Withstanding the flow
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Chapter 4

A DEFINITION OF NORMOVOLEMIA AND CONSEQUENCES FOR CARDIOVASCULAR CONTROL DURING ORTHOSTATIC AND ENVIRONMENTAL STRESS

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**ABSTRACT**

The Frank-Starling mechanism describes the relationship between stroke volume and preload to the heart, or the volume of blood that is available to the heart - the central blood volume. Understanding the role of the central blood volume for cardiovascular control has been complicated by the fact that a given central blood volume may be associated with markedly different central vascular pressures. The central blood volume varies with posture and, consequently, stroke volume and cardiac output (CO) are affected, but with the increased central blood volume during head-down tilt, stroke volume and CO do not increase further indicating that in the supine resting position, the heart operates on the plateau of the Frank-Starling curve which, therefore, may be taken as a functional definition of normovolemia. Since the capacity of the vascular system surpasses the blood volume, orthostatic and environmental stress including bed rest/microgravity, exercise and training, thermal loading, illness, and trauma/hemorrhage is likely to restrict venous return and CO, and the cardiovascular responses are determined primarily by their effect on the central blood volume. Thus during environmental stress, flow redistribution becomes dependent on sympathetic activation affecting not only skin and splanchnic blood flow, but also flow to skeletal muscles and the brain. This review addresses the hypothesis that deviations from normovolemia significantly influence these cardiovascular responses.
INTRODUCTION

The most common clinical evaluation of the circulation is by reporting heart rate (HR) and arterial pressure and it was on the initiative of Harvey Cushing that Riva-Rocci’s mercury sphygmomanometer was introduced to medicine and forwarded to monitoring arterial pressure in patients during surgery. Arterial pressure, however, is a regulated variable that is maintained during, e.g., hemorrhage until blood loss exceeds about one litre. Consequently, arterial pressure is not a reliable index of the intravascular volume and it is unlikely that normovolemia can be defined or monitored based on blood pressure or HR. It may be considered that when arterial pressure becomes the target of treatment, e.g., with administration of sympathomimetic drugs to restore blood pressure, it is at the expense of regional flow and may be even the brain. Also, the experience is that fluid infusion guided by focus on blood pressure allows for wide variation in the administered volume. In contrast, cardiac output (CO) and especially cardiac stroke volume are sensitive to deviations in preload. With the development of techniques like trans-oesophageal and thoracic echocardiography or Doppler, arterial pulse wave analysis or determination of CO by lithium kinetics, several alternatives to the traditional dye dilution and pulmonary catheterisation techniques have become available. These techniques facilitate continuous, and even non-invasive evaluation of not only volume treatment of patients but also the effect of environmental stress on the circulation.

This review focuses on the possibility to define normovolemia on the basis of the Frank-Starling “law of the heart”. For supine healthy humans, the heart is operating on the plateau of the Frank-Starling curve since further expansion of the central blood volume does neither increase stroke volume nor CO. The influence of environmental stress including posture, microgravity, heat, exercise, hemorrhage and shock on the central blood volume and its consequence for cardiovascular control are considered in this review.

STARLING’S LAW OF THE HEART FOR HUMANS

Stroke volume of the heart depends on its preload or on the volume of blood that the heart is provided with, often indicated by its filling pressure (central venous pressure for the right ventricle and pulmonary capillary wedge pressure for the left ventricle), and the relationship between stroke volume and one of the two filling pressures is termed the Frank-Starling mechanism because of the pioneering studies by Otto Frank and Starling and colleagues. The Frank-Starling mechanism or the “law of the heart” was established in a physiologic canine preparation, but is widely accepted also to apply to the intact organism. This hypothesis has now been evaluated for humans with emphasis on the filling volume of the heart rather than its filling pressures. Since central vascular pressures increase, e.g., with pressure breathing and positive end-expiratory pressure ventilation, which are associated with a reduction in central blood volume and CO, preload expressed as volume rather than the so-called filling pressure to the heart is relevant for its function. Stroke volume is directly dependent on the volume provided to the heart and hence suitable to estimate cardiac preload in resting humans. A maximal value of stroke volume (and also CO and mixed venous oxygenation) is achieved in the supine position since a further increase in central blood volume by head-down tilt, causing a 7% increase in diastolic filling volume of the heart, is of no consequence, indicating that the maximum value of the Starling curve is
reached (Figure 4.1). This has been confirmed in supine healthy subjects where a fluid challenge does not increase stroke volume or CO. With the extreme 90° head-down tilt position causing a 16% increase in diastolic volume a reduction (12%) in stroke volume is observed indicating that the “right” descending part of the Starling curve is also a physiological phenomenon. Conversely, in the head-up position CO is reduced by more than 1 l·min⁻¹ with a concomitant ~10% fall in mixed venous oxygenation reflecting that in upright humans about 70% of the blood volume is positioned below the level of the heart. This orthostatic redistribution takes place since the location in the vascular tree where venous pressure is independent of posture is at the level of the diaphragm, while the volume indifference point is somewhat lower, i.e. at the level of the abdomen or the pelvis.

**Figure 4.1** Oesophageal Doppler aortic flow velocity during goal-directed fluid treatment with illustration of the Starling curve. Actual volume optimization using oesophageal Doppler technique utilizing flow velocity of blood in the descending aorta to estimate stroke volume in a 79-year-old male undergoing surgery. Panels depict the oesophageal Doppler signal and derived values of stroke volume (SV), cardiac output (CO) and heart rate (HR) before optimization (A), after 200 ml of colloid (B) and 400 ml of colloid (C) where the top of the Starling curve was considered to be reached since additional colloid administration did not result in >10% increase in SV. Hereafter colloid infusion was discontinued and additional boluses only administered if SV decreased >10%.
ORTHOSTATIC STRESS

Accordingly, from the supine to the erect position, there is a significant displacement of blood to the lower parts of the body with a similar reduction in the central blood volume. The first circulatory event upon assumption of the upright position, either passive or active, is a gravitational displacement of blood away from the thorax filling the veins of dependent regions of the body resulting in a fall in central venous return. This shift in blood volume distribution is estimated to 300-800 ml of which 50% takes place within the first few seconds. The central blood volume is further challenged by an estimated 10% or ~500 ml reduction after 5 min and 15–20% or ~750 ml reduction after 10 min reflecting a shift in the balance between transcapillary fluid loss and gain with distension of dependent veins. Accordingly, features affecting the central blood volume play a key role in the cardiovascular response to posture.

Since the capacity of the vasculature is larger than the total blood volume, distribution of the blood volume is critical for maintenance of arterial pressure and regional flow. Cardiovascular reflexes controlling sympathetic activation operate to translocate blood volume from the peripheral to the central circulation as a countermeasure to the circulatory effects of gravitational stress, while the veno-arterial reflex elevates total peripheral resistance. If humans stand still, however, they may faint, usually with a concomitant decrease in HR and arterial pressure. This reflex, named a vasovagal syncope, is activated when central blood volume is reduced by ~30% due to gravitational pooling in the upright posture or by, e.g. hemorrhage or pressure breathing hindering venous return to the heart. The associated reduction in arterial pressure is attributed to a Bezold-Jarisch-like reflex, an eponym for the responses (apnoea, bradycardia and hypotension) demonstrated following intravenous injection of veratrum alkaloids in experimental animals. The respiratory effects are mediated through pulmonary vagal afferents and the bradycardia and vasodepression through cardiac vagal afferents that induce vasodilatation in skeletal muscles even at the expense of flow to the brain.

During graded orthostatic stress plasma volume normalized for lean body mass relates to time to presyncope. This suggests that individuals with a large plasma volume tolerate postural stress and supports that venous return is the critical variable during orthostatic stress. A lower orthostatic tolerance in women seems associated with decreased cardiac filling rather than reduced responsiveness of vascular resistance during orthostatic challenges. Also, in the upright position subjects intolerant to orthostatic stress tend to demonstrate a larger increase in calf filling volume than tolerant subjects.

The orthostatic fall in venous return affects the central blood volume and thus stroke volume with a decline in CO despite the increase in HR. Furthermore, both middle cerebral artery mean blood velocity and frontal lobe oxygenation decrease in association with the postural reduction in CO even though mean arterial pressure increases. The postural decrease in middle cerebral artery mean blood velocity and frontal lobe oxygenation is not accounted for by the associated reduction in the arterial carbon dioxide tension and seems at odds with the concept of cerebral autoregulation, i.e. that cerebral blood flow is relatively constant within a wide range of perfusion pressures. Accordingly, either central blood volume or more likely CO influences the lower limit of

A definition of normovolemia and consequences for cardiovascular control during orthostatic and environmental stress
cerebral autoregulation and, therefore, cerebral perfusion both at rest and during exercise.\textsuperscript{253-257}

Despite the assault of posture on central blood volume and, in turn, CO and cerebral perfusion, humans can stand erect as long as their circulation is supported by a reflex increase in vasomotor tone. Vasomotor tone limits fluid accumulation in the lower extremities and the increase in total peripheral resistance maintains arterial pressure.\textsuperscript{258-260} As known from soldiers standing in line however, a vasovagal syncope can be elicited when humans stand still illustrating that there is a need to activate leg muscles to prevent accumulation of blood and fluid in dependent parts of the body in order to maintain orthostatic tolerance.\textsuperscript{246, 261-263}

Taken together these findings are contrary to the “upright set-point” hypothesis for defining a “normal state” of the circulation in humans.\textsuperscript{221} Only in the supine position stroke volume, CO and mixed venous oxygenation are maximal for rest\textsuperscript{4} at minimal sympathetic activation. The need for activation of cardiovascular reflexes for circulatory postural adaptation, questions whether, in healthy humans, central blood volume is optimised to support the circulation in the upright position. In quadruped animals, the heart is placed at the level of, or below the main part of the circulation and any, even small deviation from that premises, as when the giraffe lowers its head to drink, challenges the circulation since preload to the heart and, therefore, CO declines because of venous pooling in the neck.\textsuperscript{264} However, the anatomy of humans is much different since a great part of the musculature is located in the extremities. Consequently, even when humans position themselves on four extremities as quadruped animals, still much of musculature and, hence blood volume is below heart level. Only in the supine and prone positions is preload to the heart comparable with that established for standing quadruped animals. These considerations are consistent with the notion that the blood volume that fosters a maximal stroke volume, CO and mixed venous oxygen saturation corresponds to the central blood volume that manifests in supine humans, i.e. when the heart is at the level of the main part of the vasculature.

**Microgravity and bed rest**

Bed rest and being exposed to microgravity during spaceflight lower the threshold for orthostatic intolerance.\textsuperscript{265-267} Orthostatic intolerance may develop quickly after even a brief parabolic flight and is associated with an exaggerated fall in total peripheral resistance suggesting that autonomic cardiovascular function alters rapidly after changes in gravity.\textsuperscript{268} During spaceflight plasma volume declines within the first day\textsuperscript{269} with a reduction in red cell mass by diminished cell survival via an undefined mechanism and a possibly decreased production of new erythrocytes.\textsuperscript{270} In microgravity and with bed rest, the central blood volume is initially increased because of reduced venous pooling in the extremities. The effect of an increased central blood volume is an elevated central venous pressure and via influence from, e.g. increased release of plasma atrial natriuretic peptide and a reduction in plasma antidiuretic hormone (also referred to as vasopressin), total blood volume becomes reduced by renal excretion. According to a model approach of body fluid volume regulation that includes a “set-point” regulatory mechanism, the result is what has been addressed to as a new lower set-point for total body water.\textsuperscript{271} The
reverse phenomenon is observed in patients with orthostatic hypotension related to sympathetic failure, for whom the improvement during the day by postural renal retention of salt and water is enforced by an increased blood volume established by head-up sleeping and/or by administration of mineralocorticoids.

The corollary that cardiovascular and fluid regulatory systems seek the “upright set point” in microgravity constitutes a central hypothesis for studies on acclimation to microgravity. The reduction in blood volume and in stroke volume during spaceflight results in development of orthostatic intolerance upon return to gravity. A symptomatic decline in blood volume is also common to humans after prolonged bed rest, and especially hospitalization. Such post bed rest hypovolemia is attributed to redistribution of the diminished blood volume due to the lack of an effect of gravity.

With stroke volume directly related to central blood volume and left ventricular end-diastolic volume, the excessive postural fall in stroke volume characterises the reduced orthostatic intolerance related to bed rest that has been attributed to a combination of hypovolemia and cardiac atrophy. Restoration of plasma volume improves the condition but the observation that only a single day of bed rest reduces sympathetic nerve responses to lower body negative pressure (LBNP) does not support that cardiac “atrophy” is the primary mechanism. However, it remains debated whether orthostatic intolerance after bed rest is related to insufficient increase in sympathetic discharge in response to a greater postural reduction in stroke volume. Whatever the opinion about the benchmark for sympathetic activity, the adaptation of the cardiovascular system to microgravity is a handicap on return to Earth. Hypovolemia on return to Earth is manifested by a reduced pulse pressure, a lower stroke volume, and a large increase in HR during standing, often with orthostatic intolerance.

Furthermore, both bed rest and microgravity reduce exercise tolerance. Simulated microgravity by prolonged head-down bed rest restricts upright exercise capacity with a reduction in maximal pulmonary oxygen uptake ($\text{VO}_{2\text{,max}}$). The finding that $\text{VO}_{2\text{,max}}$ is maintained in the absence of gravity but is reduced immediately on return to Earth is attributed to a reduced blood volume with a lower stroke volume and CO. Yet, submaximal exercise performed daily in space is ineffective to improve orthostatic tolerance unless additional exposure to simulated gravity is applied. Of interest, a single bout of maximal leg exercise restored the reduction in plasma volume as induced by head-down tilt bed rest because of greater fluid intake and reduced urine volume during the following 24 h. An explanation may be that thirst is provoked by the post-exercise reduction in central blood volume also manifested as a restricted pulmonary diffusion capacity due to a lower amount of red blood cells to receive carbon monoxide.

**HEAT STRESS**

During heating the vasculature of the skin dilates and is, therefore, increasingly perfused in order to decrease body temperature. Consequently, the central blood volume is reduced with a concomitant decrease in preload. An upward and leftward displacement of the Starling curve is demonstrated and the ascending part of the curve also becomes steeper. Yet, the reduced central blood volume is the likely explanation for the increasing tendency of orthostatic intolerance in heat stressed individuals, since even a
minor reduction in central blood volume with the standing position causes large reductions in stroke volume.

**Exercise Capacity and Training**

During exercise, an important function of the cardiovascular system is to supply oxygen to active skeletal muscles. Oxygen delivery depends on the transport capacity of the cardio-respiratory system including the volume of blood available. During exercise the major adaptive mechanism is to increase CO and thereby generate a greater perfusion pressure for blood flow which partially restores the blood flow deficit in the active muscles.

During low intensity exercise, muscle oxygen delivery is prioritised by enhanced vascular conductance and the central blood volume is supported by splanchnic vasoconstriction. However, during intense whole-body exercise blood pressure regulation and, therefore, vasoconstriction becomes of importance also for working skeletal muscles.

Ideally, perfusion to exercising skeletal muscles is regulated to match oxygen delivery to demand. Yet, venous oxygenation decreases during maximal exercise to very low levels (<10%) and oxygen delivery becomes dependent on flow. Thus, when CO can no longer support adequate flow, muscle metabolic capacity is affected restricting working muscle as during whole-body exercise. For maintained exercise, perfusion of the brain is of particular importance and accordingly middle cerebral artery mean blood velocity and frontal lobe oxygenation increase during dynamic exercise. However, the capacity to increase cerebral perfusion is attenuated or absent in patients with cardiac insufficiency. Similarly when during cycling the ability to increase CO is limited by cardio-selective β1-adrenergic blockade in healthy subjects, the increase in middle cerebral artery mean blood velocity and frontal lobe oxygenation is equally reduced although mean arterial pressure is maintained. Conversely, in patients with heart failure, cerebral blood flow is reduced substantially but increases after cardiac transplantation. Thus, it seems that not only during orthostatic stress but also during exercise, cerebral blood flow participates in overall flow regulation that prioritises maintained blood pressure at the expense of flow.

Oxygen delivery to the working muscles is a major determinant of $\dot{V}O_2\text{max}$ attained during large muscle group exercise. Elite endurance athletes possess a high $\dot{V}O_2\text{max}$ primarily due to a high CO and the blood volume expansion associated with exercise training contributes to improve aerobic power. The main difference between endurance-trained athletes and sedentary individuals is maximal stroke volume. The lowered stroke volume in trained subjects during exercise associated with dehydration appears largely related to an increase in HR in response to a reduction in blood volume. During exercise humans lose weight by sweating, but even after weight is restored by drinking, central blood volume remains reduced for many hours following exercise and plasma volume is expanded by further drinking as thirst is maintained. Central blood volume is reduced following exercise due to muscle oedema provoked by the combined effects of elevated perfusion pressure and muscle vasodilatation associated with exercise. Also, cutaneous vasodilatation induced by the elevated body temperature contributes to the reduction of central blood volume. Even though body temperature normalises and
muscle oedema is cleared rapidly after exercise, muscle blood volume remains elevated for several hours.

The reduced central blood volume following exercise is reflected in the levels of hormones that regulate fluid balance, including plasma vasopressin (antidiuretic hormone) and atrial natriuretic peptide. Plasma vasopressin remains elevated while plasma atrial natriuretic peptide is low following exercise and both hormonal changes act to limit urine production resulting in positive fluid balance. As mentioned, during bed rest and space flight, central blood volume is maintained elevated and plasma volume is down-regulated by a reverse hormonal profile to that established following exercise.

An intrinsic problem with whole-body exercise is that, due to vasodilatation, the total capacity of the vasculature outweighs the total blood volume, restricting venous return and thus CO. Restriction of maximal CO implies that oxygen delivery sets a limit to VO2 max with a reduction in regional (muscle, brain) blood flow and, therefore, requires active vasoconstriction. Due to the limitation of CO in humans, sympathetic restraint of metabolic vasodilation in the active muscles when standing or exercising is important for arterial pressure regulation. The reflex pressor response is marked by a rise in sympathetic activation with vasoconstriction that in itself limits the ability to improve blood flow to the underperfused contracting muscles or brain. Examples of differentiated regulation of blood flow during whole body exercise are arm vasoconstriction to an extent that affects oxygen delivery to and utilisation by working skeletal muscles, reduction of leg blood flow, and brain perfusion when the increase in CO is restricted by cardio-selective β1-adrenergic blockade. Thus, the impaired systemic and skeletal muscle aerobic capacity that precedes fatigue is largely related to the failure of the heart to maintain CO and oxygen delivery to locomotive muscle limiting duration and intensity of exercise.

Exercise training increases blood volume both in healthy subjects and in subjects with orthostatic intolerance but whether training-induced plasma volume changes improve athletic performance is debated. Expansion of plasma volume usually occurs immediately, but erythrocyte volume expansion takes weeks. The plasma volume expansion one day following intense exercise is related to a reduced transcapillary filtration rate for albumin suggesting a role for local transcapillary forces in the leg muscle favouring albumin retention in the vascular space after exercise. It is less clear why the red cell volume increases in response to training. Bone marrow is stimulated by erythropoietin released mainly from the kidneys to produce hemoglobin. In that regard the regular finding of reduced arterial oxygen saturation and especially oxygen tension during whole body exercise may be important. However, exposure to high altitude hypoxemia increases hemoglobin production, but the acute increase in hematocrit is caused by loss of plasma volume. Conversely, end-stage kidney disease is associated with anemia attributed to low erythropoietin production and erythropoietin administration is integrated in the treatment of these patients. Thus, whole-body exercise, in addition to the exercise-induced hypoxemia stimulus for erythropoietin production, may stimulate hemoglobin production via sympathetically-induced reduction in kidney blood flow. In rowers, for whom arterial hypoxemia is prevalent, approximately 10% of the athletes present with a hematocrit above the ‘doping’ limit of 50% applied to, e.g., cycling. The increase in total hemoglobin is an important adaptation to training because VO2 max is
related to red cell volume or to hemoglobin.\textsuperscript{337} In an apparent paradox, athletes often present somewhat low hemoglobin concentrations (or hematocrit: 44\% versus 46\% in untrained) because of the enlarged plasma volume. For athletes plasma and red cell volume may be 61 and 46 ml·kg\textsuperscript{-1}, respectively, compared to reference values of 46 and 33 ml·kg\textsuperscript{-1}, respectively, for men\textsuperscript{337} and training-induced increase in both plasma and red cell volume support preload to the heart.

During exercise, central blood volume contributes to the level of sympatho-excitation established as reflected by HR. For example, at supine rest HR may be 60 beat·min\textsuperscript{-1} and increase to 80 beat·min\textsuperscript{-1} when standing but HR decreases 10 beat·min\textsuperscript{-1} during contraction of the leg muscles in the upright position.\textsuperscript{246} Muscle contractions increase sympathetic activity but the concomitant enhancement of central blood volume and central venous pressure by the muscle pump elicits a “paradoxical” reduction in sympathetic activity.\textsuperscript{165, 246, 259} Also, during running a smaller central blood volume manifests as a lower central venous pressure and less distension of the atria, as reflected by the plasma level of atrial natriuretic peptide. Furthermore, the lowest HR increase in response to exercise is observed in the supine position.\textsuperscript{338} Thus there is a lower HR during rowing compared to running despite the higher $\text{VO}_2\text{max}$ established by the larger active muscle mass during rowing (Figure 4.2).\textsuperscript{1} Similarly, the lowering of HR both at rest and during exercise in response to endurance training likely resembles the positional effect on central blood volume.\textsuperscript{339}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Lower heart rate during rowing vs. running. Heart rate during rowing vs. running (*$P<0.05$), despite a higher oxygen uptake while rowing. Modified from Yoshiga and Highuchi.\textsuperscript{1}}
\end{figure}
Blood volume encompasses volumes of both red cells and plasma that change rapidly in response to physical activity. For example, plasma volume is elevated by 20% following short term training and it decreases during bed rest or space flight. The enlargement of plasma volume following training and the reduction in plasma volume when central blood volume remains elevated as during bed rest or space flight suggests that central blood volume rather than total blood volume is the regulated variable.

The effects of training on a subject’s tolerance to orthostatic stress are less clear with reports indicating improvement, no change or even deterioration. Athletes may develop structural cardiac changes with a steeper slope of the left cardiac pressure – stroke volume relationship indicating a greater reduction in stroke volume for a given decrease in pressure during an orthostatic challenge. This may be of benefit when exercising but it leads to a considerable reduction in stroke volume during orthostasis.

Ogoh et al. demonstrated a changed central venous pressure -central blood volume relationship in endurance-trained subjects indicating changes in the mechanical properties of the right heart as well. The implication is that highly fit subjects depend more tightly on the preservation of venous return to maintain CO in the upright body position. The effects of fluid expansion related to endurance training as an intervention to improve orthostatic tolerance appear to be paradoxically offset by cardiac remodelling and reduced effectiveness of baroreceptor control mechanisms. Orthostatic intolerance in deconditioned subjects is related to hypovolemia and possibly cardiac atrophy, and to attenuated carotid baroreflex responsiveness and a larger compliance of the heart in the highly fit. The debate as to the effect of physical training on an individual’s tolerance to orthostatic stress may come to an end by accepting the existence of an ‘optimal level of fitness’, ill-defined as it is, located between the deconditioned and the highly trained state. In practice, extreme levels of aerobic fitness associated with orthostatic intolerance are likely to be achieved only by elite military personnel or athletes. The finding that the usual increase in carotid baroreflex responsiveness during head-up tilt is attenuated in endurance-trained subjects provides an explanation for the predisposition to orthostatic hypotension and intolerance in athletes. In moderately fit individuals improvement of the aerobic capacity usually enhances orthostatic tolerance.

Thus, it seems reasonable to advise exercise training to people who do not easily tolerate standing but to what extent is less certain. In addition to the effects of increasing aerobic capacity, resistance training (weight lifting) may reduce venous pooling by increasing muscle tone. In contrast, e.g. swimming training does not lead to greater orthostatic tolerance than training for running. The opposite effects may be seen following prolonged inactivity. Improving the aerobic capacity of moderately fit individuals increases the plasma volume and is usually associated with improved orthostatic tolerance. The beneficial effect of a training programme in improving orthostatic tolerance was demonstrated in identical twins who fainted during passive tilting. After a three-week training program applied to one of them, a subsequent head-up tilt induced faint could be elicited in the untrained twin only. This observation contrasts to the propensity of highly trained individuals towards a lower tolerance to orthostatic stress than untrained people, paraphrased as ‘trained men can run, but they cannot stand’.
Chapter 4

HEMORRHAGE

The changes in HR and arterial pressure during a progressive reduction in central blood volume by hemorrhage illustrate how central blood volume can be followed in humans.\textsuperscript{11, 353} The first documented observations are from World War II in air raid casualties with hypovolemic shock,\textsuperscript{354, 355} in volunteers bleeding large amounts,\textsuperscript{356} and in patients with serious hemorrhagic shock where the finding of a low HR was unexpected.\textsuperscript{12, 357}

During the first stage of hemorrhage, corresponding to a reduction of the blood volume by approximately 15\%, a modest increase in HR (<100 beats·min\(^{-1}\)) and total peripheral resistance compensate for the blood loss with maintenance of a near normal arterial pressure.\textsuperscript{51, 353} The second stage is marked by a decrease in HR, total peripheral resistance and arterial pressure when the central blood volume becomes reduced by \(~30\%\) attributed to a Bezold-Jarisch-like reflex.\textsuperscript{19, 238, 358, 359} When blood loss continues, arterial pressure declines further and tachycardia (>120 beats·min\(^{-1}\)) becomes manifest; this third stage probably reflects the transition to irreversible shock.\textsuperscript{353, 360} Sander-Jensen et al.\textsuperscript{361} showed in patients with serious blood loss that their HR was initially low and increased only after repletion of the volume deficit. This observation underscores that the traditional teaching that hemorrhage is diagnosed easily by a reflex tachycardia and a low arterial pressure is not legitimate.

Values for arterial pressure and HR are easily obtained and continue to serve as monitors for volume treatment in hypotension and shock. This approach seems physiological when considering that arterial pressure is the principal cardiovascular variable monitored by the body through the baroreceptors\textsuperscript{362} but may be less relevant in old healthy subjects in whom HR changes during post-exercise hypotension are insignificant.\textsuperscript{215} Cardiac stroke volume and CO still play a subservient role although it is flow, not pressure that the tissues are in need of.\textsuperscript{363} For instance, in patients with septic shock, artificially increasing mean arterial pressure beyond \(~65\) mmHg does not improve established variables of tissue perfusion.\textsuperscript{364} Nevertheless, a value for mean arterial pressure rather than flow continues to be the major target of treatment with fluids and inotropic agents.

Thus the traditional description of hypovolemic shock\textsuperscript{365, 366} contrasts to the non-linear relationships of HR and arterial pressure with a volume loss in both humans\textsuperscript{358, 361} and animals.\textsuperscript{367, 368}

NORMOVOLEMIA

According to studies in humans at rest and under different types of environmental stress, a functional definition of ‘normovolemia’ would be by its ability to provide the heart with an optimal central blood volume, i.e. that cardiac pumping capacity is not limited by its preload.\textsuperscript{369} Hypovolemia may be characterised by a reduced preload to the heart, i.e. with stroke volume and CO becoming dependent on central blood volume. A sensitive and specific measure of early reductions in central blood volume is CO\textsuperscript{15} and documenting that CO increases with volume loading is taken to imply that a patient is preload-responsive.\textsuperscript{214} In contrast, the intravascular volume may be expanded beyond the volume that can provide for a ‘maximal’ CO at rest. By interpolation between hypo- and hypervolemia,
functional normovolemia is the point in the cardiac preload-output relationship at which CO does not increase further under circumstances where venous return is unimpeded.\textsuperscript{4}

**APPLICATIONS TO CLINICAL MEDICINE**

In clinical medicine central blood volume rather than the total blood volume is to be balanced between hypovolemic shock and development of pulmonary and peripheral oedema. With the functional perspective of normovolemia, volume treatment should be provided to secure a resting CO that is not preload limited.\textsuperscript{72,165} There are several reservations in providing volume treatment primarily on the basis of cardiovascular variables.

Physiology is concerned with regulation of cardiovascular variables such as mean arterial pressure, regional blood flow,\textsuperscript{15,370} vascular resistance and blood volume,\textsuperscript{371} whereas clinical practise focuses on the information that such variables provide for treatment. Therefore, it is problematic that no single variable responds exclusively to a reduced central blood volume.\textsuperscript{72} Under various conditions, normal or average circulatory values do not apply to the individual, or to a given disease or condition.

Acute blood pressure lowering in hypertensive patients may reduce cerebral perfusion.\textsuperscript{372} Conversely, even a normal mean arterial pressure may induce cerebral hyperperfusion and death in a patient with acute liver failure.\textsuperscript{373} Comparable to what happens to skeletal muscle blood flow during exercise, regional flow is allowed to increase for as long as it does not affect mean arterial pressure. However, when CO is restricted and challenges mean arterial pressure, flow to exercising muscles, and to the brain, becomes limited.\textsuperscript{245} Under these conditions monitoring of cerebral blood flow is indicated, but continuous measurement of regional blood flow is not regularly available in the clinical setting. Since cerebral blood flow is related to CO independent from arterial pressure, maintaining CO may prevent undetected cerebral hypoperfusion and monitoring of CO under these circumstances becomes mandatory.

The most common volume assessment still used in intensive care units is central venous pressure, together with pulmonary artery wedge pressure. Most often stroke volume or CO are related to either central venous pressure, mean pulmonary artery pressures or pulmonary artery wedge pressure.\textsuperscript{343,374} The implicit assumption is that pressure changes in parallel with the central blood volume, but in some cases the reverse may be true. In patients there may be no correlation between stroke volume and central pressures while there is a tight relation between stroke volume and the filling of the heart.\textsuperscript{343,375} Recent studies have questioned the correlation between these estimates of ventricular filling pressures and CO. Healthy volunteers demonstrate a lack of correlation between initial central venous pressure and pulmonary artery wedge pressure and both end-diastolic ventricular volume and stroke volume.\textsuperscript{376} Also with changes in central blood volume as elicited by tilting head-up and head-down, stroke volume changed with the thoracic fluid content rather than with the central vascular pressures.\textsuperscript{4} These findings question central venous pressure and pulmonary artery wedge pressure as useful predictors of ventricular preload\textsuperscript{377} and support the notion that the function of the heart relates to its volume rather than to its so-called filling pressures.\textsuperscript{4}

The classical method for determination of central blood volume is by a dye-dilution estimate
of CO with a concomitant determination of transit time.\textsuperscript{378} The tight coupling of CO with the filling volume of the heart, even in situations where a relationship between CO and central filling pressures is lost, illustrates the feasibility of evaluation of cardiac preload by echocardiography.\textsuperscript{375} As most methods for measuring central blood volume require extensive apparatus, it is useful to apply Ohm’s law to the body and evaluate volume directly by electrical impedance plethysmography.\textsuperscript{263, 379-381} Such assessment of the volume of the body, and more specifically of the volume contained within the central vessels and the heart, is readily available (Figure 4.3).

![Figure 4.3 Left ventricular stroke volume and thoracic electrical admittance. Relationship between cardiac output and preload (thoracic admittance) during progressive central hypovolemia by passive head-up tilt at 60° in 9 healthy humans (1 female) with median age 29 (range 22 - 39) yr., height 183 (170 - 191) cm, and weight 75 (68 - 82) kg. Respectively, the supine and tilt positions are indicated, with the duration in the head-up position in minutes. Values are mean ± SE. Modified from Van Lieshout et al.\textsuperscript{4}](image)

Although estimates of changes in central blood volume are available, it is a problem that the optimal filling of the heart remains unknown. In surgery, preservation of the central blood volume is challenged by factors such as bleeding, capillary leakage and evaporation. Also anesthetic drugs applied in spinal and epidural anesthesia reduce the central blood volume\textsuperscript{382} as a result of redistribution. Establishment of normovolemia to maintain an optimal oxygen delivery to organs is intuitively rational. Whereas standard monitoring of HR and arterial pressure does not detect a reduction of central blood volume, which is a prerequisite of circulatory support, flow-related variables reflect the intravascular volume status in surgical patients, facilitating correct fluid therapy. However, fluid overload is also detrimental leading to compromised cardiac-, lung-, and gastrointestinal function\textsuperscript{383} affecting postoperative outcome.\textsuperscript{384, 386} Consequently, to avoid both hypovolemia and fluid overload in surgical patients, fluid therapy with individual maximization of flow-related hemodynamic variables, so-called goal-directed therapy, has been introduced.\textsuperscript{148}

With individualized goal-directed therapy, a volume (usually a synthetic colloid) is administered in amounts of 200-250 ml challenges. If stroke volume increases $\geq 10\%$ the
patient is regarded as being on the ascending part of the cardiac function curve (Figure 4.1) and then the fluid challenge is repeated until the ceiling of the cardiac function curve is reached. Hereafter stroke volume is monitored and a fluid challenge is only provided if a 10% decrease in stroke volume is observed. In this context, peri-operative maximization of cardiac stroke volume by means of fluid therapy improves post-operative outcome after femoral fractures, general, cardiac and major bowel surgery. Goal-directed therapy reduces gastro-intestinal complications, overall complication and hospital stay. The reduction of complications especially in the splanchnic system may be explained by improved perfusion of its vasculature and possibly by avoidance of intestinal oedema.

The implication of individualised goal-directed fluid therapy is that when a maximal stroke volume is established for patients, cardiac preload has become comparable to that of supine healthy subjects. In this context it is demonstrated that although the overall volume that has to be administered to obtain a maximal stroke volume is minor, patients with a larger deficit of clinical relevance may be identified. Use of the goal-directed approach is, however, challenged by the invasiveness of traditional monitoring modalities of stroke volume and CO. The thermodilution technique is the accepted clinical method of estimating CO, but it is discontinuous and requires the presence of a pulmonary artery catheter for as long as monitoring of CO is needed. However, advances in the area potentially provides more readily available and less invasive modalities that may encourage more widespread use of the goal-directed approach. Ultrasound and pulse wave analysis or stroke volume modelling either noninvasively from finger pressure or from intra-arterial pressure possesses the potential to track beat-to-beat changes in stroke volume and CO in humans as initiated by postural fluid shifts (Figure 4.4). The use of variation in stroke volume and pulse pressure as markers of fluid responsiveness in mechanically ventilated patients is promising but so far the evidence of favoured outcome with use of these variables is limited.
CONCLUSIONS

Environmental stress including posture, microgravity, heat, exercise hemorrhage and shock affect preload to the heart and, consequently, stroke volume and cardiac output. Both at rest and during exercise, cardiac output is preload dependent in upright humans, which results in sympathetic activation with an increase in HR and total peripheral resistance. Under these conditions, primarily flow to the splanchnic area is reduced but also flow to the brain and working skeletal muscles become affected, especially during whole body exercise. Conversely, the plateau of the Starling curve for the heart is reached when humans are supine and that observation may be applied to define normovolemia of consequence for monitoring of volume treatment of patients, and, as exemplified in this review, to explain at least part of the cardiovascular response to environmental stress.

Figure 4.4 Non-invasive stroke volume tracking during orthostatic variations in central blood volume. Tracking of a thermodilution estimate of stroke volume (solid line) by Modelflow stroke volume (broken line) from non-invasive finger blood pressure (Finapres); averaged values obtained in 10 healthy subjects. Central blood volume was manipulated by passive (tilt) and active (standing) changes in body position. Direction of changes in stroke volume are reciprocal to body position (head-up vs. supine). Modified from Harms et al.5