REVIEW ARTICLE

A definition of normovolaemia and consequences for cardiovascular control during orthostatic and environmental stress

Jasper Truijen · Morten Bundgaard-Nielsen · Johannes J. van Lieshout

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 ($\dot{Q}$) are affected, but with the increased central blood volume during head-down tilt, stroke volume and $\dot{Q}$ 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 normovolaemia. 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/haemorrhage is likely to restrict venous return and $\dot{Q}$. Consequently 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 normovolaemia significantly influence these cardiovascular responses.

Keywords Blood pressure · Cardiac output · Exercise · Stroke volume · Syncope · Volume

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Introduction

The most common clinical evaluation of the circulation is by reporting cardiac frequency (f_c) and arterial pressure and it was on the initiative of Cushing (1903) that Riva-Rocci's (1896) mercury sphygmomanometer was introduced to medicine and forwarded to monitoring arterial pressure in patients during surgery (Bogert and Van Lieshout 2005). Arterial pressure, however, is a regulated variable that is maintained during, e.g. haemorrhage until blood loss exceeds about one litre (Secher et al. 1992; Kinsella and Tuckey 2001; Harms et al. 2003; Campagna and Carter 2003; Cooke et al. 2004). Consequently, arterial pressure is not a reliable index of the intravascular volume (Lichtwarck-Aschoff et al. 1992; Lichtwarck-Aschoff et al. 1996; Pinsky 2002; Boulain et al. 2002) and it is unlikely that normovolaemia can be defined or monitored based on blood pressure or f_c (Murrell et al. 2010). 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 that may include that of the brain (Brassard et al. 2009). 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 ($\dot{Q}$) and especially cardiac stroke volume are sensitive to deviations in preload (Cooke et al. 2004; Secher and Van Lieshout 2005). With the development of techniques like trans-oesophageal and thoracic echocardiography or Doppler (Singer et al. 1989; Toska and Walloe 2002), arterial pulse wave analysis (Harms et al. 1999; Bogert and Van Lieshout 2005) and determination of $\dot{Q}$ by lithium kinetics (Kurita et al. 1997), 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 normovolaemia 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 $\dot{Q}$ (Harms et al. 2003; Jans et al. 2008; Bundgaard-Nielsen et al. 2009a, b). The influence of environmental stress including posture, microgravity, heat, exercise, haemorrhage and shock on the central blood volume and its consequence for cardiovascular control are considered in this review.
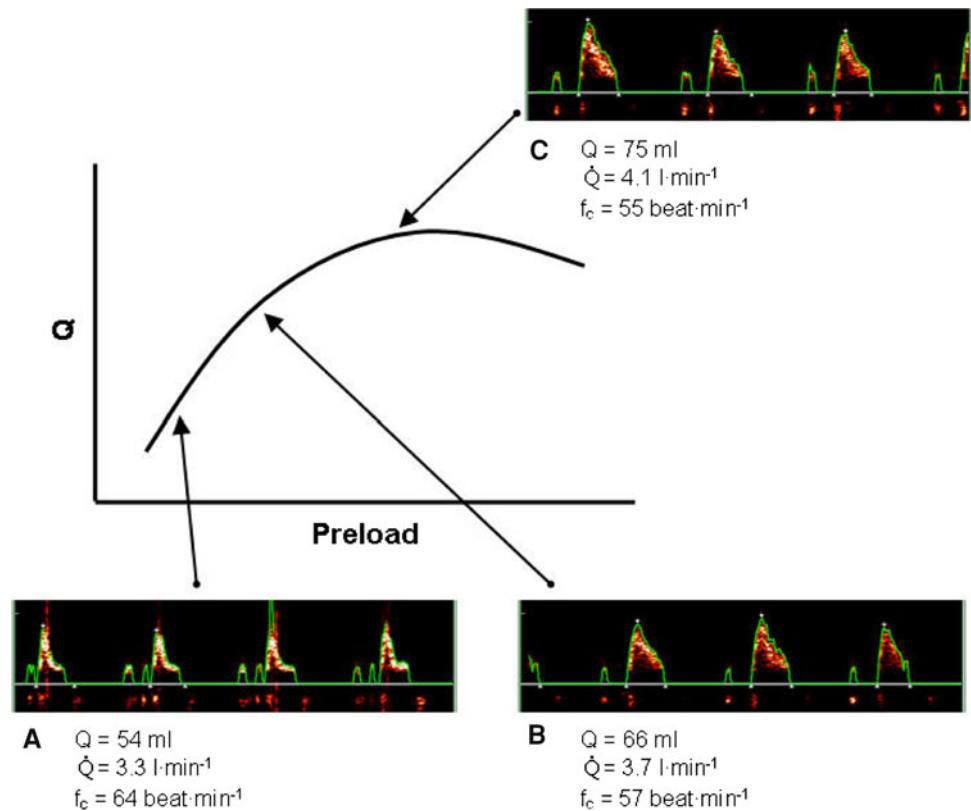
Starling's law of the heart for humans

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 (Zimmer 2002) because of the pioneering studies by Frank (1895) and Starling and colleagues (Patterson and Starling 1914; Patterson et al. 1914). 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 (Harms et al. 2003; Van Lieshout et al. 2005). An increase in central vascular pressures, e.g. with pressure breathing and positive end-expiratory pressure ventilation, is associated with a reduction in central blood volume and $\dot{Q}$, 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 $\dot{Q}$ 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 (Fig. 1c) (Harms et al. 2003; Van Lieshout et al. 2005; Jans et al. 2008). This has been confirmed in supine healthy subjects where a fluid challenge does not increase stroke volume or $\dot{Q}$. With the extreme 90° head-down tilt position causing a 16% increase in diastolic volume a reduction (12%) in stroke volume is observed (Bundgaard-Nielsen et al. 2009a, b) indicating that the "right" descending part of the Starling curve is also a physiological phenomenon. Conversely, in the head-up position $\dot{Q}$ is reduced by more than 1 l min^{-1} with a concomitant $\sim$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 (Gauer and Thron 1965; Blomqvist and Stone 1984; Vorstrup et al. 1992; Rowell 1993), while the volume indifference point is somewhat lower, i.e. at the level of the abdomen (Jarvis and Pawelczyk 2009) or the pelvis (Perko et al. 1995).

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 (Wieling et al. 2002b). 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 (Hill 1895; Amberson 1943; Matzen et al. 1991). This shift in blood volume distribution is estimated to 300–800 ml (Blomqvist and Stone 1984) of which 50% takes place within the first few seconds (Brown et al. 1949; De Marées et al. 1973; Kirsch et al. 1980; Smith and Ebert 1990). The central blood volume is further challenged by an estimated 10% or $\sim$500 ml reduction after 5 min and 15–20% or $\sim$750 ml reduction after 10 min (Lundvall et al. 1996) reflecting a shift in the balance between transcapillary fluid loss and gain with distension of dependent veins (Thompson et al. 1928; Tarazi et al. 1970; Hagan et al. 1978; Smith and

Fig. 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 (Q), cardiac output ($\dot{Q}$) and cardiac frequency (f_c) 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 Q. Hereafter colloid infusion was discontinued and additional boluses only administered if Q decreased >10%

C   Q = 75 ml
$\dot{Q}$ = 4.1 l·min⁻¹
f_c = 55 beat·min⁻¹

A   Q = 54 ml
$\dot{Q}$ = 3.3 l·min⁻¹
f_c = 64 beat·min⁻¹

B   Q = 66 ml
$\dot{Q}$ = 3.7 l·min⁻¹
f_c = 57 beat·min⁻¹

Ebert 1990). Accordingly, features affecting the central blood volume play a key role in the cardiovascular response to posture (van Heusden et al. 2006).

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 (Henriksen and Skagen 1986) elevates total peripheral resistance. However, if humans stand still they may faint, usually with a concomitant decrease in f_c and arterial pressure. This reflex, named a vasovagal syncope (Lewis 1932; Van Lieshout et al. 2003b), is activated when central blood volume is reduced by ∼30% due to gravitational pooling in the upright posture or by, e.g. haemorrhage or pressure breathing hindering venous return to the heart. The associated reduction in arterial pressure is attributed to a Bezold–Jarisch-like reflex (Jarisch 1941), an eponym for the responses (apnoea, bradycardia and hypotension) demonstrated following intravenous injection of veratrum alkaloids in experimental animals (Aviado and Guevara 2001). The apnoea is 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 (Jacobsen et al. 1994; Kinsella and Tuckey 2001; Aviado and Guevara 2001; Campagna and Carter 2003; Mitchell et al. 2009; Hamner et al. 2010).

Time to presyncope during graded orthostatic stress relates to plasma volume normalized for lean body mass (El-Sayed and Hainsworth 1996). This suggests that individuals with a large plasma volume tolerate postural stress better (Wieling et al. 2002b), and supports that venous return is the critical variable during orthostatic stress. A lower orthostatic tolerance in women (Meendering et al. 2005) seems associated with decreased cardiac filling rather than reduced responsiveness of vascular resistance during orthostatic challenges (Fu et al. 2004). Also, in the upright position subjects intolerant to orthostatic stress tend to demonstrate a larger increase in calf filling volume than tolerant subjects (de Chantemele et al. 2004).

The orthostatic fall in venous return affects the central blood volume and thus stroke volume with a decline in $\dot{Q}$ despite the increase in f_c. Furthermore, both middle cerebral artery mean blood velocity and frontal lobe oxygenation decrease in association with the postural reduction in $\dot{Q}$ (Secher et al. 2008) even though mean arterial pressure increases (Van Lieshout et al. 2001). The postural decrease in middle cerebral artery mean blood velocity (Levine et al. 1994; Zhang et al. 1998; Pott et al.

2000) and frontal lobe oxygenation (Harms et al. 2000) is not accounted for by the associated reduction in the arterial carbon dioxide tension (Immink et al. 2006, 2009) 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 (Lassen 1964; Panerai 1998). Accordingly, either central blood volume or more likely $\dot{Q}$ influences the lower limit of cerebral autoregulation and, therefore, cerebral perfusion both at rest and during exercise (Ide et al. 1998, 1999a; Ogoh et al. 2005a, 2007; Nissen et al. 2009a).

Despite the assault of posture on central blood volume and, in turn, $\dot{Q}$ 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 (Jacobsen et al. 1993; Ray et al. 1993; Ng et al. 1995). As known from soldiers standing in line 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 (Mayerson and Burch 1940; Madsen et al. 1998; Van Lieshout et al. 2001; Krediet et al. 2006).

Taken together these findings are contrary to the "upright set point" hypothesis for defining a "normal state" of the circulation in humans (Gauer and Thron 1965). Only in the supine position stroke volume, $\dot{Q}$ and mixed venous oxygenation are maximal for rest (Van Lieshout et al. 2005) 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 declines because of venous pooling in the neck (Brondum et al. 2009). 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, $\dot{Q}$ 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 exposure to microgravity during spaceflight lower the threshold for orthostatic intolerance (Khan et al. 2002; Wieling et al. 2002a; Eckberg 2003). 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 (Schlegel et al. 2001). During spaceflight plasma volume declines within the first day (Hinghofer-Szalkay and White 2008) with a reduction in red cell mass by diminished cell survival via an undefined mechanism and a possibly decreased production of new erythrocytes (Alfrey et al. 1996). 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 through 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 (Sawka et al. 2000). 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 (Bradbury and Eggleston 1925) is enforced by an increased blood volume established by head-up sleeping (MacLean and Allen 1940; Cooper and Hainsworth 2008), salt loading (Cooper and Hainsworth 2002) and/or by administration of mineralocorticoids (Sancho et al. 1976; Van Lieshout et al. 2000).

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 (Watenpaugh et al. 2001) results in development of orthostatic intolerance upon return to gravity (Buckey et al. 1996). A symptomatic decline in blood volume is also common to humans after prolonged bed rest, and especially hospitalization. Such post bed rest hypovolaemia is attributed to redistribution of the diminished blood volume due to the lack of an effect of gravity (Alfrey et al. 1996).

With stroke volume directly related to central blood volume (Van Lieshout et al. 2005) and left ventricular end-diastolic volume (Levine et al. 2002), the excessive postural fall in stroke volume characterises the reduced orthostatic intolerance related to bed rest that has been attributed to a combination of hypovolaemia and cardiac

atrophy (Levine et al. 1997; Mtinangi and Hainsworth 1998; Pawelczyk et al. 2001). Restoration of plasma volume improves the condition (Takenaka et al. 2002), but the observation that only a single day of bed rest reduces sympathetic nerve responses to lower body negative pressure does not support that cardiac "atrophy" is the primary mechanism (Khan et al. 2002). 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 (Shoemaker et al. 1999; Levine et al. 2002; Khan et al. 2002; Ertl et al. 2002; Kamiya et al. 2003; Eckberg 2003). Whatever the opinion about the benchmark for sympathetic activity, the adaptation of the cardiovascular system to microgravity is a handicap on return to Earth (Wieling et al. 2002a). Hypovolaemia on return to Earth is manifested by a reduced pulse pressure, a lower stroke volume, and a large increase in f_c during standing, often with orthostatic intolerance (Buckey et al. 1996; Alfrey et al. 1996; Levine et al. 2002; Gisolf et al. 2005).

Furthermore, both bed rest and microgravity reduce exercise tolerance (Levine et al. 1996; Watenpaugh et al. 2000) and simulated microgravity by prolonged head-down bed rest restricts upright exercise capacity with a reduction in maximal pulmonary oxygen uptake ($\dot{V}O_{2\,max}$) (Watenpaugh et al. 2000). The finding that $\dot{V}O_{2\,max}$ 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 $\dot{Q}$ (Levine et al. 1996). Yet, submaximal exercise performed daily in space is ineffective to improve orthostatic tolerance (Greenleaf et al. 1989) unless additional exposure to simulated gravity is applied (Watenpaugh et al. 2000; Schneider et al. 2002). Of interest, the reduction in plasma volume as induced by head-down tilt bed rest was restored by a single bout of maximal leg exercise because of greater fluid intake and reduced urine volume during the following 24 h (Convertino et al. 1996). 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 (Rasmussen et al. 1992; Hanel et al. 1997).

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 (Cai et al. 2000c; Wilson et al. 2007). An upward and leftward displacement of the Starling curve is demonstrated and the ascending part of the curve also becomes steeper (Wilson et al. 2009). 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 (Mortensen et al. 2008). 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 $\dot{Q}$ and thereby generate a greater perfusion pressure for blood flow which partially restores the blood flow deficit in the active muscles (O'Leary and Joyner 2006). During low intensity exercise, muscle oxygen delivery is prioritised by enhanced vascular conductance and the central blood volume is supported by splanchnic vasoconstriction (Doe et al. 1996; Noble et al. 1997). However, during intense whole-body exercise blood pressure regulation and, therefore, vasoconstriction develops also for working skeletal muscles (Volianitis and Secher 2002).

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 $\dot{Q}$ can no longer support adequate flow, muscle metabolic capacity is affected restricting working muscle as during whole-body exercise (Mortensen et al. 2008). 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 (Jørgensen et al. 1992; Hellstrøm et al. 1996a; Ide et al. 1999b). However, the capacity to increase cerebral perfusion is attenuated or absent in patients with cardiac insufficiency (Hellstrøm et al. 1996b) or atrial fibrillation (Ide et al. 1999a). Similarly when during cycling the ability to increase $\dot{Q}$ is limited by cardio-selective β-1 adrenergic blockade in healthy subjects, the increase in middle cerebral artery mean blood velocity (Ide et al. 1998) and frontal lobe oxygenation is equally reduced although mean arterial pressure is maintained (Seifert et al. 2008). Conversely, in patients with heart failure, cerebral blood flow is reduced substantially but increases after cardiac transplantation (Gruhn et al. 2001). Thus, it seems that not only during orthostatic stress but also during exercise, cerebral blood flow participates in overall flow regulation that prioritizes maintained blood pressure at the expense of flow.

Oxygen delivery to the working muscles is a major determinant of $\dot{V}O_{2\,max}$ attained during large muscle group exercise (Gonzalez-Alonso and Calbet 2003). Elite endurance athletes possess a high $\dot{V}O_{2\,max}$ primarily due to a high $\dot{Q}$ (Levine 2008) 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 (Ekblom and Hermansen 1968). The lowered stroke volume in trained subjects during exercise associated with dehydration appears largely related to an increase in f_c (Fritzsche et al. 1999) in response to a reduction in blood volume (Gonzalez-Alonso et al. 2000). 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 (Convertino et al. 1996). 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 (Cai et al. 2000c). Even though body temperature normalises and muscle oedema is cleared rapidly after exercise (Clausen et al. 1973; Rasmussen et al. 1992), muscle blood volume remains elevated for several hours (Hanel et al. 1997).

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 (Hanel et al. 1997). 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 $\dot{Q}$ (Andersen and Saltin 1985; Noakes and Ekblom 2008). Restriction of maximal $\dot{Q}$ implies that oxygen delivery sets a limit to $\dot{V}O_{2\,max}$ (Volianitis and Secher 2002; Calbet et al. 2004) with a reduction in regional (muscle, brain) blood flow and, therefore, requires active vasoconstriction (Secher et al. 1977; Savard et al. 1988; Wagner and Secher 2008). Due to the limitation of $\dot{Q}$ 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 (Ide et al. 1998; Van Lieshout et al. 2001; Ogoh et al. 2005a, b; O'Leary and Joyner 2006; Secher et al. 2008). Examples of differentiated regulation of blood flow during whole-body exercise are arm vasoconstriction (Calbet et al. 2007) to an extent that affects oxygen delivery to and utilisation by working skeletal muscles (Volianitis and Secher 2002), reduction of leg blood flow (Pawelczyk et al. 1992), and brain perfusion (Ide et al. 1998; Seifert et al. 2008) when the increase in $\dot{Q}$ is restricted by cardio-selective β_1-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 $\dot{Q}$ and oxygen delivery to locomotive muscle (Gonzalez-Alonso and Calbet 2003) limiting duration and intensity of exercise (Mortensen et al. 2008).

Exercise training increases blood volume both in healthy subjects and in subjects with orthostatic intolerance (Saltin et al. 1968; Convertino et al. 1980; Greenleaf et al. 1989; Gillen et al. 1991, 1994; Hainsworth 1998; Winker et al. 2005) but whether training-induced plasma volume changes improve athletic performance is debated (Nose and Montain 2008). Expansion of plasma volume usually occurs immediately, but erythrocyte volume expansion takes weeks (Sawka et al. 2000). The plasma volume expansion 1 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 (Haskell et al. 1997; Mack et al. 1998). 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 haemoglobin. In that regard the regular finding of reduced arterial oxygen saturation and especially oxygen tension during whole-body exercise may be important (Dempsey and Wagner 1999). However, exposure to high altitude hypoxaemia increases haemoglobin production, but the acute increase in haematocrit is caused by loss of plasma volume (Heinicke et al. 2003). Conversely, end-stage kidney disease is associated with anaemia 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 hypoxaemia stimulus for erythropoietin production, may stimulate haemoglobin production via sympathetically induced reduction in kidney blood flow (Bodary et al. 1999). In rowers, for whom arterial hypoxaemia is prevalent (Nielsen et al. 2002), approximately 10% of the athletes present with a haematocrit above the 'doping' limit of 50% applied to, e.g. cycling (Johansson et al. 2009). The increase in total haemoglobin is an important adaptation to training because

$\dot{V}O_{2\,max}$ is related to haemoglobin mass (Heinicke et al. 2001). In an apparent paradox, athletes often present somewhat low haemoglobin concentrations (or haematocrit: 44 vs. 46% in untrained) because of the enlarged plasma volume. For athletes plasma and red cell volume may be 61 and 46 ml kg^{-1}, respectively, compared to reference values of 46 and 33 ml kg^{-1}, respectively, for men (Heinicke et al. 2001) and training-induced increase in both plasma volume and red cell mass support preload to the heart.

During exercise, central blood volume contributes to the level of sympatho-excitation established as reflected by f_c. For example, at supine rest f_c may be 60 beat min^{-1} and increase to 80 beat min^{-1} when standing but f_c decreases 10 beat min^{-1} during contraction of the leg muscles in the upright position (Van Lieshout et al. 2001). 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 (Ray et al. 1993; Van Lieshout et al. 2001; Secher 2009). 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 f_c increase in response to exercise is observed in the supine position (Stenberg et al. 1967). Thus, there is a lower f_c during rowing compared to running despite the higher $\dot{V}O_{2\,max}$ established by the larger active muscle mass during rowing (Fig. 2) (Yoshiga and Higuchi 2002). Similarly, the lowering of f_c both at rest and during exercise in response to endurance training likely resembles the positional effect on central blood volume (Ogoh et al. 2003).
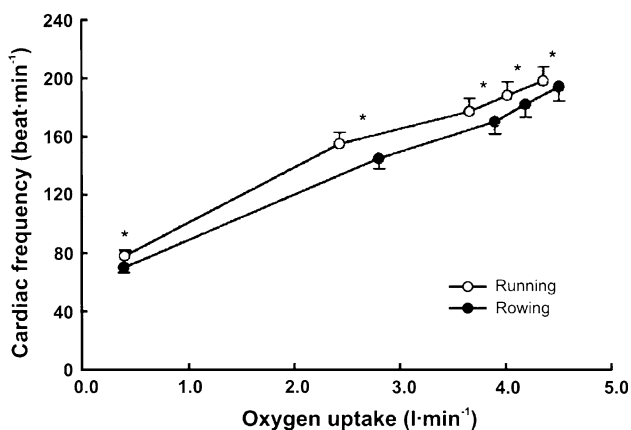
Fig. 2 Lower cardiac frequency during rowing versus running despite a higher oxygen uptake while rowing. Cardiac frequency rowing versus running (*$P < 0.05$). Modified from Yoshiga and Higuchi (2002)

Blood volume encompasses both red cell mass and plasma volume 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 (Saltin et al. 1968; Alfrey et al. 1996). 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 (Secher 2009).

The effects of training on a subject's tolerance to orthostatic stress are less clear with reports indicating improvement, no change or even deterioration (Stegemann 1976; Convertino 1987, 1993). 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 (Fu et al. 2004). This may be of benefit when exercising but it leads to a considerable reduction in stroke volume during orthostasis (Levine et al. 1991). Ogoh et al. (2003) 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 $\dot{Q}$ 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 hypovolaemia and possibly cardiac atrophy (Pawelczyk et al. 2001), 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 (Van Lieshout 2003). In practice, extreme levels of aerobic fitness associated with orthostatic intolerance are likely to be achieved only by elite military personnel or athletes (Ogoh et al. 2003). 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 (Ogoh et al. 2003). In moderately fit individuals improvement of the aerobic capacity usually enhances orthostatic tolerance (Carroll et al. 1995; Mtinangi and Hainsworth 1999).

Thus, it seems reasonable to advise exercise training to people who do not easily tolerate standing but to what

extent is less certain (Wieling et al. 2002b; Van Lieshout 2003). In addition to the effects of increasing aerobic capacity, resistance training (weight lifting) may reduce venous pooling by increasing muscle tone (Lightfoot et al. 1994; Mayerson and Burch 1940). In contrast, e.g. swimming training does not lead to greater orthostatic tolerance than training for running (Franke et al. 2003). The opposite effects may be seen following prolonged inactivity (Menninger et al. 1969; Convertino et al. 1989). Improving the aerobic capacity of moderately fit individuals increases the plasma volume and is usually associated with improved orthostatic tolerance (Wieling et al. 2002b). The beneficial effect of a training programme in improving orthostatic tolerance was demonstrated in identical twins who fainted during passive tilting. After a 3-week training program applied to one of them, a subsequent head-up tilt-induced faint could be elicited in the untrained twin only (Allen et al. 1945). 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' (Greenleaf et al. 1981).

Haemorrhage

The changes in f_c and arterial pressure during a progressive reduction in central blood volume by haemorrhage illustrate how central blood volume can be followed in humans (Jacobsen and Secher 1992; Secher et al. 1992). The first documented observations are from World War II in air raid casualties with hypovolaemic shock (Grant and Reeve 1941; McMichael 1944), in volunteers bleeding large amounts (Shenkin et al. 1944), and in patients with serious haemorrhagic shock where the finding of a low f_c was unexpected (Van Lieshout and Secher 1999; Kinsella and Tuckey 2001).

During the first stage of haemorrhage, corresponding to a reduction of the blood volume by approximately 15%, a modest increase in f_c (<100 beats min^{-1}) and total peripheral resistance compensate for the blood loss with maintenance of a near normal arterial pressure (Schadt and Ludbrook 1991; Jacobsen and Secher 1992). The second stage is marked by a decrease in f_c, total peripheral resistance and arterial pressure when the central blood volume becomes reduced by $\sim$30% attributed to a Bezold–Jarisch-like reflex (Jarisch 1941; Murray et al. 1968; Matzen et al. 1991; Esler et al. 1995). 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 (Jacobsen and Secher 1992; Kirkman and Little 1994). Sander-Jensen et al. (1986) showed in patients

with serious blood loss f_c was initially low and increased only after repletion of the volume deficit. This observation underscores that the traditional teaching that haemorrhage is diagnosed easily by a reflex tachycardia and a low arterial pressure is not legitimate.

Values for arterial pressure and f_c 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 (Eckberg and Sleight 1992) but may be less relevant in old healthy subjects (Secher and Van Lieshout 2010) in whom f_c changes during post-exercise hypotension are insignificant (Murrell et al. 2010). Cardiac stroke volume and $\dot{Q}$ still play a subservient role although it is flow, not pressure that the tissues are in need of (Nichols and O'Rourke 2005). For instance, in patients with septic shock, artificially increasing mean arterial pressure beyond $\sim$65 mmHg does not improve established variables of tissue perfusion (LeDoux et al. 2000). 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 hypovolaemic shock (Wiggers 1950; Chien 1967) contrasts to the non-linear relationships of f_c and arterial pressure with a volume loss in both humans (Murray et al. 1968; Sander-Jensen et al. 1986) and animals (Rasmussen et al. 1999; Krantz et al. 2000).

Normovolaemia

According to studies in humans at rest and under different types of environmental stress, a functional definition of 'normovolaemia' 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 (Ejlersen et al. 1995b). Thus, hypovolaemia may be characterised by a reduced preload to the heart, i.e. with stroke volume and $\dot{Q}$ becoming dependent on central blood volume. A sensitive and specific measure of early reductions in central blood volume is stroke volume (Cooke et al. 2004) and documenting that stroke volume increases with volume loading is taken to imply that a patient is preload-responsive (Pinsky 2002). In contrast, the intravascular volume may be expanded beyond the volume that can provide for a 'maximal' $\dot{Q}$ at rest. By interpolation between hypo- and hypervolaemia, functional normovolaemia is the point in the cardiac preload–output relationship at which $\dot{Q}$ does not increase further under circumstances where venous return is unimpeded (Van Lieshout et al. 2005).

Applications to clinical medicine

In clinical medicine central blood volume rather than the total blood volume is to be balanced between hypovolaemic shock and development of pulmonary and peripheral oedema. With the functional perspective of normovolaemia, volume treatment should be provided to secure a resting $\dot{Q}$ that is not preload limited (Secher and Van Lieshout 2005; Bundgaard-Nielsen et al. 2007a). 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 (Vatner 1974; Cooke et al. 2004), vascular resistance and blood volume (Ludbrook 1969), 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 (Secher and Van Lieshout 2005). 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 (Immink et al. 2004). Conversely, even a normal mean arterial pressure may induce cerebral hyperperfusion and death in a patient with acute liver failure (Larsen et al. 1995). 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 $\dot{Q}$ is restricted and challenges mean arterial pressure, flow to exercising muscles, and to the brain, becomes limited (Secher et al. 2008). 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 $\dot{Q}$ independent from arterial pressure, maintaining $\dot{Q}$ may prevent undetected cerebral hypoperfusion and monitoring of $\dot{Q}$ 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 $\dot{Q}$ are related to either central venous pressure, mean pulmonary artery pressures or pulmonary artery wedge pressure (Levine et al. 1991; Perhonen et al. 2001). 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 (Thys et al. 1987; Levine et al. 1991). Recent studies have questioned the correlation between these estimates of ventricular filling pressures and $\dot{Q}$; 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 (Kumar et al. 2004). 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 (Van Lieshout et al. 2005). These findings question central venous pressure and pulmonary artery wedge pressure as useful predictors of ventricular preload (Godje et al. 1998) and support the notion that the function of the heart relates to its volume rather than to its so-called filling pressures (Van Lieshout et al. 2005).

The classical method for determination of central blood volume is by a dye dilution estimate of $\dot{Q}$ with a concomitant determination of transit time (Sjöstrand 1953). The tight coupling of $\dot{Q}$ with the filling volume of the heart, even in situations where a relationship between $\dot{Q}$ and central filling pressures is lost, illustrates the feasibility of evaluation of cardiac preload by echocardiography (Thys et al. 1987). 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 (Nijboer 1970; Cai et al. 2000a, b; Krediet et al. 2006). 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 (Fig. 3).

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 anaesthetic drugs applied in spinal and epi(peri)dural anaesthesia reduce the central blood volume (Arndt et al. 1985) as a result of redistribution. Establishment of normovolaemia to maintain an optimal oxygen delivery to organs is intuitively rational. Whereas standard monitoring of f_c 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 (Holte et al. 2002) affecting post-operative outcome (Lobo et al. 2002; Brandstrup et al. 2003; Nisanevich et al. 2005). Consequently, to avoid both hypovolaemia and fluid overload in surgical patients, fluid therapy with individual maximization of flow-related haemodynamic variables, so-called goal-directed therapy, has been introduced (Bundgaard-Nielsen et al. 2007b).

With individualized goal-directed therapy, a volume (usually a synthetic colloid) is administered in amounts of
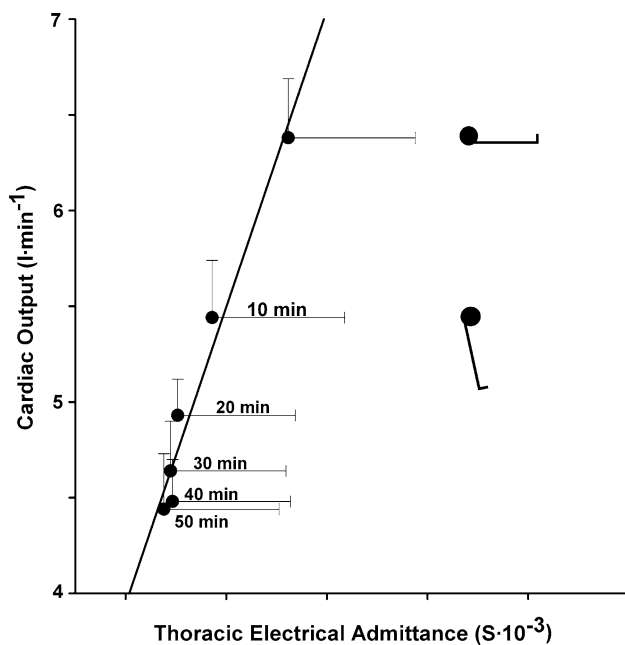
Fig. 3 Left ventricular stroke volume and thoracic electrical admittance. Relationship between cardiac output and preload (thoracic admittance) during progressive central hypovolaemia by passive head-up tilt at 60° in 9 healthy humans (1 female) with median age 29 (range 22–39) years, height 183 (170–191) cm, and weight 75 (68–82) kg. 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. (2005)

200–250 ml challenges. If stroke volume increases ≥10% the patient is regarded as being on the ascending part of the cardiac function curve (Fig. 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 (Grocott et al. 2005; Bundgaard-Nielsen et al. 2007a). In this context, peri-operative maximization of cardiac stroke volume by means of fluid therapy improves post-operative outcome after femoral fractures (Sinclair et al. 1997; Venn et al. 2002), general (Gan et al. 2002; Pearse et al. 2005), cardiac (Mythen and Webb 1995; McKendry et al. 2004) and major bowel surgery (Conway et al. 2002; Wakeling et al. 2005; Noblett et al. 2006). Goal-directed therapy reduces gastro-intestinal complications, overall complication and hospital stay (Bundgaard-Nielsen et al. 2007a). The reduction of complications especially in the splanchnic system may be explained by improved perfusion of its vasculature (Mythen and Webb 1995) 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 (Jans et al. 2008; Bundgaard-Nielsen et al. 2009a, b). In this context it is
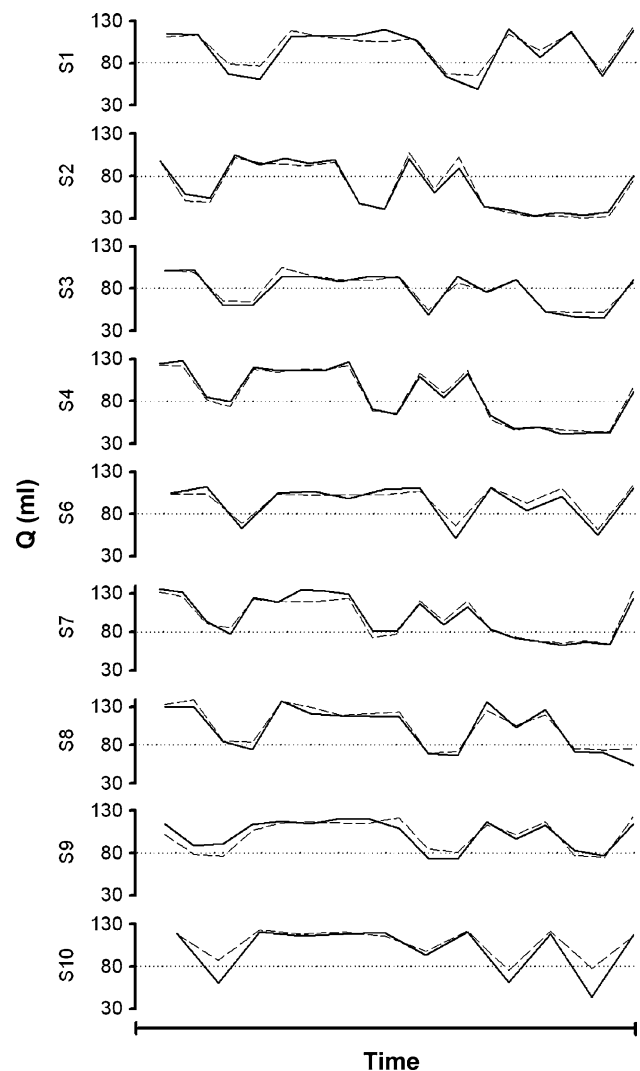
Fig. 4 Non-invasive stroke volume tracking during orthostatic variations in central blood volume. Tracking of a thermodilution estimate of stroke volume (Q, *solid line*) by Modelflow stroke volume (*broken line*) from non-invasive finger blood pressure (Finapres); averaged values obtained in 10 healthy subjects. Central blood volume was manipulated by passive (tilt) and active (standing) changes in body position. Direction of changes in stroke volume is reciprocal to body position (head-up vs. supine). Modified from Harms et al. (1999)

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 (Jenstrup et al. 1995; Ejlersen et al. 1995a; Bundgaard-Nielsen et al. 2009a, b). Use of the goal-directed approach is, however, challenged by the invasiveness of traditional monitoring modalities of stroke volume and $\dot{Q}$. The thermodilution technique is the accepted clinical method of estimating $\dot{Q}$, but it is discontinuous and requires the presence of a pulmonary artery catheter for as long as monitoring of $\dot{Q}$ 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 (Bundgaard-Nielsen et al. 2007b; Kehlet and Bundgaard-Nielsen 2009). Ultrasound (Sugawara et al. 2003; Van Lieshout et al. 2003a) and pulse wave analysis or stroke volume modelling either non-invasively from finger pressure (Eeftinck Schattenkerk et al. 2009) or from intra-arterial pressure (Antonutto et al. 1994; Harms et al. 1999; Nissen et al. 2009b) posses the potential to track beat-to-beat changes in stroke volume and $\dot{Q}$ in humans as initiated by postural fluid shifts (Fig. 4) (Harms et al. 1999). 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 (Lopes et al. 2007).

Conclusions

Environmental stress including posture, microgravity, heat, exercise haemorrhage and shock affect preload to the heart and, consequently, stroke volume and $\dot{Q}$. Both at rest and during exercise, $\dot{Q}$ is preload dependent in upright humans, which results in sympathetic activation with an increase in f_c 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 normovolaemia 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.

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