is exaggerated in autonomic failure patients compared with healthy humans (Figure 4).

**Figure 4.**
Cardiovascular response to standing in patients with autonomic failure and healthy subjects. The supine resting values (from -60 to 0 s) and the first (from 0 to -60 s) and the last minute of standing (from -60 to 0 s) are shown. Boxes indicate standing. **Bold lines:** patients, **Dotted lines:** healthy subjects. Systolic and diastolic blood pressure (BP), heart rate (HR) changes in stroke volume (SV) cardiac output (CO) and total peripheral resistance (TPR). Note the reduced capacity to increase systemic vascular and larger fall in cardiac output in autonomic failure patients.
This excessive fall in cardiac output is ascribed to increased venous pooling and impaired cardiac inotropic and chronotropic responses (14, 100, 256). However the importance of impairment of inotropic and chronotropic responses as a cause of reduced orthostatic tolerance is debated (310). For instance pharmacological blockade of inotropic and chronotropic responses does not play an important role in the adaptation to the upright posture (280). This is also illustrated in patients with a cardiac transplant who do not develop orthostatic hypotension (7, 174, 256). Studies in patients with autonomic failure stress the importance of disturbances in body fluid homeostasis (53). However the link between day-to-day variation in orthostatic complaints and subtle changes in plasma volume is as yet not well understood (53, 193, 256, 290).

Treatment of orthostatic hypotension in autonomic failure is focused on symptoms rather than actual arterial pressure. Increasing patient awareness of factors that may lower blood pressure like meals, heat, post-exercise and standing in line, is of importance (165). Volume expansion by salt loading, salt retaining drugs (mineralocorticoids) and sleeping in head-up tilt position is the primary therapeutic approach (165, 292, 306). Patients with orthostatic hypotension related to sympathetic dysfunction and persons with recurrent vasovagal syncope may combat their symptoms of cerebral hypoperfusion when tensing leg muscles by leg crossing with prolongation of the tolerated standing time (33, 131, 132, 134, 267, 285, 286, 291). Vasoconstrictive drugs usually play a minor role in the treatment, with the exception of the alpha-agonist midodrine. It is a promising therapeutic agent providing for constriction of both arterial resistance and venous capacitance vessels (112, 124, 306).

**Cerebral blood flow and posture**

The brain, which weighs approximately 1400 grams is about 2 % of body weight, receives 50 to 60 ml·100 g⁻¹·min⁻¹ of blood which is 12 to 15 % of resting cardiac output. Total cerebral oxygen uptake is 3 to 3.5 ml·100 g⁻¹·min⁻¹ of oxygen accounting for 15 to 20 % of total body basal metabolic rate (225). Mental confusion becomes prominent with a 50-60% reduction in cerebral blood flow compromising cerebral oxygenation (162, 183), and securing brain blood flow under all circumstances is a major endeavour of nature.

Cerebral blood flow is dynamically adjusted to changes in the perfusion pressure, the metabolic activity of the brain, humoral factors, and probably autonomic nerve activity (40). The relative constancy of the overall craniospinal volume, the cerebrovascular anatomy, and the variations in cerebral perfusion pressure to the ever-changing position of the cerebral circulation relative to the heart make the intracranial hemodynamics complex (293). Control of cerebral blood flow compromises the arterial cerebrovascular bed, the large cerebral veins, and the processes associated with the production and reabsorption of cerebrospinal fluid (76, 281, 293). A characteristic feature of the cerebral circulation is that the cerebral blood flow
tends to remain relatively constant over a range of systemic blood pressure, termed cerebral autoregulation. The actual range of pressures may vary between subjects (142, 200). Cerebral autoregulation is regulated by local and systemic mechanisms (293).

The proposed local mechanisms of cerebral autoregulation operating at the level of cerebral vascular muscle tone include myogenic, metabolic, neural and endothelial factors (142, 200). Carbon-dioxide is a potent vasodilator of cerebral vessels and cerebral blood flow increases with hypercapnia independent of cerebral autoregulation. Conversely, hypocapnia induces constriction of the smaller cerebral arteries (Figure 5) (1, 40, 91, 126, 178, 216).

Figure 5.
Effect of hypocapnia and hypercapnia on cerebral blood velocity. Open box indicates hyperventilation with a hypocapnia and a cerebral blood velocity decrease. Closed box indicates breath holding resulting in hypercapnia and cerebral blood velocity increase.
Cerebral autoregulation is traditionally divided in a static and a dynamic component (197). Cerebral autoregulation is thought to have both fast- and slow-acting regulatory components spanning the range of prevailing demands on cerebral blood flow in everyday life (1, 277). Dynamic cerebral autoregulation refers to the ability to restore cerebral blood flow in the face of arterial blood pressure changes within seconds and reflects the latency of the cerebral vasoregulatory system (198). Static cerebral autoregulation reflects the overall efficiency of the system. For the maintenance of sufficient cerebral perfusion in upright humans the lower limit of cerebral autoregulation is of special interest. This lower limit of cerebral autoregulation is identified in humans subjected to pharmacologically and posture induced hypotension (141). Patients with orthostatic hypotension related to sympathetic failure tolerate a reduction in arterial blood pressure remarkably well, suggesting that the lower limit of cerebral autoregulation is not a fixed value and that it may shift toward a lower arterial blood pressure (274).

In the upright position, the cerebral arteries are positioned 30 cm above the heart, and their perfusion pressure is reduced (224). Both the position of the cerebral circulation and the reduction in cardiac output challenge cerebral blood flow, and although the postural reduction in the transcranial Doppler determined middle cerebral artery blood velocity (22, 150, 239, 322), the near-infrared spectroscopy determined cerebral oxygenation (89, 99, 162) and the nitric oxide determined cerebral blood flow (235) is kept limited via cerebral autoregulatory mechanisms (287), orthostatic intolerance is not uncommon in healthy subjects (222).

During standing up, the rapid initial drop in cerebral perfusion pressure takes place too fast to be counterregulated. This makes the initial drop in cerebral blood flow proportional to the driving pressure and explains the transient fall in cerebral blood flow velocity during standing up (293). The postural reduction in cerebral blood flow and oxygenation during orthostatic stress are not completely understood (Figure 6). The reduction in cerebral blood flow takes place even though the cerebral perfusion pressure remains within what is considered to be its autoregulatory range (106).

During orthostatic stress in humans, arterial and end-tidal carbon dioxide tension decrease (18, 68, 185, 248, 249, 287) and since hypocapnia in itself lowers cerebral blood flow by vasoconstriction, the postural decrease in cerebral blood flow has been attributed to the postural decline in arterial carbon dioxide. The decrease in end-tidal carbon dioxide during standing is due to an increase of end-tidal volume and functional residual capacity, a decrease in cardiac output and a gravity related ventilation/perfusion mismatch (68). The decrease in cerebral blood flow has been attributed to the associated postural decrease in arterial carbon dioxide, but this decline in arterial carbon dioxide accounts for approximately half of the orthostatic influence on cerebral artery mean blood velocity (106, 249). In consequence, other factors than arterial carbon dioxide alone contribute to the postural decrease in cerebral perfusion and oxygenation. Sympathetic outflow and carbon dioxide may affect cerebral perfusion independently during orthostatic stress (144), and the postural decrease in cerebral
Cerebral perfusion has been attributed, at least in part, to cerebral vasoconstriction by an increase in sympathetic cerebrovascular tone (190, 320, 321). A relationship between cerebral blood flow and cardiac output is found by demonstrating that both the mean cerebral blood velocity and the near-infrared spectroscopy determined cerebral oxygenation decrease in association with the postural reduction in cardiac output (245). This reduction in cerebral perfusion takes place even though mean arterial pressure increases (287) further indicating an important role of sympathetic activation for regulation of cerebral blood flow (245). In support, both mean cerebral blood velocity and cerebral oxygenation increase when the standing position is supplemented by a leg crossing manoeuvre that attenuates sympathetic activity by enhancing cardiac output (287). Also both at rest and during exercise, increases or decreases in cardiac output with volume expansion or application of lower body negative pressure alter cerebral blood flow velocity respectively in a linear fashion when mean arterial pressure and arterial carbon dioxide were kept constant (190). Taken together, there is evidence for a relationship between cardiac output and cerebral blood flow velocity beyond the influence of blood pressure (245, 287, 293).
Outline of this thesis

This thesis addresses methodological, (patho)physiological and therapeutical aspects of the cardio- and cerebrovascular system in healthy subjects and in patients with sympathetic failure during orthostatic stress, attempting to find at least a partial answer to the following questions:

1) Is continuous stroke volume tracking feasible by modelling arterial flow from non-invasive finger pressure (Chapter 2.3)?

2) Can normovolemia be considered as the point in the cardiac preload-output relationship where cardiac output does not increase further under circumstances where venous return is unimpeded (Chapter 3.1)?

3) Does cardiac stroke volume relate to changes in thoracic fluid content rather than to the concomitant changes in central vascular pressures during manipulation of the central blood volume (Chapter 3.2)?

4) Which cardio-cerebrovascular mechanisms are involved in the improvement of postural tachycardia syndrome related to inactivity (Chapter 4.1)?

5) How are orthostatic symptoms in patients with orthostatic hypotension due to sympathetic failure related to cerebral perfusion and oxygenation (Chapter 4.2)?

6) How do orthostatic manoeuvres in patients with orthostatic hypotension due to sympathetic failure improve cerebral perfusion (Chapter 4.3)?