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Cardiovascular function after long-term bed rest

by

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ABSTRACT

On earth, daily activities involve standing, changes of posture and various types of muscle action, all of which challenge the cardiovascular regulation. Removal of the orthostatic stress for a longer period, as during spaceflight or head-down tilt bed rest, consistently results in cardiovascular deconditioning.

The principal aim of this thesis was to improve the understanding of cardiovascular deconditioning, as reflected in altered structure and control after long-term spaceflight and bed rest. Apart from an initial methodological study, all results are based on two head-down tilt bed rest experiments with durations of 42 and 120 days, and on five spaceflights with durations of 6 to 13 months.

In the initial study, the separate effects of voluntary motor activation and muscle chemoreflex activation on arterial baroreflexes in healthy young men were examined. It was found that the elevation of arterial blood pressure is mainly caused by muscle ischemia, whereas the heart rate response is entirely due to somatomotor activation.

These conclusions provided a basis for the following study, aiming to characterized the cardiovascular responses to isometric muscle action during and after spaceflight and after bed rest. The responses to isometric lower arm contraction were determined, and it was concluded that impaired cardiovascular responses to isometric muscle action do contribute to the cardiovascular deconditioning after spaceflight and bed rest.

In the two bed rest studies, cardiac output (CO) and stroke volume (SV) were determined, and marked reductions were found in both CO and SV, in both supine and upright posture, during rest and during 50 watt pedalling. The time-course of the deconditioning and recovery of SV in the different conditions indicates that SV reductions in the upright posture after bed rest are mainly due to an impaired preload, and recuperate swiftly as plasma volume recovers. On the other hand, SV reductions in the supine posture during exercise, showed a slow, progressive decline during bed rest, and a protracted recovery after bed rest, strongly suggesting an altered cardiac morphology and probably a decreased heart size.

In the 120-day bed rest study, impairments in blood-pressure control during rest and exercise were also assessed. It was found that bed rest causes markedly increased blood-pressure deviations during rapid tilts at exercise, indicating impaired reflex and/or effector organ function. Furthermore, it was found that bed rest causes attenuated baroreflex sensitivity for chronotropic responses to arterial pressure stimuli, although this appears to be of modest functional significance. The finding of a reduced degree of mechanical interaction between the two ventricles provided indirect evidence of reduced cardiac size during and after bed rest. Hemodynamic and baroreflex impairments had similar time courses, suggesting that reductions of cardiac size may be a common denominator for both of these types of hemodynamic and baroreflex impairments. Despite these changes, the ability to maintain the arterial blood pressure during steady-state conditions was found to be preserved after bed rest

Keywords: microgravity, simulated weightlessness, carotid baroreflex, static exercise, muscle chemoreflex, orthostasis, tilting, leg exercise, blood pressure, heart rate, stroke volume

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LIST OF ABBREVIATIONS

CDP	Carotid distending pressure
CO	Cardiac output
CVP	Central venous pressure
DARP	Diastolic arterial receptor pressure (halfway between carotid level and heart level)
EMG	Electromyogram
HDT	Head down tilt bed rest
HR	Heart rate
LBNP	Lower body negative pressure
LVEDV	Left ventricular end diastolic volume
MAP	Mean arterial pressure
MAPH	Mean arterial pressure at the level of the heart
MARP	Mean arterial receptor pressure
MSNA	Muscle sympathetic nerve activity
PP	Arterial pulse pressure
SARP	Systolic arterial receptor pressure (halfway between carotid level and heart level)
SE	Standard error of the mean
STPD	Standard temperature and pressure dry
TPC	Total peripheral conductance
TPR	Total peripheral resistance
TTI	Trans-thoracic impedance
$\dot{V}O_{2max}$	Maximal oxygen uptake
W	Watt

INTRODUCTION

REST IN BED have been a most regular prescription, and innumerable patients have been sent to bed for rehabilitation and restoration of health. Still at this date, the general public entertain the notion that if you are sick, you should stay in bed.

The Second World War seemed to spur the understanding that bed rest, although necessary in many cases, in it self is accompanied by cardiovascular deconditioning and muscular atrophy. After the War, in 1944, Dr. T. R. Harrison (1944) chaired a symposium on "The Abuse of Rest in the Treatment of Disease". This symposia came to mark the beginning of the "early ambulation" practice for hospitalised patients, and the medical community began to realize that the common, very extensive bed rest regimens were often of more harm than good (Keys 1945; Asher 1947). During the following years a small number of studies took place that demonstrated cardiovascular and muscular deconditioning during prolonged bed rest (Taylor *et al.* 1945; Taylor *et al.*1949).

In the early 1960s, the American and Russian Space Race commenced. Development of technology needed for spaceflight have produced thousands of "spin-offs" that contribute to improving everyday life ((http://www.sti.nasa.gov/tto/). In the medical community, space related research have helped to develop CAT-scans, MRI, dialysis and advanced pacemakers (Anonymous 2000; Halberg *et al.* 1999).

This enormous technological endeavour was naturally accompanied by medical research concerning whether humans could endure extended periods of microgravity; for a historical review see (West 2000). One of the most significant physiological findings from the Space exploration is undoubtedly that humans actually adapt quite well to microgravity, and can stay, function and work in space for extended periods of time (Graveline and McCally 1962).

The Space Race also boosted research on the physiological effects of long-term bed rest, since bed rest mimics microgravity by reducing (but not eliminating) the hydrostatic gradients that act upon the body. It was shown that bed rest is a fairly good model of microgravity regarding both muscular and cardiovascular effects (Miller *et al.* 1964), and during the following years a number of experimenters studied the effects of bed rest (Vogt *et al.* 1965; Vallbona *et al.* 1967; Saltin *et al.* 1968; Hyatt *et al.* 1969; Schiefeling 1969), including various methods to prevent cardiovascular deconditioning (Miller *et al.* 1965; Chase *et al.* 1966; Stevens *et al.* 1966a; Stevens *et al.* 1966b; Stevens *et al.* 1966c; Vogt 1966).

Thus, medical microgravity research has significantly improved our understanding of human physiology (Sulzman 1996); for reviews on adaptations to microgravity see Charles and Lathers (1991), Blomqvist (1996) and Fortney *et al.* (1996). Furthermore, due to the fortunate analogy between microgravity and bed rest, the microgravity research also turns-out to be most relevant for all bed ridden patients back on Earth.

A number of excellent reviews have been written regarding normal

cardiovascular control and function (*e.g.* Blomqvist 1983; Rowell 1996), and regarding cardiovascular function after bed rest and spaceflight (*e.g.* Charles and Lathers 1991; Blomqvist 1996; Convertino 1996a; Fortney *et al.* 1996; Watenpaugh and Hargens 1996).

The following sections of the introduction review previous findings that are of most relevance to put the present thesis in appropriate perspective. The review focuses on both long-term spaceflight and bed rest, due to their striking analogy. Only a few references are given to Russian original research due to the limited availability in the English language, instead review papers are quoted .

Hemodynamic consequences of spaceflight and bed rest

Gauer and Thron (1965) proposed that the normal state in humans is that in upright posture, and that the setpoints for cardiovascular variables are those in the upright posture. Results from spaceflight and bed rest support this, in as much as most cardiovascular variables assume values closer to those in the upright posture, than the initial supine values after some adaptation. This notion is quite appealing, considering that humans have adapted to hunt, run, fight and flight in the upright posture for about 6 million years (Senut *et al.* 2001). Therefore, the cardiovascular regulation in human is quite unique due to our upright posture Only a few animals experience similar hydrostatic pressure gradients (Burggren *et al.* 1997). For that reason, animal experiments are only mentioned in this thesis when clearly relevant.

Adaptations to spaceflight and bed rest are not harmful *per se*, however, functional limitations arise when resuming normal activity and posture. The term cardiovascular deconditioning (Keys 1945) usually describes a combination of reduced exercise capacity and orthostatic intolerance that ensues when assuming upright posture after bed rest or spaceflight.

Several studies, most of them Russian, have suggested that bed rest in a -4° to -8° head down tilt (HDT) position causes a more rapid and somewhat larger changes than horizontal bed rest, and thus closer mimic the changes during spaceflight (Kakurin *et al.* 1976; Fortney *et al.* 1996, pp. 892-893). Therefore, most bed rest experiments after the mid 1970s have been performed in the head-down tilt position, also the investigations in the present thesis.

Many researchers seek to model the cardiovascular system in hydraulic or mechanical system, and rightly so. One must keep in mind, however, that the human body is not mechanical, but chemical. All processes are in essence chemical reactions in a fluid environment, and in all cells there is a continuous replacement of proteins and molecules. These processes directly cause the proteins, cells, tissues and organs to adapt to shifting demands. Both spaceflight and bed rest lead to significant adaptive changes, of which a few may be of concern when returning to normal gravity, or upright posture.

Plasma volume loss

When moving from upright to supine position, approximately 700 to 900 ml of blood is redistributed from the lower body into the central

circulation (Fortney *et al.* 1996, p. 891; Rowell 1996). Most of this is diverted to the heart and the lungs, and central venous pressure (CVP) reaches a maximum around 1.9 cm H_2O above baseline after 30 min (Nixon *et al.* 1979). And, as stated by the classical Starling relationship, cardiac output increase immediately by 20% to 30% (Bevegård *et al.* 1960; Soubiran *et al.* 1996). This stimulates an increased diuresis within a few hours that reaches a maximum early the first day (Maillet *et al.* 1994), and returns to pre-bed rest levels within three days (Graveline and McCally 1962). CVP, however, return to pre-head down tilt values after only 90 min (Nixon *et al.* 1979). Thus, the fast return in CVP is not dependent on diuresis, but rather on increased cardiac output, and decreased arterial and venous tone (Essandoh *et al.* 1987; Pannier *et al.* 1991).

The plasma volume reduction during bed rest averages 15%. Most of that reduction occurs during the first 24 hours, and it is fully developed within two to three days. After that a corresponding loss of red blood cells and haemoglobin occurs (Greenleaf *et al.* 1977; Convertino 1996b; Johansen *et al.* 1997; Drummer *et al.* 2000). Until recently, the same was thought to take place upon entering microgravity during spaceflight. However, it has been shown that CVP is not increased, but decreased immediately upon entering microgravity (Buckey *et al.* 1993), and that this decrease persists for hours to days (Kirsch *et al.* 1984; Kirsch *et al.* 1986). The decrease in CVP occur despite an experienced fluid shift to the central circulation, that begins already in the pre-launch position (Linnarsson *et al.* 1998), with facial puffiness appearing during the first day in space (Thornton *et al.* 1977; Vorobyov *et al.* 1983). It is possible that a different configuration of the thorax can explain this. As the chest relaxes in microgravity, it becomes more spherical and this could increase intrathoracic volume (White and Blomqvist 1998), enabling an increased central blood volume despite decreased CVP. However, this hypothesis is not unchallenged (West and Prisk 1999). The facial puffiness gradually disappears during the following days (Vorobyov *et al.* 1983), probably reflecting the decrease in plasma volume and total body water. Thus, the exact mechanisms behind the reduced plasma volumes during spaceflight and bed rest remain undefined. Historically, the reductions were attributed to the Gauer-Henry reflex (Gauer and Thron 1965), whereby an increased central blood volume increases CVP and stimulates cardiopulmonary low-pressure baroreceptors. Vagal afferents then inhibits hypothalamic vasopressin release. However, it seems that central blood volume, and not CVP is the primary regulated variable in humans, and that cardiopulmonary baroreceptors are more sensitive to volume than to pressure (Fortney *et al.* 1996, pp. 896-898). Besides, an increased central blood volume does not necessarily cause increased CVP (White and Blomqvist 1998). Furthermore, in primates it has been shown that several parallel systems contribute to the volume regulation, and selective blockade of one or more of these only have minor effects (Fortney *et al.* 1996, pp. 896-898). Thus, in humans it is likely that several systems, cardiopulmonary reflexes, atrial reflexes (atrial natriuretic peptide), renal reflexes (urodilatin), arterial

baroreflexes, intracranial regulatory system, and possibly others, all aid to maintain a constant central blood volume (Convertino *et al.* 1990b; Fortney *et al.* 1996, p. 896).

Impaired muscle function

Spaceflight and bed rest without extensive countermeasures all result in reductions of muscular strength and increased fatigability, where postural muscles are affected the most (Convertino 1996a, pp. 821-823).

Already in 1949, Taylor *et al.* (1949) described that three to four weeks of bed rest caused an impaired hand coordination, which indicates an impaired neuromuscular performance. However, they did not find significantly reductions in maximal handgrip strength. Also, after 6 weeks HDT, Berg *et al.* (1997) showed a somewhat greater loss of strength in isometric knee extension relative to the reduction in muscle cross sectional area , and found that maximal EMG decreased, but sub maximal EMG increased for a given load. This activation pattern suggests a decreased neuromuscular performance. Antonutto *et al.* (1999) found reductions in maximal explosive power of the lower limbs to 67% of pre-flight values after one-month spaceflight (one subject) and to 45% after six-month spaceflight (three subjects) . In the same subjects the muscle mass of the lower limbs assessed by MRI decreased by only 9-13%, irrespective of flight duration (Zange *et al.* 1997). These data indicate that the decreased muscular performance after spaceflight and bed rest is at least partly due to a modification of muscle control and motor unit recruitment, and it has been thought that a decreased demand on the musculature results in an initial decline in the neural control of the muscle, followed by a reduction in muscle mass. However, contrary to these studies, Ferretti *et al.* (2001) found no decrease in power related to cross sectional area in thigh muscles after 42 days HDT. Thus, this issue remains controversial.

Cardiac impairment

Recently Perhonen *et al.* (2001b) described cardiac volume and mass reductions after spaceflight, and after bed rest. They used gated MRI, which is considered the gold standard for the assessment of myocardial mass (Devereaux *et al.* 1997). They studied four astronauts after 10 days of spaceflight, without inflight exercise as countermeasure, and they found a strong tendency to reductions in cardiac mass (LV mass) by 12±6.9% ($p=0.07$). They also studied five subjects during bed rest, and left ventricular end diastolic volume (LVEDV) decreased by 14±1.7% after two weeks, and remained decreased at a similar level to the end of the study (6 to 12 weeks). Left ventricular mass decreased by 8.0±2.2% after 6 weeks with an additional atrophy of 7.6±2.3% in three subjects who remained in bed for 12 weeks.

Several earlier studies have shown impaired cardiac function after spaceflight and bed rest, and thus indicated morphological changes that Perhonen *et al.* (2001b) have defined. Saltin *et al.* (1968) demonstrated decreases in cardiac output and stroke volume in five men during maximal dynamic exercise after 20 days bed rest, and noted a similar tendency to decrease during rest. The decrease in stroke volume was relatively larger than the decrease in heart volume, which suggests an altered cardiac morphology.

Furthermore Levine *et al.* (1997) showed that two weeks of HDT leads to decreased stroke volume and a less distensible ventricle.

Echocardiography studies after 84 days spaceflight suggested decreased left ventricular mass in three out of four astronauts (Henry *et al.* 1977). In addition, two later studies have shown significantly decreased LVEDV and stroke volume during five months and 25 days spaceflight respectively (Herault *et al.* 2000; Arbeille *et al.* 1992).

In another study by Perhonen *et al.* (2001a) they compared seven men who undertook two weeks of HDT, with a control group that received intravenous furosemide to induce hypovolemia in them to the same extent as in the HDT group. The authors found steeper Starling-curves in the HDT subjects than in the control-group, and they also found a leftward shift in the pressure-volume curves and decreased lower-body negative pressure (LBNP) tolerance in the HDT subjects. Their results demonstrated that, in addition to a reduction in plasma volume, presumably a ventricular remodelling takes place during HDT. This remodelling was shown to render a greater reduction in stroke volume during orthostatic stress (*i.e.* lower-body negative pressure) after HDT than during hypovolemia alone, which would augment orthostatic intolerance.

To conclude, all current evidence show that spaceflight and bed rest, if performed without extensive countermeasures, cause myocardial atrophy. Morphological data are for understandable reasons not available from humans. However, animal experiments have shown myocardial degeneration with decreased cell cross sectional area in rat after 14 days spaceflight and after 14 days hind limb suspension (Goldstein *et al.* 1992), altered myocardial structure after 12,5 days of spaceflight (Philpott *et al.* 1990), and increased cardiac compliance in monkeys after bed rest (Koenig *et al.* 1998).

The cellular mechanisms behind the reduced mass remain unclear. It may be caused by a reduction in myocardial cell size or by induced cell death (*i.e.* apoptosis). Apoptosis occurs in both cardiac (Narula *et al.* 1996; Olivetti *et al.* 1997) and in skeletal myocytes in heart-failure patients (Adams *et al.* 1999). If spaceflight and bed rest induce apoptosis, it could be a most serious consequence since it is generally considered that cardiac myocytes are unable to divide. On the other hand, new findings indicate that cardiac myocytes may have potential for regeneration (Kajstura *et al.* 1998). Taken together, cardiac muscle, as well as skeletal muscle, has been shown to be an adaptive organ, with potential for plastic changes (Sieck and Regnier 2001). Form follows function, and demand determines shape, size and contractile properties of both cardiac (Russell *et al.* 2000) and skeletal muscle (Fitts *et al.* 2000; Russell *et al.* 2000).

As an interesting parallel, Katsume *et al.* (1992) demonstrated markedly smaller left ventricular dimensions in both end-diastole and end-systole and smaller left atrial dimensions in chronically bedridden elderly patients, compared to age matched control subjects. Opposite effects are caused by exercise and training, where cardiac hypertrophy is common (Pluim *et al.* 2000). As little as six weeks of moderate training by sedentary individuals

increases left ventricular mass (Shapiro and Smith 1983). These increases are reversible, and the hypertrophy recedes in a similar amount of time when training is discontinued. Furthermore, highly trained athletes who voluntarily reduced their training for 6 to 34 weeks showed significant decreases in ventricular septal thickness (Maron *et al.* 1993). These studies further emphasize that the cardiac muscle is a dynamic tissue, able to respond and adapt to shifting demands in a relatively short time.

Reduced exercise capacity

Long-term bed rest (*i.e.*, with a duration of several weeks) results in reduced supine and upright exercise capacity (Taylor *et al.* 1949; Ferretti *et al.* 1998) and reduced maximal O_2 consumption ($\dot{V}O_{2max}$) (Chase *et al.* 1966; Convertino *et al.* 1985; Kashihara *et al.* 1994; Levine *et al.* 1996; Ferretti *et al.* 1997). In a review of 19 independent bed rest studies, Convertino (1996a) showed that $\dot{V}O_{2max}$ decrease by about 0.85% per day of bed rest, with reductions ranging from -14 to -35% after 28 to 30 days of bed rest . Few studies have been performed on the exercise capacity after spaceflight. Data from early long-term spaceflights indicate maintained exercise performance during extended spaceflight (Rummel *et al.* 1976; Vorobyov *et al.* 1983), although reductions are common immediately post flight. The difference compared to bed rest is most likely explained by the extensive exercise protocols employed during spaceflight, in contrast to the absolute rest during bed rest experiments. The $\dot{V}O_{2max}$ would most certainly be reduced without inflight exercise, considering the reduced blood volume, muscle mass, and cardiac and vascular impairments (Watenpaugh and Hargens 1996, p. 651).

Both muscular and cardiovascular changes contribute to the reduction in exercise capacity, yet cardiovascular limitations appear to play the greater role: Ferretti *et al.* (1997) modelled the relative contribution from the factors limiting $\dot{V}O_{2max}$ in man after HDT and estimated the cardiovascular contribution to at least 70%. Thus, a key factor contributing to the decreased exercise capacity is an impaired O_2 transport (Saltin *et al.* 1968; Hung *et al.* 1983; Ferretti *et al.* 1998).

Cardiovascular control after spaceflight and bed rest

Several studies have shown an altered autonomic balance during spaceflight and bed rest, for reviews see Leach *et al.* (1983) and Shoemaker *et al.* (1998b). In-flight muscle sympathetic nerve activity (MSNA) measurements during a 16-day long spaceflight showed, contrary to what could be expected, an increased activity throughout the full flight duration (Ertl 1998). During bed rest, the reported results regarding sympathetic activation vary substantially. Several shorter studies describe attenuated MSNA burst frequency (Shoemaker *et al.* 1998b), reduced circulating noradrenaline (Convertino *et al.* 1998) or reduced urinary catecholamine excretion (Goldstein *et al.* 1995; Sigaudo *et al.* 1998). Others have found increased MSNA (Kamiya *et al.* 2000b). Increased levels of catecholamines are consistently found on the landing day after spaceflight, but is presumably related to the increased stress levels during the landing procedure, and may not reflect values during

spaceflight (Fritsch-Yelle *et al.* 1994; Whitson *et al.* 1995).

After longer exposure though, Kamiya *et al.* (2000a) found increased MSNA both during (day 60) and immediately after a 120 day long bed rest. Thus, it is possible that both spaceflight and bed rest causes an initial attenuation of sympathetic activity, lasting for days to weeks, followed by a state of increased activity. Other studies also suggest altered autonomic control after spaceflight and bed rest. Convertino *et al.* (1997b) studied the vascular responses to sympathetic stimuli after 14 days of bed rest, and found altered heart rate and vasoconstrictor responses suggesting an increased β_1 and β_2 receptor sensitivity, without affecting vascular α_1-responses. An altered balance between cardiac and vascular sensitivity to sympathetic stimuli could lead to elevated heart rate and insufficient vasoconstriction upon orthostatic stimuli. Cooke *et al.* (2000) found indices of reduced cardiac vagal activity after nine months spaceflight, and Kamiya *et al.* (2000b) demonstrated an imbalance between sympathetic vasoconstrictor traffic and nitric oxide release that might contribute to elevated peripheral vascular resistance following bed rest.

An interesting difference has been found during stand tests on the landing day between orthostatic intolerant subjects who exhibit significantly lower adrenergic responses than orthostatic tolerant subjects (Fritsch-Yelle *et al.* 1996). Similarly, Shoemaker *et al.* (1999) found blunted MSNA responses to orthostatic stimuli in orthostatic intolerant subjects, compared to responses in orthostatic tolerant subjects after 14 days bed rest.

Cardiopulmonary baroreflex resetting

Peripheral vasoconstriction is mainly controlled by the cardiopulmonary baroreflex (Johnson *et al.* 1974;Abboud *et al.* 1979), and reflex peripheral vasoconstriction is the key mechanism of increasing total peripheral resistance (TPR), so that vasoconstriction defends arterial blood pressure during orthostatic challenges. HDT, and the associated reduction in CVP, may cause the cardiopulmonary baroreflex stimulus-response relationship, as assessed by LBNP, to shift so that responses for peripheral vascular resistance (Convertino *et al.* 1994) and heart rate (Crandall *et al.* 1994) occur in a lower range of CVP values. An autonomic resetting of low-pressure baroreceptors to operate at lower CVP would be potentially compromising, since the vascular system is satiable, having only a limited vasoconstrictive capacity. Both the resetting and increased sensitivity of the cardiopulmonary baroreflex might cause reduced reserve capacity for further vasoconstriction. On the other hand, Baisch *et al.* (2000) argue that most of the altered responses to LBNP during microgravity may be explained by the fluid deficit alone.

Arterial baroreflex impairment

The arterial blood pressure is closely controlled by the arterial baroreflex, which receives inputs mainly from aortic and carotid baroreceptors. In normal subjects, the arterial baroreflex will buffer deviations from the desired arterial pressure by raising vascular tone to increase total peripheral resistance (TPR), and by increasing heart rate and cardiac output (Eckberg *et al.* 1992; Shi *et al.* 1993). During spaceflight and bed rest, the

baroreceptors still receive stimuli from the continuous arterial pulsations during the heart cycle, but all pressure changes due to posture are eliminated. This decrease in stimulation has been shown to reduce the carotid-cardiac chronotropic baroreflex sensitivity during rest, after bed rest (Convertino *et al.* 1990a; Engelke *et al.* 1995) and after spaceflight (Fritsch *et al.* 1992; Fritsch-Yelle *et al.* 1994).

Only two studies have been performed on the arterial-cardiac chronotropic baroreflex sensitivity during exercise after bed rest; Haruna and Suzuki (1997) and Sundblad *et al.* (2000b). In contrast to previous studies on resting subjects (Convertino *et al.* 1990a) (Convertino *et al.* 1992; Fritsch *et al.* 1992; Fritsch-Yelle *et al.* 1994), the baroreflex sensitivity was found to be unchanged after 20 and 42 days of HDT, respectively, in the two studies during exercise.

In addition, Haruna and Suzuki (1997) tested the baroreflex sensitivity during sitting and supine rest and found that post-HDT sensitivity was reduced when tested in supine rest but not during sitting rest and not, as already mentioned, during exercise.

Arterial structure and control

Previous studies indicate that impaired vascular responses to upright posture may contribute to post-spaceflight orthostatic intolerance (Buckey *et al.* 1996a; Fritsch-Yelle *et al.* 1996; Saltin *et al.* 1968; Shoemaker *et al.* 1998a)

In a classical experiment, Saltin *et al.* (1968) found an increased arterio-venous oxygen difference at a given oxygen uptake during sub maximal exercise (pedalling) after bed rest, while the cardiac output response was unaltered. These data suggest an inadequate peripheral vasodilatation after bed rest. Shoemaker *et al.* (1998a) demonstrated attenuated vascular reactivity after 14 days bed rest, so that peak vasodilatory responses were attenuated. In addition, the ability to constrict an already dilated bed was diminished. Changes in vascular reactivity have also been demonstrated in animals after hind limb unloading as a model of HDT; Purdy *et al.* (1998) and Delp (1999) found impaired arterial contractile responses to standardised stimuli.

Venous compliance

Most studies (*e.g.* Convertino *et al.* 1989; Louisy *et al.* 1997; Pavy-Le Traon *et al.* 1999) but not all (Bonde-Petersen *et al.* 1994) show that venous compliance is increased after HDT. Atrophy of the leg musculature secondary to long-term HDT (Convertino *et al.* 1989; Suzuki *et al.* 1994; Berg *et al.* 1997) might contribute to an increase in venous compliance (Fortney *et al.* 1996, pp. 906-907). Increased leg venous compliance after HDT is also associated with impaired venous emptying, which might further impair venous return to the heart (Louisy *et al.* 1997). This impaired vascular response, or excessive blood pooling in the legs, might contribute to post-spaceflight (Buckey *et al.* 1996a; Fritsch-Yelle *et al.* 1996) and post-HDT orthostatic intolerance (Shoemaker *et al.* 1998a). In a meta-analysis of several HDT studies, Pavy-Le Traon *et al.* (1999) demonstrated a significant correlation between increased lower-limb distensibility and orthostatic intolerance after HDT.

Orthostatic intolerance

Orthostatic intolerance is usually defined as an excessive increase in heart rate upon standing, in combination with signs of hypotension. After longer head-down-tilt bed rest and spaceflight there are signs of orthostatic intolerance in about half of the exposed individuals (Taylor *et al.* 1949; Miller *et al.* 1964; Buckey *et al.* 1996a; Traon *et al.* 1998). As discussed earlier, reductions of plasma volume, impaired cardiovascular control and possibly impaired cardiac function all contribute to post spaceflight and post bed rest orthostatic intolerance. One of the largest single risk factors, however, is simply tallness (Pavy-Le Traon *et al.* 1999). Other stressors may also contribute to the post-spaceflight and post-bed rest orthostatic intolerance. Motion sickness may play an important role (Yates and Kerman 1998), and after parabolic flight, half of the subjects showed impaired orthostatic tolerance, and were unable to finish a 10 min stand test (Schlegel *et al.* 2001). It has been shown that the vestibular organs contribute to maintain cardiovascular control in cats (Jian *et al.* 1999). In humans, head-down neck flections produce a rapid decrease in calf and forearm blood flow (Essandoh *et al.* 1987) and increases MSNA during LBNP (Ray 2000). In addition, body-rotations (in yaw) decrease the sensitivity of the carotid baroreflex (Convertino *et al.* 1997a). Thus, vestibular adaptations and desensitisation during spaceflight and to some extent during bed rest, may contribute to an impaired cardiovascular control.

Countermeasures

Several methods have been adopted in order to reduce spaceflight and bed rest induced deconditioning. Countermeasures that currently are in use include (Hargens 1994; Anonymous 1997):

1. Extensive exercise during all spaceflights over 3 months, and in most shorter ones. The amount of exercise varies since no standard protocol has been determined.
2. Isotonic saline 'load' consisting of salt tablets (8g NaCl) with about 960 ml fluid two hours before re-entry to increase plasma volume (Bungo *et al.* 1985).
3. Anti-G suit inflation to approximately one psi (52 mmHg) during re-entry and landing provides protection against blood pooling.
4. Liquid Cooling Garment provides conductive cooling, to minimize heat-induced peripheral vasodilatation to improve comfort.
5. Seats that allows astronauts to lie on their backs, perpendicular to the gravitational vector, in an attempt to minimize the orthostatic impact on the cardiovascular system during re-entry.

Other countermeasures have been investigated either during spaceflight or during bed rest, however they are not routinely used due to insufficient evidence regarding their effectiveness. Exposures to LBNP in space, at the same time as an oral saline fluid load is consumed have showed some benefit (Hyatt and West 1977; Grigoriev 1983). Exercise during LBNP (Lathers and Charles 1993; Lee *et al.* 1997; Watenpaugh *et al.* 2000), and adrenergic β-blockade during bed rest (Sandler *et al.* 1985) may be useful . Acute graded exercise

protocol designed to reach maximal effort performed within 24 hours of re-entry have improved orthostatic tolerance (Convertino 1987; Moore *et al.* 2001). In addition, an elasticised garment (Penguin Suit) is often worn by Russian Cosmonauts. The Penguin Suite contains rubber bands woven into the fabric, extending from the shoulders to the waist and from the waist to the lower extremities, that provides continuous exercise for antigravity muscles. Furthermore, upon return to earth, Russian Cosmonauts commonly use special inelastic pants to reduce peripheral blood pooling. Some countermeasures like thigh-cuffs seemed promising (Stevens *et al.* 1966a) but were later shown to have no effect (Custaud *et al.* 2000), while others have given unwanted side effects, like oral cortisone (Bohnn *et al.* 1970).

Thus, a large number of potential countermeasures against muscular and cardiovascular deconditioning have been evaluated. Despite this, no set of countermeasures have so far been able to fully prevent cardiovascular deconditioning and orthostatic intolerance (Charles and Lathers 1991, p. 1013; Convertino 1996c, pp. 832-834; Fortney *et al.* 1996, p. 909; Gazenko *et al.* 1986). Most researchers, however, seem to agree that exercise during spaceflight and bed rest reduces muscle atrophy and to some extent prevent bone loss and cardiovascular deconditioning (Miller *et al.* 1965; Convertino 1996a, pp. 832-834; Fortney *et al.* 1996, p. 909), although the type and amount of exercise remains unclear (Greenleaf *et al.* 1989). Consequently, the key component for developing more effective set of countermeasures is an imprived understanding of the cardiovascular adaptations to spaceflight and bed rest.

Perspectives

As gravity is an inescapable factor forming life on earth, it is remarkable that the human physiology in general, and the cardiovascular system in particular, is adaptable to such an extent that humans can not only tolerate, but also perform well during microgravity conditions. Moreover, upon return from spaceflight or when resuming upright posture after bed rest, all of these adaptations seem to be reversed, though the time-course of the recovery is still only partially described.

Aims and hypotheses

The major objective of this thesis was to improve the understanding of cardiovascular deconditioning, as reflected in altered structure and control after long term spaceflight and bed rest.

The aim of *Paper I* was to elucidate the separate effects of voluntary motor activation and muscle ischemia (*i.e.* muscle chemoreflex activation) on arterial baroreflexes by determining complete sets of baroreflex response parameters during sudden alterations of carotid sinus distending pressure in men at rest, during isometric arm contractions and in post-contraction ischemia. Furthermore, the characterization of the interactions between the arterial baroreflex and the muscle chemoreflex would enable an interpretation of the simplified pressor response test utilized in *Paper II*.

The hypothesis was that isometric arm contractions shift the baroreflex response curve to operate around a higher level of heart rate and mean

arterial pressure, while post-contraction ischemia alone causes the baroreflex to operate around an unchanged heart rate but an increased arterial pressure, as compared to rest.

The aim of *Paper II* was to characterize the cardiovascular responses to isometric muscle action during and after very long term spaceflight and bed rest by determining the heart rate and mean arterial pressure responses to two minutes of isometric lower arm contraction.

It was hypothesized that impaired cardiovascular responses to isometric muscle action and muscle chemoreflex stimulation contribute to the cardiovascular deconditioning after spaceflight and head-down-tilt bed rest. Since arm muscles are not ordinarily weight-bearing, it could be reasoned that these muscles would not be so much influenced during spaceflight and HDT. Thus, the inputs to cardiovascular control during isometric handgrip would be the same as on the ground, at least for a certain relative effort. Therefore, any change in the cardiovascular responses to isometric handgrip would primarily reflect an altered central processing and/or an alteration of the mode in which the effector organs (heart, blood vessels) responded to efferent signals.

The aim of *Paper III* was to characterize cardiac performance after 42 days bed rest by determining cardiac output and stroke volume during exercise in supine and upright positions.

It was hypothesized that, if cardiac performance became impaired by structural changes after bed rest, stroke volume limitations would be more apparent during exercise in a supine position, which normally require a larger stroke volume than either rest, or exercise in an upright position. In addition, it was hypothesized that these impairments would be of a different character with respect to upright and supine exercise; in upright exercise, hypovolemia should be the dominant factor, whereas possible structural limitations of diastolic function, if any, should become apparent in the supine position.

The aim of *Paper IV* was to bring the findings in *Paper III* further by examing cardiac output and stroke volume during rest in supine and upright positions. Furthermore, In this three times longer study (120 days) it was allowed to access the subjects not only after but also during (day 60 and day 113) the bed rest, which enabled an evaluation of the time-course of the adaptations.

The hypotheses from *Paper III* were extended, and it was reasoned that if structural changes were a mechanism for decreased cardiac performance, changes would develop gradually over time. On the other hand, if a reduced cardiac preload were the primary problem, stroke volume reductions would be more apparent at rest while in an upright position, when venous return is impeded by gravity, and there is no peripheral muscle pump. Furthermore, since reductions in plasma volume have been shown to develop within a matter of days during HDT (Fortney *et al.* 1996), stroke volume decrements caused by reduced preload would be expected to develop relatively fast.

The aim of *Paper V* was to assess the relative impacts of baroreflex and hemodynamic impairments during and after very long-term bed rest and during both rest and exercise.

It was hypothesized that during bed rest there would be a degradation of both central control and effector organ functions, but with a preserved ability to maintain the principal control variable, the arterial blood pressure, though only during steady-state conditions. Impairments of reflex and effector organ functions would primarily become evident during sudden orthostatic challenges, and manifest themselves as larger than normal, but short-lasting deviations of arterial blood pressure. It was also hypothesized that these blood-pressure deviations would be more apparent during exercise than at rest, since factors such as a stroke volume limitation would be more critical with a greater need for tissue perfusion. Lastly, it was hypothesized that reductions of cardiac size would be a common denominator for both hemodynamic and baroreflex impairments, and therefore have similar time courses.

METHODS

In the present thesis, all protocols and measurements were designed to investigate physiological functions in intact human, and aimed at using stimuli in a physiological range, while causing minimal disturbance of normal reactions. In addition, methods should allow repeated measurements over time. Thus, only non-invasive methods have been used.

All experiments were conducted in accordance with ethical guidelines in the Declarations of Helsinki.

Subjects & study design

Paper I - The carotid baroreflex function during isometric contraction and ischemia

Ten male subjects were studied and had the following characteristics: a mean age of 24 years (the age range was 22 to 25 years), a mean weight of 73,5 (60 to 69) kg and a mean height of 1,79 (1,69 to 1,90) m. They all had normal findings in a physical examination, normal resting ECG and normal blood pressure.

The experimental procedures had been approved by the Ethical Committee of Karolinska Institutet.

Paper II - The pressor response to isometric contraction during 6 to 13 months spaceflight

Four male subjects, with a mean age of 44 years (the age range was 37 to 51 years), were studied before (baseline) and after 6 to 13 months of spaceflight onboard the MIR Space Station. Two of these subjects were studied repeatedly during the spaceflight. One of these subjects was also studied after a second spaceflight. While in space, all subjects performed exercise, and periodically wore the previously described Penguin Suite, to reduce deconditioning. After landing, the subjects wore anti-gravity pants (passive, inelastic pants that also cover the lower abdomen), and continued to do so part of the time for the nearest days.

All experimental procedures had been approved by the Medical Board of the European Space Agency.

Paper III - Cardiovascular performance during exercise after 42 days bed rest

Eight male subjects entered the HDT study, but one withdrew due to persistent back pain. The seven subjects that completed the bed rest had the following characteristics: a mean age of 28±1 year (mean ± SE), a mean height of 1,78±0.01 m and a mean weight of 73±4 kg. The subjects were confined to a hospital area for 15 days prior to the bed rest, and for the first 13 days after the bed rest. During the bed rest, absolute no deviations were allowed from the head-down tilt position and no muscular exercise or muscle function tests were performed. Compliance with the HDT protocol was ensured by constant video surveillance. The subjects had constant access to medical care, and received physiotherapeutic prophylaxis against venous thrombosis.

Pre-bed rest control (baseline) experiments were performed at 14, 11 and 6 days before bed rest commenced. No measurements were performed during the bed rest. Experiments after the HDT were

started in the afternoon, 8 hours after rising from the bed rest (R0). A medical examination, including a stand-test and exposure to LBNP, was conducted during this period, as reported by Pavy-Le Traon *et al.* (1998). Additional recovery measurements were conducted at 2 (R2), 4 (R4), 8 (R8), 12 (R12), and 32 (R32) days respectively, after the bed rest.

The bed rest and all experimental procedures had been approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Toulouse I, France.

Paper II, IV and V - Cardiovascular performance and control during rest and exercise after 120 days bed rest

Six male subjects entered the HDT study and had the following characteristics: a mean age of 31 years (the age range was 23 to 42 years), a mean height of 1,81 (1,75 to 1,90) m, and a mean weight of 80 (63 to 114) kg before and 83 (66 to 112) kg after the bed rest. These subjects acted as a control group for another parallel study on the effects of various countermeasures (Yamashita-Goto *et al.* 2001), and for that reason they were not submitted to any countermeasures. The week before and after the bed rest, the subjects performed 30 minutes of light exercise in the morning. During the bed rest, the subjects performed no exercise except for the two periods of 50W pedalling, as part of the present study, at day 60 and day 113. The subjects were free to assume prone, supine or lateral positions, while remaining in the -6° position. The total time in postures deviating from -6° was 940 min per subject (0.5% of the total duration), of which 440 min (~4 min/day) was in +6° and the remaining time (~4 min/day) in positions between +30° and +90°. The subjects had constant access to medical care, and received daily physiotherapeutic prophylaxis against venous thrombosis.

The baseline rest protocol was performed one to two weeks before initiation of the bed rest, and the baseline exercise protocol was performed at one week before the bed rest began. During the bed rest, experiments were performed on day 60 (D60) and day 113 (D113). At the conclusion day of HDT (*i.e.*, recovery day zero [R0]), experiments were performed less than 6 hours after the subjects rose from their beds. Thereafter, experiments were performed after recovery days 3, 10, and 14 to 17, termed R3, R10 and R15.

The bed rest and all experimental procedures had been approved by the Russian National Committee of Bioethics at the Russian Academy of Science.

Experimental techniques

The neck-chamber technique

Changes in the carotid sinus distending pressure were generated by the application of positive or negative pressure in a neck chamber. The chamber enclosed both sides and the front of the neck, from the mandibular level to the sternum and clavicles, see Fig. 1, (Eckberg *et al.* 1975). Each stimulation consisted of a 15 s period of constant (non-pulsatile) pressure or suction. The rate of pressure change in the chamber was over 800 mmHg/s, to ensure that the full pressure was applied before the next systolic peak.

Carotid stimulations were controlled by a circuit that opened a valve with a 40 ms delay after an R-wave. Six different levels of pressures allowed a full determination of the carotid baroreflex response curve.

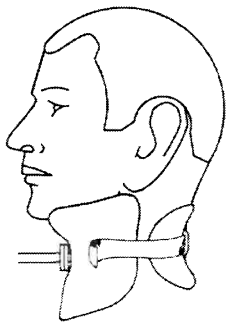

Fig. 1. The neck chamber device encloses the anterio-lateral parts of the neck, and the applied suction or pressure acts to increase or decrease the pressure gradient over the carotid vessel wall.

The rapid tilt technique

Experiments were performed with the subject positioned on a tilt-board, on which a cycle-ergometer was mounted with the crank axis at the level of the heart in supine position (Fig. 2.).

During rest, the subjects had their feet in a resting position below the pedals. In the upright posture, the subjects were mainly supported by a bicycle saddle mounted on the tilt table, and not by the footrest, which prevented unintentional leg muscle load during upright rest.

The tilt-board allowed the subject to be tilted from supine to upright, and back, during rest and during continuous pedalling. Each tilt took about two seconds to complete.

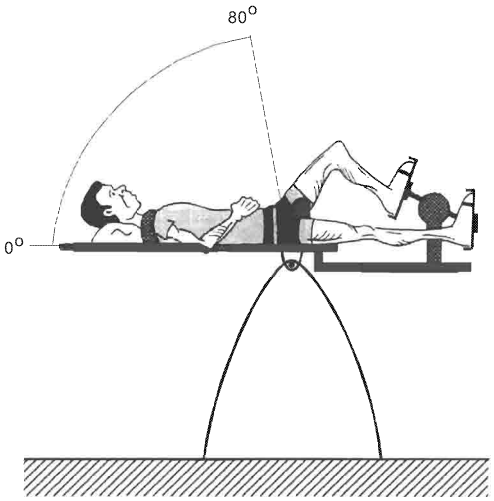

Fig. 2. Schematic drawing of the tilt table that was used for both the rest-tilt and the exercise tilt protocol. During rest, the pedals were removed and a footrest was mounted beneath. However, while in the upright posture, the subjects were mainly supported by a bicycle saddle mounted on the tilt table, and not by the footrest. Illustration courtesy of Dr. Ola Eiken.

Experimental protocols

Paper I - The carotid baroreflex function during isometric contraction and ischemia

The experiments were performed in one session either in the morning, two hours after a light caffeine-free breakfast, or in the afternoon, two hours after a light, caffeine-free lunch.

The subjects performed isometric contractions at 30% of maximal contraction force, with the right hand, in sitting position.

Each subject performed six sequences, with 15 min resting periods between sequences. Each sequence included 3.5 min rest, 2.5

min isometric lower arm contraction, and 3 min arterial arm occlusion with relaxed muscles (*i.e.* post-contraction ischemia). Each of the six sequences included three baseline carotid stimulations before start of contraction, two carotid stimulations 45 and 105 s after the onset of contraction, and three carotid stimulations 30, 105 and 165 s after the onset of arterial occlusion. Occlusion was obtained by inflating a cuff around the upper arm, and when the cuff pressure had reached over 200 mmHg the subject was instructed to relax his arm. The levels of neck suction (-20, -40, -60, and -80 mmHg) and pressure (+20 and +40 mmHg) were varied in a pseudorandom mode. All subjects maintained the 30% contraction level throughout the contraction periods.

Paper II - The pressor response to isometric contraction during 6 to 13 months spaceflight

Similar protocols to determine the pressor response were used both for the 120-day bed rest and for the spaceflight experiments. The maximal voluntary contraction force was determined once each test day, prior to the test-session. The highest force generated during two one-second long maximal contractions was taken as the maximal. Each test consisted of one-minute resting recording followed by two minutes of sustained handgrip with the dominant hand at a contraction equivalent to 30% of the maximal voluntary contraction force. On earth, all tests were performed in both supine and upright positions, except for two subjects, where the experiments were performed only in the seated position. In space, the subjects were free to assume the most suitable posture.

Paper III - Cardiovascular performance during exercise after 42 days bed rest

This protocol was designed to evaluate hemodynamic changes after the 42 days bed rest during steady state supine and upright exercise, and all data were collected during steady-state 50W pedalling. The low load of 50W was chosen in order to enable a reasonably long period of steady-state aerobic exercise. The upright exercise periods were limited to 3 min to avoid confounding orthostatic hypotensive reactions, and were well tolerated by all subjects. To obtain steady state exercise conditions, the subjects first performed supine exercise for 6 min, and were then tilted upright for 3 min. Rebreathings were performed and data were collected during the last minute in upright posture. Similarly, the rebreathings in supine position were performed after 6 min of exercise. This was repeated 3 times, with interposed rest periods to provide time for the clearance of rebreathing gases.

Paper IV - Cardiovascular performance during rest and exercise during and after 120 days bed rest

This protocol was designed to evaluate changes both during exercise (as in *Paper III*) and during rest, during and after the 120-day long bed rest. During supine rest, data were collected after a minimum of 6 minutes of quiet and undisturbed supine rest. During upright rest, data were collected after 1 min of rest in the upright position. The measurements were repeated twice in each posture. The time in upright position for each measurement never exceeded 2 minutes, and was well tolerated by all subjects. After the

rest protocol, a similar protocol was performed for steady-state 50 W dynamic leg exercise, during which data were collected after 2 minutes in the upright position, and the measurements were repeated twice in each posture. The longer upright time was allowed because orthostatic reactions were considered less likely during dynamic leg exercise than at rest, as shown in *Paper III*.

Paper V - Cardiovascular control during rest and exercise during and after 120 days bed rest

This protocol was designed to evaluate hemodynamic changes to rapid tilts both during rest and during exercise, during and after the 120 days long bed rest. The rest protocol was composed of 2 min supine rest, followed by a rapid up tilt and 1 min upright rest, followed by a rapid downtilt, and 2 min supine rest. This was repeated 5 times. The subsequent exercise protocol was similar, but had 2 min long upright exercise periods. The subjects were tilted while pedalling. All hemodynamic variables were recorded beat-by-beat throughout the protocol.

Measurements

Rebreathing

Cardiac output (CO) and oxygen uptake were determined in both bed rest studies; for the 42-day long bed rest during supine and upright exercise, and for the 120-day long bed rest during both rest and exercise, in supine and upright posture. CO and oxygen uptake were obtained through a multiple gas rebreathing technique, as described by Sackner *et al.* (1975) and (Bonde-Petersen *et al.* 1980). The system used for rebreathing measurements, described in more detail by Verbanck *et al.* (1996), consisted of a gas analyser (mass spectrometer), a gas supply system, a rotary valve fitted to a rebreathing bag, a flow meter, and a mouthpiece. The rebreathing-gas mixture contained 0.63% C_2H_2, 0.3% $C_{18}O$, 5% Ar, 45% O_2, and the remainder N_2. Wash-out periods between repeated rebreathings were interposed to provide time for inert gas clearance. The rebreathing procedures were rehearsed several times prior to the experiments, during which the amount of rebreathing gas was adjusted to the subject's preferences (from 1.5 to 2.0 litres).

Beat-by-beat recordings

All parameters were continuously recorded using computer-based data handling systems. Beat-by-beat *heart rate* was acquired from ECG chest electrodes with combined amplifiers and beat-by-beat tachometers. Continuous recordings of *arterial blood pressure* in the right middle finger were obtained with photo-plethysmographic devices (Finapres). The Finapres device has previously been shown to provide recordings of mean arterial blood pressure in close agreement with concomitant invasive recordings (Imholz *et al.* 1990). During the carotid baroreflex stimulations (*Paper I*), the *pressure inside the neck chamber* was continuously monitored by a pressure transducer. During the tilt experiments (*Paper III, IV* and *V*), a fluid-filled tube coupled to a pressure transducer (Sensortechnics Gmbh, Pucheim, Germany) provided continuous information on the difference in *hydrostatic pressure* between the finger cuff and a reference point at the intersection of a transverse line from the fourth

intercostal space at the sternum to the mid-axillary line (*i.e.* heart level). *Trans-thoracic impedance* (TTI) was recorded from tape electrodes round the lower part of the thorax at the xiphoid level and at the base of the neck, as described by Kubicek *et al.* (1970). TTI^{-1}, the transthoracic conductance was used as an index proportional to intrathoracic fluid volume (Ebert *et al.* 1986).

Data analysis

Beat-by-beat recordings

Off-line analysis, including beat-by-beat computation of mean arterial pressure (MAP), compensated for the difference in hydrostatic pressure between the finger and the heart (MAP_H), between the finger and the carotid (MAP_C), and at a level halfway between the carotid and the heart (MARP; Mean Arterial Receptor Pressure). This level was chosen since arterial baroreceptors are located both in the carotid arteries and in aorta. Systolic and diastolic pressures were also compensated to the MARP level, and termed SARP and DARP. Carotid distending pressure (CDP; *Paper I*) was calculated as the difference between MAP_C and the pressure inside the neck chamber. The pulse pressure was calculated for each cardiac cycle as the difference between SAP and the pre-systolic DAP Heart rate, R-R interval (RRI) and mean blood pressure is, by definition, not known until after a cardiac cycle is completed. In the present analysis, these data were shifted in time to be located in the RRI when they actually occurred.

Rebreathing

Off-line analysis of the rebreathing procedures was performed with a program written in Pascal to calculate cardiac output (CO). Stroke volume (SV_r) was then calculated as $SVr = \frac{CO}{HR}$, and total peripheral resistance (TPR) as $TPR = \frac{MAPH}{CO}$, where MAP_H is the concomitant mean arterial pressure at the level of the heart. Total peripheral conductance (TPC) was calculated as TPR^{-1}.

Oxygen uptake was computed from the linear fall of O_2 concentration in the lung-bag system during rebreathing, and the lung-bag system volume was determined by insoluble inert gas dilution. The accuracy of this method is, by definition, not as high as that of methods measuring oxygen uptake over a longer period of time

Beat-by-beat stroke volume

The beat-by-beat stroke volume (SV_P) was derived from the contour of the arterial pressure curve as described by Jellema *et al.* (1996). Here SV_P is computed as $SVp = \frac{AS}{ZAo}$, where A_S is the area under the systolic pressure profile and Z_{Ao} is the virtual aortic impedance. This method includes corrections for variation in Z_{Ao} caused by changes in arterial pressure and HR, which are due to changes in aortic cross section and compliance (pressure and age-dependent) and to reflections of the pressure waveform from the periphery (influenced by HR). SV_P was calculated as:

$$SVP = \frac{AS}{ZAo} \times \frac{1320 + HR \times 10 - Age \times (0.28 \times MAPH - 16)}{2000}$$

where HR is the instantaneous heart rate (in beats/min), MAP_H is mean arterial pressure at the level of the heart in the same beat, and Z_{Ao} is the concomitant calibrated aortic

impedance. Stroke volume measurements from rebreathing, $SVr = \frac{CO}{HR}$, obtained separately for rest and exercise, at 0° and 80° (*Paper IV*), were used to calibrate the Z_{Ao} (Antonutto *et al.* 1995). During the tilt transients, Z_{Ao} was assumed to change with the same time course as the hydrostatic pressure difference signals obtained from the fluid-filled catheters. From the beat-by-beat SV_P estimates, beat-by-beat cardiac output (CO_P) was computed as $SV_P \times HR$, and total peripheral resistance (TPR_P) was computed as $TPR_P = \frac{MAP_H}{CO_P}$.

Evaluation of the carotid baroreflex - Paper I

Recordings from identical neck-suction levels were averaged for each subject, using the instant of the onset of the carotid stimulus for time alignment. The peak or nadir of heart rate and MAP responses during each neck-suction period was determined from individual average time courses. Baroreflex response curves for heart rate and for MAP were synthesized as follows. First pre-stimulus baseline (prevailing) levels for heart rate, MAP and CDP were computed from all neck-suction sequences. For each neck-suction level, peak or nadir changes of heart rate and MAP were added to or subtracted from the prevailing levels, and plotted as a function of CDP.

Two types of baroreflex response curves were synthesized: a) six-segment curves obtained by interpolation between the NS/NP levels (*Paper I*, Fig. 1), and fitted logistic functions (this thesis, Fig. 3) as described by Kent *et al.* (1972). From the six-segment curves, range, maximum slope, and optimum point were determined for each subject. The procedure to fit logistic functions to individual baroreflex response curves did not converge into unique, best-fit sets of fitting parameters for all subjects and conditions. Thus, group mean curve parameters obtained from the interpolated curves were utilised to synthesise logistic curves roughly characterising carotid-cardiac and carotid-MAP responses for the group.

Hemodynamic evaluation of tilts during rest and exercise – Paper V

Beat-by-beat systolic and mean arterial pressure, heart rate, and RRI were analysed for tilt-induced peaks and nadirs. Tilt-induced blood pressure and chronotropic responses (ΔSARP, ΔMARP, ΔHR, ΔRRI) were determined as the difference between an average immediately before a tilt and a subsequent peak or nadir. For each subject, rest and exercise condition, tilt direction and experiment day, five sets of data were obtained, one for each tilt repetition. The highest and the lowest values were discarded and an average was computed from the three remaining values. This procedure was chosen to minimize the impact of spurious peak and nadir readings.

Arterial-cardiac chronotropic baroreflex sensitivity was computed as the ratio of a tilt-induced chronotropic response over the preceding blood pressure response (Linnarsson *et al.* 1996; Sundblad *et al.* 2000b). To make comparison with previous studies easier, baroreflex sensitivity estimates were obtained both as ΔHR/ΔMARP and as ΔRRI/ΔSARP.

The ranges of SARP and MARP fluctuations were determined over whole up-tilt and down-tilt sequences,

as an index of the over-all efficiency of the blood-pressure control to meet short-term orthostatic challenges. Corresponding ranges were obtained also for the tilt-induced changes of beat-by-beat heart rate, stroke volume, and cardiac output.

Beat-by-beat, tilt-induced SV_P transients were analysed for signs of ventricular interdependence. Ventricular interdependence is defined as interference with the left ventricular performance as a result of a sudden increase of right ventricular diastolic filling (Robotham and Mintzner 1979; Brinker *et al.* 1980; Sundblad *et al.* 2000b).

The continuous SV_P recordings were analysed for two signs of ventricular interdependence; first, short-lasting depressions of SV_P early during down tilt (Sundblad *et al.* 2000b), second, breath-synchronous fluctuations (Toska and Eriksen 1993) in both supine and upright posture. Breath-synchronous SV fluctuations were analysed by a Discrete Fourier Transformation. For each tilt, segments 50 to 5 s before up tilt and 35 to 5 s before down tilt were analysed. The amplitude of the respiration-synchronous peak in the high-frequency power spectrum (0.15 – 0.4 Hz, Anonymous 1996) was taken, and averaged for each subject, condition, and experimental day.

Statistics

Paper I

Changes in baroreflex sensitivity between conditions were analysed using a paired Student's t-test for dependent variables. Significance was accepted at a p-value below 0.05, with Bonferroni's correction for repeated comparisons.

Paper II, IV and V

Statistical analysis was performed using analysis of variance (ANOVA) with Dunnet's Post-hoc test where applicable. Trends were assessed by multiple regression over time. Significance was accepted at p-values below 0.05. Results are expressed as mean ± standard error (SE).

Paper III

Differences between pre- and post-bed rest measurements were analysed using the Student's t-test with Bonferroni's correction for multiple comparisons. Differences in exercise cardiac output, stroke volume and TPC were analysed only for pre-bed rest compared to R0 and to R9, due to the small number of subjects.

RESULTS

Paper I

In this study, complete sets of curve parameters for arterial baroreflex response curves both during isometric arm contraction and during post-contraction ischemia were defined in man. The definition of the optimum points on the arterial baroreflex response curves for heart rate and MAP enabled us to determine to what extent arterial baroreflex curves are shifted by isometric contraction and post-contraction ischemia. Compared to rest, contraction caused a displacement of the carotid-cardiac response curve to a 14 beats/min higher heart rate and to a 9 mmHg higher CDP as given by the displacement of the optimum point. Corresponding values for MAP were +20 mmHg and +18 mmHg respectively. During occlusion the carotid-cardiac response curve was displaced vertically compared to contraction, *i.e.* to the same heart rate level as during rest but to a 14 mmHg higher CDP level than rest. At the same time, the carotid-MAP response curve was displaced horizontally to 8 mmHg lower CDP values compared to contraction. For all conditions, prevailing and optimum points for heart rate did not differ significantly. Ranges and maximum slopes for heart rate and MAP baroreflex response curves did not differ between conditions.

Figure 3 summarises the significant differences between the baroreflex response curves from the three conditions. Group mean data have been utilized to synthesize logistic curves illustrating carotid-cardiac (Fig 3a) and carotid-MAP (Fig 3b) baroreflex response curves for the three conditions.

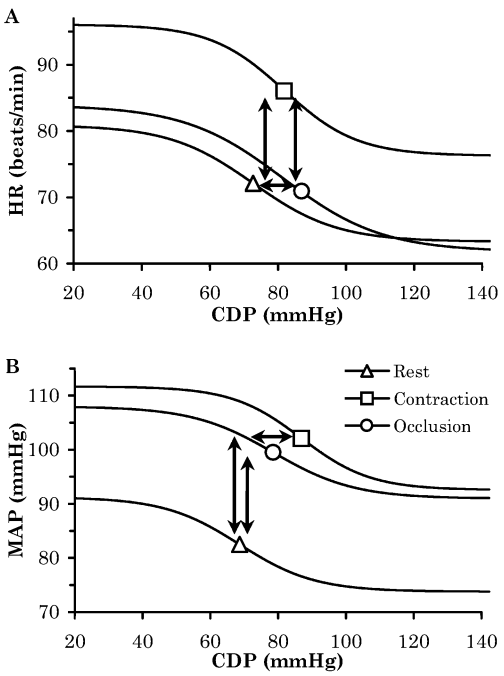

Fig. 3. Carotid baroreflex response curves during control, isometric exercise and occlusion. Panel (A) describes the relationship between heart rate and CDP, and panel (B) describes the relationship between MAP and CDP. The symbols indicate operational points; arrows indicate significant differences. Adapted from *Paper I.*

Paper II

All six subjects completed the bed rest study, and the four cosmonauts completed all scheduled experimental sessions before (n=4+1), during (n=2) and after (n=4+1) spaceflight. All subjects showed increases in MAP during the sustained hand grip varying from 4 to 45 mmHg and the heart rate response varied from -2 beats/min to more than +30 beats/min. Supine and upright heart rate responses were similar. MAP responses in upright position were generally 2-5 mmHg higher than when supine, however this trend was not significant. Due to the limited amount of data, supine and upright sessions were pooled.

Bed rest

The maximal voluntary contraction decreased over 20% from baseline to day 60 and remained significantly reduced throughout the sessions. Heart rate during rest did not show any significant changes during the bed rest, except for day 0 after the bed rest, when upright heart rate was increased by 10.5 beats/min compared to baseline. MAP during supine rest was significantly increased by 7.5 mmHg at day 0 after the bed rest compared to baseline. Handgrip-induced responses of both MAP and heart rate decreased from baseline to D60 and thereafter remained lowered throughout the experiments, including the last session at R15. Compared with baseline, heart rate responses were reduced by 54%, and MAP responses by 43% at day 0 after the bed rest.

Spaceflight

In the two cosmonauts studied during spaceflight the maximal voluntary contraction (MVC) showed a tendency to decrease (-9%) after 60 days spaceflight. The cosmonaut studied after a repeated flight showed a progressive decrease in MCV. During his first spaceflight (180 days), the MVC was 100 kPa, declining to 90 kPa after 69 days spaceflight. Already two days after return to normal gravity he performed 100 kPa, and after 25 days of recovery 120 kPa. After the second, longer spaceflight (389 days) he only performed 70 kPa day 0 to day 14 after landing, and after 52 days of recovery 80 kPa.

In space resting heart rate decreased significantly from 76 beats/min to 57 beats/min at flight day 5 to 6, thereafter resting heart rate resumed values slightly below pre-flight. MAP did not show any significant changes. Both cosmonauts studied in space tended to have lowered heart rate responses to sustained hand grip in space compared to baseline, while the MAP responses decreased for one and increased slightly for the other. All cosmonauts showed significantly reduced MAP responses at landing day (-79%) and day 1-4 (-35%), while the heart rate responses were not significantly changed. Statistical comparisons were not performed for other experiment days due to the small number of subjects.

Paper III

Seven subjects completed the HDT.

Stroke volume decreased markedly immediately after bed rest in both the supine and the upright position (25±3% and 33±5% respectively), followed by a partial recovery at R2 (Fig. 4a). There was a discrepancy between the two postures, whereby stroke volume when upright had recovered within 32 days, whereas stroke volume in the supine position had not.

In general, similar findings were apparent in cardiac output after the HDT; at R0, cardiac output decreased by 19±3% in the supine, and by 20±3% in the upright position (Fig. 4b). However, whereas stroke volume had partially recovered between R0 and R2 for the upright posture, the immediate cardiac output decrease in the supine position persisted to a significant extent for at least one month.

The discrepancy between postures with respect to the time-course of the recovery was further emphasised by the postural differences in stroke volume. These differences had not changed immediately after HDT, but were decreased after 32 days, indicating a difference between the recovery in the two positions.

Oxygen uptake during pre-bed rest 50W exercise was 760±80 ml/min STPD, in both supine and upright, and there were no significant changes after the bed rest.

The heart rate during exercise was elevated for 12 days in both the supine and upright positions, but was not significantly different from the pre-bed rest values after 32 days. The elevation in heart rate at R0 was 22±5% in the upright, and 10±4% in the supine position. At R32 the difference in heart rate between supine and upright was less than before the bed rest.

The mean differences in thoracic blood volume between postures, as estimated by the difference in inverse TTI (ΔTTI^{-1}), averaged 2.5±0.2 mS throughout the study, and did not show any significant changes between experimental days. A 2.5 mS difference corresponds to a change in CVP by 4-5 mmHg (Ebert *et al.* 1986).

Results regarding responses to rapid tilt transients during this bed rest are presented by Sundblad *et al.* (2000a).

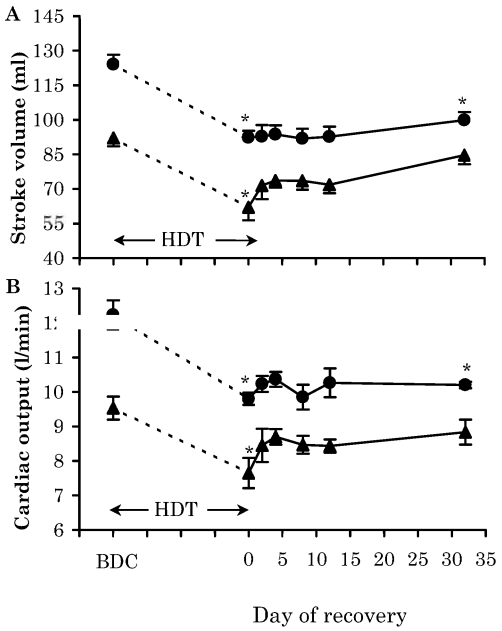

Fig. 4. Stroke volume (panel A) and cardiac output (panel B) during exercise after 42 days bed rest. Supine steady-state (●) and upright steady-state (▲). Group averages ± SE at baseline conditions (BDC); first day after bed rest (0), and after 2, 4, 8, 12 and 32 days of recovery. Significant changes compared to baseline conditions are indicated by (*); note that only R0 and R32 were statistically tested ($p<0.05$). Adapted from *Paper III.*

Paper IV

All six subjects completed the bed rest and the scheduled protocols. All continuously recorded hemodynamic variables reached a steady state early within the first minute after either up- or down-tilts.

Steady-state mean arterial pressure (MAP) during both rest and exercise showed no consistent change during or after HDT, as compared to baseline conditions (*Paper IV*, Fig. 2 and 3).

Heart rate tended to increase during HDT in all conditions (Paper IV, Fig 4). Steady-state exercise in the upright posture showed a marked increase, by 17.6±3.8% to D60, remained elevated by 20.1±4.2% at D113, 19.7±4.0% at R0, and partially recovered at R3 to 12.1±4.2%, but no full recovery to baseline values occurred, even at R15 (+9.1±4.2%).

The stroke volume showed a marked decrease during HDT (Fig. 5, panel A). At rest, the stroke volume decrease was significant at D60 in both postures. During upright exercise, stroke volume decreased at D60 and showed a slight tendency to decrease further at D113 and R0. During supine exercise, stroke volume did not decrease significantly between baseline and D60; however, at D113, the decrease was significant, and there was a tendency for further decrease at R0. During exercise, the stroke volume at R0 was significantly lower than at D60, while the stroke volume at D113 tended to be lower than at D60 (p=0.05). During recovery there was a tendency to increase at R3 that was less pronounced at R15, where the stroke volume during both supine and upright exercise remained significantly reduced.

The time courses of cardiac output during HDT are presented in Fig 5, panel B. At rest, the decrease was significant only at D60, although a tendency to decrease was also found at D113 and R0. During exercise, in both the supine and upright positions, there was a tendency for cardiac output to decrease at D60, there was a significant decrease at D113, and a there was a tendency for further decrease at R0.

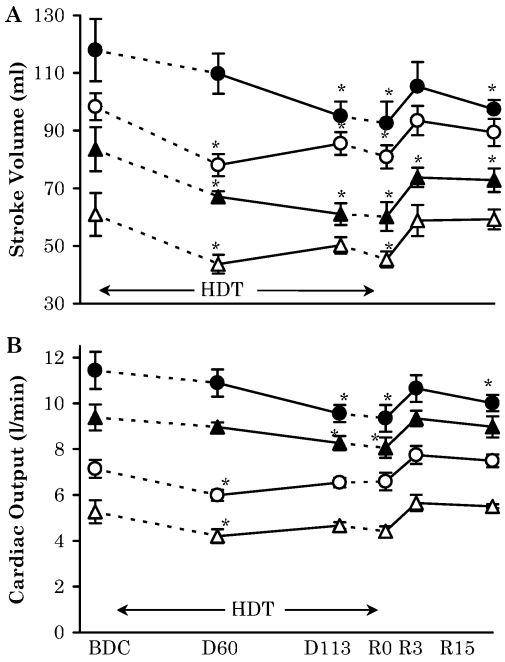

Fig. 5. Stroke volume (panel A) and cardiac output (panel B) after 120 days HDT. Supine steady-state (O) and upright steady-state (Δ); open symbols indicate rest, and filled symbols indicate exercise. Group averages ± SE at baseline conditions (BDC), day 60 (D60) and day 113 (D113) of the bed rest; first day after bed rest (R0), after 3 (R3) and after 14 to 17 days of recovery (R15). Significant changes compared to baseline conditions are indicated by (*) ($p<0.05$). Adapted from *Paper IV*.

During supine exercise, the decrease progressed so that cardiac output at R0 was significantly lower than at D60, and that cardiac output at D113 tended to be lower than D60 (p=0.06). After HDT, cardiac output showed a tendency to recover as early as R3; whereas, this tendency was less marked at R15, where cardiac output during upright exercise still differed from baseline conditions. The difference in cardiac output at rest between the supine and upright positions remained fairly constant throughout the study; upright cardiac output averaged 67% to 74% of corresponding supine values. Upright cardiac output during exercise averaged 83% to 89% of supine cardiac output, with a significant trend (p=0.03) toward a gradual decrease with time in the postural difference, from 2.05±0.44 l/min at baseline conditions to 1.04±0.18 l/min at R15.

The total peripheral conductance showed decreases similar to those of cardiac output and stroke volume, during and after HDT (*Paper IV*, Fig 7).

During supine and upright rest, TTI^{-1} was significantly decreased at R0, and thereafter showed a rapid recovery until R3 (*Paper IV*, Fig 8). The time course of TTI^{-1} during exercise tended to show a similar pattern, although the increase in TTI^{-1} did not differ significantly from baseline conditions (*Paper IV*, Fig 9).

The oxygen uptake averaged 833±54 ml/min during supine exercise, and 803±44 ml/min during upright exercise. There were no changes during or after HDT.

Paper V

Both at rest and during exercise, the sudden transitions between 0° and 80° and the reverse were associated with large but short-lasting changes in blood pressure, heart rate and cardiac output. The amplitudes of these blood-pressure fluctuations (*Paper V*, Fig. 3) did not change with time at rest, but during exercise tilt-induced fluctuations of SARP and MARP were markedly increased during and after the bed rest. Thus, the sum of down-tilt induced transient increases and up-tilt induced transient decreases of SARP was increased to 163±13% and 168±16% of baseline at D60 and D113, respectively. Corresponding values during recovery were 157±15%, 144±20%, and 154±26%, at R0, R3, and R15, respectively, that is with no significant recovery during the post-bed rest period.

The amplitudes of tilt-induced heart rate fluctuations (*Paper V*, Fig 4) did not change significantly with time when determined at rest, but during exercise heart rate fluctuations at down tilt were significantly increased (Paper V, Fig. 4) to 142 ± 14 and 133 ± 7 % of baseline on D60 and D113, respectively. Amplitudes of tilt-induced heart rate fluctuations did not differ from baseline after the bed rest.

At rest, tilt-induced stroke volume transients did not differ from baseline during and after the bed rest. During exercise, the sum of down-tilt induced transient stroke volume increases and up-tilt induced transient stroke volume decreases averaged 72±90 ml at baseline and was significantly increased to 160±20% of baseline at D60, and averaged 115-142%

thereafter, but with no significant difference from baseline.

For the arterial-cardiac chronotropic baroreflex sensitivity (*Paper V*, Fig 5) at rest, the only significant alterations of sensitivity compared to baseline were for ΔRRI/ΔSARP on R0. During exercise, however, the sensitivity computed as ΔRRI/ΔSARP was significantly depressed throughout the bed rest and recovery periods, and both for up and down tilts. For up tilt, ΔRRI/ΔSARP was significantly reduced to 55±8 and 55±9% of baseline at D60 and D113 with no further change after the bed rest, when ΔRRI/ΔSARP averaged 49±6, 54±8, and 45±9% at R0, R3, and R15, respectively. Exercise sensitivity computed as ΔHR/ΔMARP during down tilt was not changed during the bed rest but tended to be depressed during up tilt from D60 and onwards ($p = 0.055–0.096$) and was significantly depressed compared to control on R15.

Both in supine and upright posture, breath-synchronous stroke volume fluctuations (*Paper V*, Fig. 8) were significantly reduced on R0. In supine, there were reduced amplitudes from D60 and onwards with no signs of recovery on R15.

The down-tilt induced initial stroke volume dip (*Paper V*, Fig. 8) was significantly decreased in amplitude on D113 during exercise and tended to be so at rest as well ($p = 0.06$).

Immediately at the onset of the up tilt, there was an increase of cardiac output (*Paper V*, Fig 9) with approximate amplitude and duration of 2 l/min and 10 s, respectively. Thereafter there was a marked drop of cardiac output that stabilized on a new and lower level after approximately another 10 s. This pattern occurred in the whole group, where the amplitude of the initial overshoot at up tilt was greatly reduced during and after bed rest, but recovered during the 15-day post-bed rest observation period (*Paper V*, Fig 10).

Time delays (*Paper V*, Table 1) from the instant of 30° tilt angle until the onset of tilt-induced changes in heart rate and MARP, and response times until peak/nadirs of the same variables did not differ between experimental days. MARP started to change as soon as the tilt started and approximately one second before 30° tilt angle was reached. Heart rate started to change later than MARP; at rest, the delay from the onset of MARP change was about one s during up tilt and about four s during down tilt. Both at rest and during exercise, the peak/nadir responses of heart rate occurred later during up tilt than during down tilt.

DISCUSSION

In the following, the most significant findings from the present studies are summarised and discussed in relation to the previous findings presented in the introduction, and an attempt is made to evaluate the impact of spaceflight and bed rest on cardiovascular function and control.

Reflex control of the cardiovascular system during isometric exercise

The main purpose of the circulation is to provide adequate oxygen and nutritients to the tissues in general and to the central nervous system in particular, and to remove carbon dioxide and metabolic breakdown products. During increased demands, as during exercise, the system must respond instantaneously by increasing and to some extend redirect the blood flow.

The cardiovascular responses to isometric muscle action were first described by Alam and Smirk (1937) and include marked elevations of arterial blood pressure. Heart rate and total peripheral resistance responses may vary, but the arterial pressure is invariably increased, so it is reasonable to assume that the arterial blood pressure is the primary regulated variable of the cardiovascular response. However, at sustained isometric contractions at intensities over 15% of maximal, the reflexively elevated arterial blood pressure fails to increase muscle blood flow in the contracting muscle where the increased tissue pressure overcomes the perfusion pressure (Humpreys and Lind 1963). Despite this, the arterial blood pressure continues to increase in proportion to the contraction intensity (Lind and McNicol 1967; Freyschuss 1970).

The only way to increase the arterial pressure is by increasing TPR or CO and an increase in CO is a constant finding during isometric muscle action (Pawelczyk *et al.* 1997), to which an increased cardiac contractility makes an important contribution (Nobrega *et al.* 1997). However, actual determinations of TPR have shown varying results. Pawelczyk *et al.* (1997) found no increase in TPR during static handgrip, whereas others have found increases (Bergenwald *et al.* 1981). These somewhat conflicting conclusions may be explained by considering the elastic properties of the vascular system, where an increase in cardiac output is balanced by an increased vascular tone (central or myogenic autoregulation, or both) not to cause a fall in TPR and a consequent failure to maintain an increased MAP.

There are at least two types of afferent information that can influence the cardiovascular responses to a sustained isometric contraction: first, somatomotor activation (central command, input from mechanoreceptors) and second, stimulation of chemo sensitive nerve endings in the contracting and increasingly ischemic muscle. (Rowell 1996, Ch. 8.).

Several studies have shown that there is a substantial increase of MSNA after the first minute of sustained hand grip (Mark *et al.* 1985; Scherrer *et al.* 1990) and a decreased radial artery diameter (Olesen *et al.* 1995) suggesting vasoconstriction in important

vascular beds. Thus the key component of the hemodynamic response to isometric exercise appears to be an increased vascular tone to counteract the passive widening of resistance vessels caused by the increase in cardiac output (Pawelczyk *et al.* 1997), thereby enabling the MAP increase (Rowell and O'leary 1990; Sheriff *et al.* 1998).

Dynamic muscle activity is associated with a rapid resetting of the arterial baroreflex to a higher pressure without a change in gain (Rowell and O'leary 1990; Potts *et al.* 1993; Papelier *et al.* 1994; Rowell *et al.* 1996, pp 770-840; Fadel *et al.* 2001). That is, the prevailing arterial pressure remains on the high-gain portion of the baroreflex function curve, and the strength of control of arterial pressure is unaltered.

To our knowledge, the full ranges of baroreflex response curves have not previously been characterised during isometric exercise. Thus, the major findings in *Paper I* were that carotid-MAP baroreflex response curves were shifted to operate at higher carotid distending pressures, during both isometric lower arm contraction (about +20 mmHg) and post-contraction ischemia (about +15 mmHg), with no apparent change in range or sensitivity. Carotid-cardiac chronotropic responses, however, were shifted only during contraction but not in post-contraction ischemia, where an unchanged baroreflex function regulated heart rate to a level significantly lower than at rest, as a result of an elevated CDP. Thus, it appears that neither somatomotor activation, nor muscle chemoreflex afferent inflow changes the range and sensitivity of arterial baroreflexes in general, and that the baroreflex is fully functional although around higher levels of heart rate and MAP. The findings of rightwards and upwards shifted arterial baroreflex response curves with unchanged sensitivity have been hypothesized to be a result of a combination of an upwards shift of target value of for example heart rate, caused by somatomotor activation, in combination with a parallel generalized increase of sympathetic output caused by muscle chemoreflex afferent inflow (Rowell 1996, pp. 407-418).

In conclusion, neither somatomotor activation, nor ischemic stimuli appear to alter the sensitivity of arterial baroreflexes during isometric arm contraction in human. Chronotropic responses appear not to be influenced by muscle ischemia other than indirectly through the pressor response and the arterial baroreflex.

The pressor response after spaceflight and bed rest

Based on the present findings in *Paper I*, a simplified test with 2 min isometric lower arm contraction was designed, in order to investigate cardiovascular control of somatomotor activation. The hypothesis was that if heart rate responses to isometric exercise were impaired after spaceflight or bed rest, this would be related to alterations of pathways involved in central command. Impairments of the pressor response, on the other hand, would reflect alterations of pathways for ischemic stimuli.

The maximal contraction force was found to decrease both during spaceflight and bed rest. The decrease was smaller (9%) during spaceflight than during bed rest (26%), likely reflecting the lower level of arm

muscle activity during bed rest as compared to spaceflight.

Thus, one must consider whether the attenuated pressor response to sustained handgrip after simulated and actual microgravity is simply a consequence of a reduced absolute effort. If so, a loss of maximum power would cause less metabolites to be generated when contracting with less absolute tension, but same relative tension. This would cause an apparent decrease in the muscle chemoreflex. Contrary to this reasoning several previous studies have shown that both heart-rate and arterial blood pressure responses to isometric contraction are proportional to the relative contraction force developed, and independent of both the size and absolute force of involved muscle groups (Lind and McNicol 1967; Freyschuss 1970; McCloskey and Streatfeild 1975).

This relationship between relative force and pressor responses is only true if the limited flow through the contracting muscles in itself does not cause a major reduction of the conductance of the systemic circulation. When contracting larger muscle groups than the forearm alone, however, the peripheral conductance might be reduced causing a seemingly increased pressor response (Mitchell *et al.* 1980; Seals *et al.* 1983).

However, the local compression of muscular vessels during an isometric arm contraction does not influence the TPR enough to raise the arterial pressure (Rowell 1996, pp. 204-254). This was first demonstrated by Lind and McNicol (1967), later confirmed, for shorter contractions, by Freyschuss (1970). They showed that isometric contraction with one arm gives equal blood pressure and heart rate- responses as simultaneous contractions of both arms. Also, when contracting the arms with different intensities, only the arm contracting with the largest relative force determines the response.

Taken together, these findings support the notion that the relative and not the absolute force is the major determinant in the cardiovascular response. Consequently, these findings justify the assumption that the reduced maximal voluntary contraction force that was observed during and after bed rest and spaceflight was not the primary cause of the decreased response to isometric contraction at a constant relative tension.

In normal subjects, the arterial baroreflex will buffer deviations from the desired arterial pressure by raising vascular tone to increase TPR, and by increasing heart rate and cardiac output. However, if the subjects, as after spaceflight and bed rest, already exhibit an increased vascular tone (Kamiya *et al.* 2000a), or are lacking in responsiveness, then this reflex might fail to achieve the desired arterial pressure. Thus, the present set of data are compatible with the notion of an impairment of vascular regulation. This impairment appears to encompass both central command and the ischemic pressor response, since both HR and MAP responses were attenuated after spaceflight and bed rest.

Cardiac restraint on the pressor response

As reviewed in the introduction, several studies have found impaired cardiac function after spaceflight and bed rest, and so also in the present bed rest subjects (*Paper IV*). Therefore it can be considered likely

that an impaired cardiac performance contributed to the decreased pressor response after spaceflight and bed rest.

In addition, both spaceflight and bed rest causes reductions in blood volume and plasma volume (Convertino 1996a) and reduced central venous pressure (CVP) (Kirsch *et al.* 1984; Buckey *et al.* 1996b), which might compromise cardiac filling, and any impairment of cardiac filling will cause a decrease in cardiac output. During dynamic exercise the muscle pump normally supports the venous return, (Bevegård *et al.* 1960). This is not the case during static exercise. Measurements of CVP during static exercise in normal men show that the CVP is maintained at the pre-exercise level, despite the absent muscle pump and an increase in CO, indicating an active venoconstriction (Freyschuss 1970). However, after spaceflight and bed rest, the subjects exhibit low blood volumes, impaired vascular regulation, and relative tachycardia. These factors may all contribute to a reduced ventricular filling, decreased stroke volume and reduced cardiac output.

In conclusion, reduced cardiovascular responses to somatomotor activation were observed both during and after spaceflight and long-term bed rest. It can be concluded that the impaired cardiovascular response is likely due to a combination of decreased cardiac performance, reduced plasma volume and impaired neurocirculatory control. Furthermore, forearm isometric contraction can be a readily performed test for cardiovascular deconditioning.

Hemodynamics during gravitational stress at rest and during exercise

Preload at rest

As reviewed in the introduction, spaceflight and bed rest causes a reduction in plasma and blood volume. However, it has repeatedly been demonstrated that restoration of plasma volume alone is not sufficient to reverse either supine (Gaffney *et al.* 1992) or upright hemodynamics after longer bed rest (Blomqvist 1983).

Interestingly, two previous bed rest studies have shown not only a very fast plasma volume recovery after HDT, but also an overshoot exceeding baseline levels after 7 days (Fortney *et al.* 1991) to 13 days (Johansen *et al.* 1997) of recovery. This overshoot, which will increase preload, might be a means of compensating for cardiac limitations and vascular impairment, and might explain the rapid but only partial recovery that was found in heart rate, cardiac output, stroke volume and TPC (*Paper V*, Fig 4 to 7) after only three days of recovery. In the present study, decreases in TTI^{-1}, an index of central blood volume, were found immediately after the bed rest at rest (R0; *Paper V,* Fig 8 and 9). These decreases recovered fully only three days after the bed rest, probably reflecting a reduced plasma volume during bed rest, and a rapid plasma volume recovery between R0 and R3 after bed rest.

Overall, the timing of hemodynamic events at rest points to a coupling between plasma volume and preload. Our first data point at D60 is far too late to reflect the initial period of plasma volume decrement, but the absence of further reductions

in stroke volume between D60 and R0 speaks against structural cardiac alterations as an important factor at rest; this is in contrast to the reductions of stroke volume during exercise.

Moreover, there was a rapid recovery of resting stroke volume after bed rest, as would be expected if plasma volume recovery were the main factor. Both supine and upright values were normalized by R3. Finally, the constancy of the difference between supine and upright cardiac output at rest speaks in favour of a common mechanism for time-dependent alterations of cardiac output in the two postures.

The muscle pump

During standing approximately 80% to 90% of the venous volume in the legs is located in the deep muscle veins (Buckey *et al.* 1988). Each voluntary contraction can eject approximately 30% of the total venous volume from the lower limb to the central veins (Ludbrook 1966). During rhythmic exercise, this leg muscle pump has a capacity rivalling that of the left ventricle (Rowell 1996, p. 778), and facilitates both blood flow through working muscles and venous return (Folkow *et al.* 1971). More in detail, the pumping is caused by the rhythmic contractions of the muscles, which empty the surrounding veins, followed by rapid muscle relaxations, which pull the veins open and generate a negative pressure, sucking the blood into the capacitance vessels (Laughlin 1987). This mode of function does not have a direct pressure-flow relationship in the periphery, since the pump works rather as a bailer that, for each contraction of the muscles, empties the adjacent venous segments and transfers that volume to the nearest proximal segment. The capacity of the muscle pump is dependent on the force, frequency and duration of the contractions (Laughlin 1987). In the present studies, the subjects pedalled with a constant frequency and equal force on all test occasions. However, it is possible that large reductions in leg muscle volumes and muscle atrophy decrease the efficiency of the muscle pump. A muscle with a reduced cross-sectional area would expel less blood volume per contraction, even if the contraction force were to remain the same. Furthermore, it can be speculated that a muscle with a reduced volume might have a reduced rate of elastic reshaping during relaxation, thus filling more slowly between contractions.

It has been shown that the muscle pump is more efficient in the upright than the supine posture, where the effective perfusion pressure over the muscle is greater (Folkow *et al.* 1971). However, in the supine posture, the muscle pump is much less critical for the preload when cardiac output increases with exercise. An impaired muscle pump would thus lower venous return and reduce both stroke volume and cardiac output, primarily during upright exercise.

Hemodynamic and reflex responses to rapid tilts

Cardiac output transients during rapid up-tilting at rest

Beat-by-beat recordings of stroke volume and cardiac output during sudden changes in posture have been shown earlier by Sprangers *et al.* (1991), who studied transitions from supine to active standing. They described a transient increase of cardiac output immediately upon

rising to the feet, and ascribed this to a sudden increase of venous return due to the compression of deep leg veins and possibly also to compression of abdominal vessels. These explanations cannot readily be applied to the present experiments with passive up tilting.

A close inspection of the present time courses of heart rate and stroke volume at resting baseline reveals that whereas stroke volume drops only marginally during the first 5-10 s after up tilt, heart rate starts to change much earlier (*Paper V*, Fig. 9). Thus, the combination of rapidly rising heart rate and an essentially maintained stroke volume leads to the overshoot of cardiac output during a short period. The rapid onset of the heart rate change upon up-tilt contrasts with the larger delay (3 s) of the onset of the heart rate response to down-tilt (*Paper V*, Tab. 1) and similar differences in time delays between up and down tilt have been observed by Sundblad *et al.* (2000b) during very light exercise. They ascribed the difference in time delay between tilt directions to differences in sympathetic background activity when starting tilts from upright and supine. Yang *et al.* (1994) showed in dogs that a preceding train of sympathetic nerve activity to the heart markedly slowed the rate at which heart rate changed in response to a subsequent change in vagal activity. However, the disappearance of up-tilt induced overshoot of cardiac output during and immediately after bed rest (*Paper V*, Fig. 10) cannot be explained by an increased latency of tachycardia responses to up tilt; latencies of this response did not change between experimental days. Instead, the present set of data propose that it is the blood volume in the lung circulation that determines to what extent a temporary increase of the left ventricular output can be maintained despite an assumed tilt-induced reduction of right ventricular inflow during up tilt. Indeed, in a preliminary analysis of an invasive recording during rapid tilting (Fig. 6), it was found that CVP seemed to decline faster than PCWP at downtilt, and increases faster at up-tilt, suggesting that the lungs act as an preload-reservoir for the left ventricle.

As further evidence of a reduction in intrathoracic blood volume, it was shown in *Paper IV,* in the same subjects, that transthoracic impedance tended to be increased at R0 and then rapidly recover between R0 and R3. Transthoracic impedance has an inverse relationship to intrathoracic fluid volume (Petersen *et al.* 1994). There is a similar time course for changes in lung diffusion capacity (Montmerle *et al.*), also in favour of a rapid restoration of pulmonary blood volume during the first days after bed rest as plasma volume recovers (Fortney *et al.* 1991). The recovery time course of the initial overshoot upon up tilt at rest also appears to start between R0 and R3, which favours the assumption that blood volume in the pulmonary circulation is an important determinant of this overshoot phenomenon.

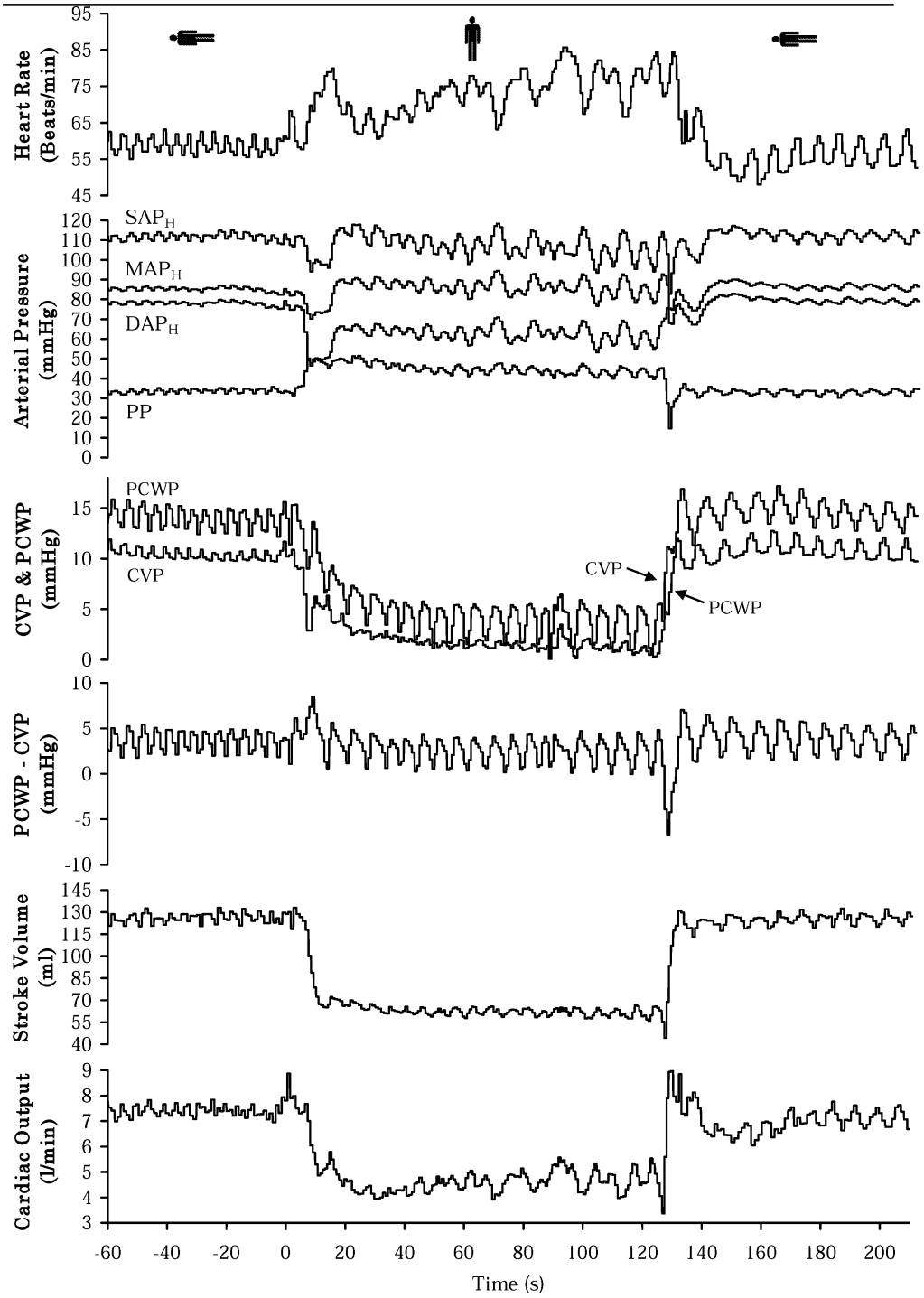

Fig. 6. Individual beat-by-beat recordings of invasive cardiovascular parameters in one resting subject during one uptilt and one downtilt. Arterial pressure is measured in the radial artery. CVP and PCWP are plotted as an average over each heart period. SV and CO are calculated from the calibrated contour of the arterial pressure curve. Vertical dotted lines indicate where the rapid up- and down-tilt takes place.
Preliminary data from P. Sundblad, J. Spaak and L. Kaijser.

Baroreflex sensitivity

To allow comparison with previous research with differing baroreflex sensitivity testing paradigms, baroreflex sensitivity was determined both as ΔHR/ΔMARP and ΔRRI/ΔSARP. The responses to up tilt and down tilt were studied separately and baroreflex sensitivity was found to be marginally reduced when studied at rest, and then only during up tilt (*Paper V*, Fig. 5). When estimated during exercise, however, baroreflex sensitivity was markedly reduced at D60 and D113, and showed no signs of recovery during the 15 days of the post-bed rest observation period. However, despite the fact that the exaggerated upright pre-tilt tachycardia at D113 and R0 recovered gradually at R3 and R15 towards the baseline level, baroreflex sensitivity as obtained from down tilts did not increase (*Paper V*, Fig. 6). Therefore, the present findings suggest a decline of baroreflex sensitivity when determined within the physiological range of arterial receptor pressure changes encountered during a sudden shift in posture. This decline was most obvious during exercise in combination with hypotensive stimuli and was not obvious at rest in combination with hypertensive stimuli.

As baroreflex sensitivity here is defined as the ratio between tilt-induced chronotropic and baroreceptor blood pressure responses, a fall in baroreflex sensitivity could be caused by a reduced chronotropic response, an increased blood pressure response, or both. It appears that the principal difference between baseline and bed rest was an 60-70% increase of the amplitude of the tilt-induced blood pressure responses to up and down tilt in combination with only a 30-40% corresponding increase of the combined chronotropic responses to up and down tilt (*Paper V*, Fig. 4). For up-tilt responses, corresponding figures were a 64-70% increase of the SARP response combined with a mere 8-14% increase of the heart rate response amplitude. Thus the approximately 50% reduction of baroreflex sensitivity to up tilt during exercise was accounted for by a relative decrease of the chronotropic responses, especially during up tilt.

Interestingly, parallel studies of baroreflex sensitivity on the same subjects were performed by Kamiya *et al.* (2000a) but using different approaches, who found attenuated spontaneous baroreflex sensitivity after both 60 and 120 days, which is in support of the present finding of reduced baroreflex sensitivity to hypotensive stimuli at rest on R0, that is one day later. The finding of Kamiya *et al.* (2000a) of attenuated arterial-cardiac baroreflex sensitivity on D60, however, is at variance with the present findings; there are, however, important methodological differences between the two ways to assess baroreflex sensitivity. Thus, the blood pressure stimulus employed by Kamiya *et al.* (2000a), namely the variation of blood pressure during spontaneous breathing, is one order of magnitude smaller than that occurring during tilt. Another difference between the methods is that of potentially confounding influences, which are of different origins in the two methods; during spontaneous breathing there are non-baroreflex links between changes of instantaneous lung volume and heart rate (Yana *et al.* 1993), whereas with whole-body tilting, non-baroreflex

influences may arise from vestibular stimulation (Ray 2000).

It can be speculated that the increased sympathetic activity in the present subjects (Kamiya *et al.* 2000a) caused decreased arterial-cardiac chronotropic baroreflex sensitivity by sympatho-vagal interaction. Heart rate responses to short-lasting arterial pressure stimuli are mainly mediated through modulation of vagal outflow to the heart (Eckberg and Sleight 1992), and there is evidence that antecedent stimulation of cardiac sympathetic nerves slows the chronotropic response to vagal stimuli so that it becomes gradual rather than instantaneous (Yang *et al.* 1994) as is the case without antecedent sympathetic stimulation (Warner and Cox 1962). Thus vagally-mediated heart rate responses to short-lasting stimuli such as breath-synchronous arterial pressure fluctuations or tilt-induced changes in MARP may not have time to develop fully in the presence of an increased sympathetic outflow to the heart. The origin of this increased sympathetic outflow after bed rest is not known; Kamiya *et al.* (2000a) speculate that a diminished cardiac size may result in a smaller inhibitory effect of cardiopulmonary baroreceptors on sympathetic outflow. Indeed, the present findings of indirect signs of reduced cardiac size are compatible with such an explanation.

Sundblad *et al.* (2000b) studied exercising subjects, who were rapidly tilted between supine and upright and the reverse during work at different intensities. They modelled the heart rate responses to tilt using varying fractional contribution of rapid vagal and slower sympathetic modulations of heart rate (Warner and Cox 1962). They found that tachycardic responses to hypotensive stimuli during up tilt were markedly slower at 100 and 150 W than at 50 W, probably because of the increasingly important role of sympathetic inputs for tachychardic responses at the higher workloads. Thus, the present set of data proposes that the greater relative effort required to perform 50 W exercise during and after compared to before bed rest also contributed during exercise to a slowing and thereby to an attenuation of tachychardic responses to hypotensive stimuli.

Time courses of baroreflex sensitivity during bed rest

The unique feature of having test sessions during the 120-day bed rest period enabled an evaluation of whether impairments of cardiovascular functions become gradually more severe with longer bed rest. The results of Kamiya *et al.* (2000a) and the present exercise results support the notion that most if not all of the attenuation of arterial-cardiac-chronotropic baroreflex sensitivity had occurred during the first 60 days of bed rest, with no additional attenuation thereafter. Although gravity-dependent loading cycles are practically eliminated during strict HDT, the beat-by-beat stimulation from cardiac activity persists, and such stimulation may be much more important than gravity-induced loading/unloading cycles for maintaining the integrity of the arterial baroreflex function. Had, on the other hand, gravity-dependent baroreceptor loading cycles been essential to maintain baroreflex function, one would have expected a gradual decline of baroreflex function over time, combined with more severe impairments.

Functional importance of baroreflex alterations

Having established that long-term bed rest results in attenuation of arterial-cardiac-chronotropic baroreflexes (Kamiya *et al.* 2000a, and the present *Paper V*), it is appropriate to consider the functional importance of this finding. Although calculation of baroreflex sensitivity from the ratio ΔHR/ΔMARP appears a less sensitive way to detect HDT-induced alterations of baroreflex sensitivity than ΔRRI/ΔSARP (*Paper V,* Fig. 5, Fig. 6) the former baroreflex sensitivity-algorithm probably provides a more fair estimate of the potential impact on the control of blood pressure, since mean arterial blood pressure changes are directly proportional to concomitant changes in heart rate. For the hypertensive stimuli during down tilt, there were no significant alterations of ΔHR/ΔMARP during either rest or exercise, and for hypotensive baroreflex stimuli during up tilt there was no significant attenuation at rest, but a trend towards baroreflex sensitivity attenuation in the exercise tests during bed rest. These results are generally in agreement with those of Sundblad *et al.* (2000a), who found no changes of ΔHR/ΔMARP in exercising men after 42 days of HDT.

Cardiac impairment after bed rest

Stroke volume was found to be reduced during supine exercise after both bed rest studies, and did not return to pre-HDT values even after 15 to 32 days of recovery. Immediately after bed rest, stroke volume reductions could be, to some extent, explained by a decrease in circulating blood volume. However, stroke volume showed only a partial recovery after 15 days of recovery (*Paper IV*) and 32 days of recovery (*Paper III*), and by both these dates, plasma volume should have been fully recovered (Fortney *et al.* 1991; Johansen *et al.* 1997). This absence of full recovery after bed rest strongly indicates a reduced cardiac size.

In the 120-day study (*Paper IV*), the reductions in stroke volume during supine exercise averaged -4.7% at D60, -18.2% at D113, and -20.9% at R0. In the 42-day study (*Paper III*), larger decreases were found in supine stroke volume that averaged -25% at R0. Other groups have also found faster and larger reductions in stroke volume during supine exercise than those found in the 120-day study. Saltin *et al.* (1968) found reductions in stroke volume by -24% in five young subjects (age ranged from 19 to 21 years) exposed to 20 days of bed rest. Several factors might explain the smaller reduction after the 120-day study described in *Paper IV*. In the 42-day study, the subjects were more restricted. No deviations were allowed from the -6° HDT position, and no exercise was allowed during the bed rest. In contrast, in the 120-day study the subjects spent on average 4 minutes per day in postures deviating more than 30° from the HDT position. However, these deviations should likely have minor influence, since it has been shown that quite extensive periods (1.5 to 2 hours) of orthostatic stress (lower-body negative pressure) are required to prevent cardiovascular deconditioning (Güell *et al.* 1991). It is more likely that, due to the small number of subjects, individual differences might have affected the results. The subjects studied in *Paper IV* differed from

those in *Paper III*, and from most previous studies, by spanning a greater range in age (23 to 42 years), weight (63 to 114 kg) and height (175-190 cm). Furthermore, the subjects in *Paper IV* exhibited a higher heart rate during upright exercise at baseline (114±3.7 beats/min; mean±SE) than those in *Paper III* (106±3.8 beats/min), suggesting a lower physical fitness level. Thus, the divergence in adaptation by these two groups emphasize that individual differences are of major importance, and demand further study. Nonetheless, the time-course of the stroke volume decline during supine exercise in *Paper IV* indicates that cardiac remodelling is slow and still in progress after 60 days bed rest.

Ventricular interdependence

In an attempt to indirectly assess changes in cardiac size after bed rest, Sundblad *et al.* (2000a) studied the response of arterial pulse pressure to sudden tilts before and after a 42 day HDT period. They observed that sudden tilts from 80° to 0° resulted in a marked and rapid increase of pulse pressure, but before that and during the first few heart beats after the down tilt there was a marked drop in pulse pressure. This transient drop was absent on the first day after the 42 day long HDT period. The most plausible explanation for this drop is direct diastolic interdependence, where a sudden increase of right ventricular inflow results in a leftward displacement of the interventricular septum during diastole, with a consequent temporary interference with left ventricular diastolic filling and left ventricular stroke volume (Robotham and Mintzner 1979; Brinker *et al.* 1980; Sundblad *et al.* 2000b).

Preliminary data from an invasive study provide further evidence for ventricular interdependence as the cause of the initial drop of pulse pressure and estimated stroke volume: in fig 6, CVP (here measured as right atrial pressure) temporarily exceeds left atrial pressure (here estimated from PCWP) early at downtilt, and at the same time as the initial pulse pressure and stroke volume drop can be observed.

Ventricular interdependence is augmented by pericardial constraint, which beyond a certain limit will not allow one ventricle to expand unless it is at the expense of the other ventricle. Eventually, however, the output from the two ventricles must match because the interposed pulmonary vasculature has a limited buffer capacity for disparities between right and left ventricular output. The disappearance of the initial pulse pressure drop on the first day after a 42-day HDT period (Sundblad *et al.* 2000a) was interpreted as a sign of decreased cardiac size, and an associated reduced degree of pericardial constraint. In the present study, beat-by-beat stroke volume was assessed, and the results could indeed confirm the predictions based on pulse pressure measurements by Sundblad *et al.* (2000a). Thus, immediately upon down tilt at baseline there was a prominent short-lasting drop of stroke volume. This drop in stroke volume preceded any tilt-induced changes in heart rate (*Paper V*, Table 1) suggesting that the transient stroke volume drop was not the result of alterations of autonomic output to the heart. The amplitude of this transient stroke volume drop tended to fall

gradually during the bed rest period and then recover gradually during the post-bed rest period. Although the same trend was seen both at rest and during exercise (*Paper V*, Fig. 9) significant reductions of the initial stroke volume dip were observed only at rest on D113 and R0. The present findings support the notion of a temporary reduction of cardiac size during and immediately after long-term bed rest. Such a reduction in size would allow the right ventricle to expand during a rapid increase in filling pressure without interfering with the diastolic filling of the left ventricle. The relatively rapid recovery of the signs of ventricular interdependence during down tilt are in contrast to the long duration of the stroke volume limitation that was observed throughout the recovery period during supine exercise after 42 days of HDT (*Paper III*) and after 120 days HDT (*Paper IV*). It must be kept in mind that the increase in right ventricular diastolic inflow during a sudden down tilt exceed that during steady-state exercise. Therefore, the diastolic volume of the heart during down tilt probably temporarily exceeded that during steady-state supine conditions, allowing ventricular interdependence to recur already at R3 as a result of the rapidly recovering plasma volume and the associated increase of cardiac preload. The present set of data thus suggest that the limitation of cardiac diastolic size after bed rest caused by a decreased compliance is a relative rather than an absolute limitation.

Respiratory stroke volume fluctuations

Marked breath-synchronous stroke volume fluctuations were observed during the pre-HDT period (*Paper V*, Fig. 7 & 9). This phenomenon has previously been described by Toska and Eriksen (1993), who determined beat-by-beat stroke volume with a suprasternal echo-Doppler probe in humans with and without parasympathetic blockade with atropine. If the fluctuations had been caused primarily by baroreflex or medullary respiratory modulation of vagal outflow, they would be attenuated or eliminated by atropine. On the other hand, if they were caused by breath-synchronous variations in right ventricular inflow and ventricular interdependence, atropine treatment would amplify the stroke volume fluctuations because of less efficient baroreflex buffering, since the baroreflex chronotropic control in the respiratory frequency range mainly relies on modulation of vagal outflow (Eckberg and Sleight 1992). There were increased stroke volume fluctuations with atropine, and Toska and Eriksen (1993) concluded that the rhythmic stroke volume decrement during each inspiration was caused primarily by ventricular interdependence. In the present study (*Paper V*), stroke volume fluctuations were quantified with spectral analysis, and both upright and supine resting stroke volume fluctuations within the respiratory frequency range were attenuated from D60 and onwards. It is of interest that whereas the initial stroke volume dip at down tilt recovers gradually during 15 days after bed rest, the breath-synchronous stroke volume variations at rest remain significantly depressed throughout the post-HDT observation period. It can be assumed that the transient increase of right ventricular inflow and filling pressure is much larger during a sudden down tilt than during a normal inspiration, so that

ventricular interdependence is more easily provoked during tilting than during normal breathing. Thus, breath-synchronous stroke volume variations, or rather absence of these, may be a more sensitive sign of an altered ventricular interaction, than rapid downtilting.

Time course of deconditioning and recovery

All together, the different indices of ventricular interdependence show signs of reduced cardiac size lasting longer than 15 days after the end of the bed rest periods. As plasma volume and diastolic filling pressures are rapidly improved after bed rest (Fortney *et al.* 1991) cardiac volumes appear to be able to be temporarily normalized by large increases in right ventricular inflow, but remains limited under more steady-state conditions. These data are compatible with structural changes of the myocardium, which are not normalized within a 15-day post-HDT period.

Summary and conclusions

The unique durations of present bed rest studies in combination with extensive experimental protocols have enabled us to put forward a coherent description of the hemodynamic adaptations to long term bed rest.

The aim of *Paper I* was to elucidate the separate effects of voluntary motor activation and muscle chemoreflex activation on arterial baroreflexes.

It was found that isometric arm contraction shifts the baroreflex response curve to operate around a higher level of heart rate and mean arterial pressure with unaltered range or sensitivity, while post-contraction ischemia alone causes the baroreflex to operate around an unchanged heart rate but an increased arterial pressure, as compared to rest. Therefore, during an isometric forearm contraction, the elevation of systemic arterial blood pressure is mainly caused by muscle ischemia, whereas the heart rate response is entirely due to somatomotor activation. These findings formed the basis for the methods that were subsequently applied in *Paper II*.

The aim of *Paper II* was to characterize the cardiovascular responses to isometric muscle action during and after very long term spaceflight and bed rest by determining the heart rate and mean arterial pressure responses to isometric lower arm contraction.

Impaired cardiovascular responses to isometric muscle action were found. The impairment included both the chronotropic response to somatomotor activation and the pressor response to muscle ischemia. This is the first direct evidence of an impaired cardiovascular response to isometric muscle action after real and simulated microgravity, and may partly explain some of the difficulties associated with returning to normal gravity and normal activity.

The aim of *Paper III* was to characterize cardiac performance after bed rest during exercise in supine and upright positions.

Marked reductions in both supine and upright stroke volume were found immediately after the bed rest, with the largest reductions for stroke volume in the supine position. Within two days, there was a partial recovery of stroke volume in the upright but not in the supine position, where

stroke volume remained reduced still after 32 days of recovery.

The rapid recovery of the plasma volume immediately after bed rest parallelled the recovery of stroke volume during upright exercise, which supports our hypothesis, that bed rest induced stroke volume reductions in an upright position mainly reflect alterations in preload.

The lack of recovery in stroke volume during supine exercise, where stroke volumes approache the upper limit, indicates that bed rest induces significant structural alterations of the heart, which takes more than one month to recover.

The aim of *Paper IV* was to bring the analysis made in *Paper III* further by determine cardiac output and stroke volume during rest in supine and upright positions. Furthermore, in this three times longer study (120 days) it was allowed to access the subjects not only after but also during (day 60 and day 113) of the bed rest, which enabled an evaluation of the time-course of the adaptations.

Bed rest was found to induce cardiac output and stroke volume reductions in both supine and upright posture, both during rest and during exercise. The stroke volume reductions during supine exercise developed gradually over time, were still in progress after 60 days of bed rest, and showed a protracted recovery. This reconfirms our hypothesis from *Paper III* that bed rest induces structural changes of the heart.

The stroke volume reductions at rest in the upright position were fully developed at the first experimental occasion during the bed rest, showed no further decline, and recovered rapidly within three days after the bed rest. As during upright exercise, this pattern parallelled that of the plasma volume loss during, and the corresponding recovery after, bed rest, and supports our second hypothesis, that bed rest induced stroke volume reductions at rest and in an upright position mainly reflect alterations in preload.

The aim of *Paper V* was to assess the relative impacts of baroreflex and hemodynamic impairments during and after very long-term bed rest and during both rest and exercise.

First, it could be confirmed that there was a preserved ability to maintain the principal control variable, the arterial blood pressure, during steady-state conditions after bed rest.

Second, it was found that bed rest caused markedly increased blood-pressure deviations during rapid tilts in exercise, and a similar but less marked tendency during rapid tilts at rest. Factors such as a stroke volume limitation are more critical during the greater need for tissue perfusion at exercise. Thus, the present findings confirm our hypothesis of an impaired reflex and effector organ function during sudden orthostatic challenges at exercise.

Third, it was found that bed rest caused an attenuated baroreflex sensitivity for vagally mediated chronotropic responses to arterial pressure stimuli after bed rest, however, this appears to be of modest functional significance both at rest and during light exercise.

Last, both hemodynamic and baroreflex impairments had similar time courses, which supports our hypothesis that reductions of cardiac size may be a common denominator for both hemodynamic and baroreflex impairments.

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REFERENCES

Abboud FM, Eckberg DL, Johannsen UJ, Mark AL. Carotid and cardiopulmonary baroreceptor control of splanchnic and forearm vascular resistance during venous pooling in man. *J Physiol (Lond)*. 286 173-184. 1979

Adams V, Jiang H, Yu J, Möbius-Winkler S, Fiehn E, Linke A, Weigl C, Schuler G, Hambrecht R. Apoptosis in skeletal myocytes of patients with chronic heart failure is associated with exercise intolerance. *J Am Coll Cardiol*. 33 (4): 959-965. 1999

Alam M, Smirk FH. Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. *J Physiol (Lond)*. 89 372-383. 1937

Anonymous. Task force on countermeasures: Final report. D1-D19. NASA, 1997

Anonymous. Spinoff 2000. In: *Spinoff*. Eds: Ferrera D, Rush Z. National Aeronautics and Space Administration, Office of Aerospace Technology, Hanover, Maryland. 2000

Antonutto G, Girardis M, Tuniz D, di Prampero PE. Noninvasive assessment of cardiac output from arterial pressure profiles during exercise. *Eur J Appl Physiol*. 72 (1-2): 18-24. 1995

Antonutto G, Capelli C, Girardis M, Zamparo P, di Prampero PE. Effects of microgravity on maximal power of lower limbs during very short efforts in humans. *J Appl Physiol*. 86 (1): 85-92. 1999

Arbeille P, Gauquelin G, Pottier JM, Pourcelot L, Guell A, Gharib C. Results of a 4-week head-down tilt with and without LBNP countermeasure: II. Cardiac and peripheral hemodynamics--comparison with a 25-day spaceflight. *Aviat Space Environ Med*. 63 (1): 9-13. 1992

Asher RA. The dangers of going to bed. *Br Med J*. 4 967-968. 1947

Baisch F, Beck L, Blomqvist G, Wolfram G, Drescher J, Rome JL, Drummer C. Cardiovascular response to lower body negative pressure stimulation before, during, and after space flight. *Eur J Clin Invest*. 30 (12): 1055-1065. 2000

Berg HE, Larsson L, Tesch PA. Lower limb skeletal muscle function after 6 wk of bed rest. *J Appl Physiol*. 82 (1): 182-188. 1997

Bergenwald L, Eklund B, Freyschuss U. Circulatory effects in healthy young men of atrial pacing at rest and during isometric handgrip. *J Physiol (Lond)*. 318 445-453. 1981

Bevegård BS, Holmgren A, Jonsson B. The effect of body position on the circulation at rest and during exercise, with special reference to the influence on the stroke volume. *Acta Physiol Scand*. 49 279-298. 1960

Blomqvist CG. Cardiovascular adjustments to gravitational stress. In: *Handbook of Physiology: The Cardiovascular System. 2nd ed*. American Physiological Society, Bethesda, Md. 1983

Blomqvist GC. Regulation of the systemic circulation at microgravity and during readaptation to 1g. *Med Sci Sports Exerc*. 28 (10 Suppl): S9-13. 1996

Bohnn BJ, Hyatt KH, Kamenetsky LG, Calder BE, Smith WM. Prevention of bedrest induced orthostatism by 9-alpha-fluorohydrocortisone. *Aerosp Med*. 41 (5): 495-499. 1970

Bonde-Petersen F, Norsk P, Suzuki Y. A comparison between freon and acetylene rebreathing for measuring cardiac output. *Aviat Space Environ Med*. 51 (11): 1214-1221. 1980

Bonde-Petersen F, Suzuki Y, Kawakubo K, Gunji A. Effect of 20 days bed rest upon peripheral capillary filtration rate, venous compliance and blood flow in arms and legs. *Acta Physiol Scand Suppl*. 616 65-69. 1994

Brinker JA, Weiss JL, Lappe DL, Rabson JL, Summer WR, Permutt S, Weisfeldt ML. Leftward septal displacement during right ventricular loading in man. *Circulation*. 61 (3): 626-633. 1980

Buckey JC, Peshock RM, Blomqvist CG. Deep venous contribution to hydrostatic blood volume changes in the human leg. *Am J Cardiol*. 62 449-453. 1988

Buckey JC, Gaffney FA, Lane LD, Levine BD, Watenpaugh DE, Blomqvist CG. Central venous pressure in space. [see comments]. *N Engl J Med*. 328 (25): 1853-1854. 1993

Buckey JC, Jr., Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Moore WE, Gaffney FA, Blomqvist CG. Orthostatic intolerance after spaceflight. *J Appl Physiol*. 81 (1): 7-18. 1996a

Buckey JC, Jr., Gaffney FA, Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Yancy CW, Jr., Meyer DM, Blomqvist CG. Central venous pressure in space. *J Appl Physiol*. 81 (1): 19-25. 1996b

Bungo MW, Charles JB, Johnson PC, Jr. Cardiovascular deconditioning during space flight and the use of saline as a countermeasure to orthostatic intolerance. *Aviat Space Environ Med*. 56 (10): 985-990. 1985

Burggren W, Farrell A, Lillywhite H. Vertebrate cardiovascular systems. In: *Handbook of Physiology: Comparative Physiology*, Ch. 4. American Physiological Society, Bethesda, Md. 1997

Charles JB, Lathers CM. Cardiovascular adaptation to spaceflight. *J Clin Pharmacol*. 31 (10): 1010-1023. 1991

Chase GA, Grave C, Rowell LB. Independence of changes in functional and performance capacities attending prolonged bed rest. *Aerosp Med*. 37 (12): 1232-1238. 1966

Convertino VA. Potential benefits of maximal exercise just prior to return from weightlessness. *Aviat Space Environ Med*. 58 (6): 568-572. 1987

Convertino VA. Exercise and adaptation to microgravity environments. In: *Handbook of Physiology. Environmental Physiology*, sect 4, vol II, ch 36. American Physiological Society, Bethesda, Md. 1996a

Convertino VA. Clinical aspects of the control of plasma volume at microgravity and during return to one gravity. *Med Sci Sports Exerc*. 28 (10 Suppl): S45-52. 1996b

Convertino VA. Exercise as a countermeasure for physiological adaptation to prolonged spaceflight. *Med Sci Sports Exerc*. 28 (8): 999-1014. 1996c

Convertino VA, Doerr DF, Stein SL. Changes in size and compliance of the calf after 30 days of simulated microgravity. *J Appl Physiol*. 66 (3): 1509-1512. 1989

Convertino VA, Kirby CR, Karst GM, Goldwater DJ. Response to muscular exercise following repeated simulated weightlessness. *Aviat Space Environ Med*. 56 (6): 540-546. 1985

Convertino VA, Doerr DF, Guell A, Marini JF. Effects of acute exercise on attenuated vagal baroreflex function during bed rest. *Aviat Space Environ Med*. 63 (11): 999-1003. 1992

Convertino VA, Doerr DF, Ludwig DA, Vernikos J. Effect of simulated microgravity on cardiopulmonary baroreflex control of forearm vascular resistance. *Am J Physiol Regulatory Integrative Comp Physiol*. 266 (6 Pt 2): R1962-1969. 1994

Convertino VA, Previc FH, Ludwig DA, Engelken EJ. Effects of vestibular and oculomotor stimulation on responsiveness of the carotid-cardiac baroreflex. *Am J Physiol Regulatory Integrative Comp Physiol*. 273 (2 Pt 2): R615-622. 1997a

Convertino VA, Ludwig DA, Gray BD, Vernikos J. Effects of exposure to simulated microgravity on neuronal catecholamine release and blood pressure responses to norepinephrine and angiotensin. *Clin Auton Res.* 8 (2): 101-110. 1998

Convertino VA, Doerr DF, Eckberg DL, Fritsch JM, Vernikos-Danellis J. Head-down bed rest impairs vagal baroreflex responses and provokes orthostatic hypotension. *J Appl Physiol.* 68 (4): 1458-1464. 1990a

Convertino VA, Polet JL, Engelke KA, Hoffler GW, Lane LD, Blomqvist CG. Evidence for increased beta-adrenoreceptor responsiveness induced by 14 days of simulated microgravity in humans. *Am J Physiol Regulatory Integrative Comp Physiol.* 273 (1 Pt 2): R93-99. 1997b

Convertino VA, Thompson CA, Benjamin BA, Keil LC, Savin WM, Gordon EP, Haskell WL, Schroeder JS, Sandler H. Haemodynamic and adh responses to central blood volume shifts in cardiac-denervated humans. *Clin Physiol.* 10 (1): 55-67. 1990b

Cooke WH, Ames JI, Crossman AA, Cox JF, Kuusela TA, Tahvanainen KU, Moon LB, Drescher J, Baisch FJ, Mano T, Levine BD, Blomqvist CG, Eckberg DL. Nine months in space: Effects on human autonomic cardiovascular regulation. *J Appl Physiol.* 89 (3): 1039-1045. 2000

Crandall CG, Engelke KA, Convertino VA, Raven PB. Aortic baroreflex control of heart rate after 15 days of simulated microgravity exposure. *J Appl Physiol.* 77 (5): 2134-2139. 1994

Custaud MA, Millet C, Frutoso J, Maillet A, Gauquelin G, Gharib C, Fortrat JO. No effect of venoconstrictive thigh cuffs on orthostatic hypotension induced by head-down bed rest. *Acta Physiol Scand.* 170 (2): 77-85. 2000

Delp MD. Myogenic and vasoconstrictor responsiveness of skeletal muscle arterioles is diminished by hindlimb unloading. *J Appl Physiol.* 86 (4): 1178-1184. 1999

Devereaux RB, Pini R, Aurigemma GP, Roman MJ. Measurement of left ventricular mass: Methodology and expertise. *J Hypertens.* 16 257-258. 1997

Drummer C, Gerzer R, Baisch F, Heer M. Body fluid regulation in micro-gravity differs from that on earth: An overview. *Pflugers Arch.* 441 (2-3 Suppl): R66-72. 2000

Ebert TJ, Smith JJ, Barney JA, Merrill DC, Smith GK. The use of thoracic impedance for determining thoracic blood volume changes in man. *Aviat Space Environ Med.* 57 (1): 49-53. 1986

Eckberg DL, Sleight P. Human baroreflexes in health and disease. University Press, New York, Oxford. 1992

Eckberg DL, Cavanaugh MS, Mark AL, Abboud FM. A simplified neck suction device for activation of carotid baroreceptors. *J Lab Clin Med.* 85 (1): 167-173. 1975

Eckberg DL, Convertino VA, Fritsch JM, Doerr DF. Reproducibility of human vagal carotid baroreceptor-cardiac reflex responses. *Am J Physiol Regulatory Integrative Comp Physiol.* 263 (1 Pt 2): R215-220. 1992

Eiken O. Responses to changed perfusion pressure in working muscles--factors to be considered in exercise testing in space flights? *Physiologist.* 32 (1 Suppl): S12-15. 1989

Engelke KA, Doerr DF, Convertino VA. A single bout of exhaustive exercise affects integrated baroreflex function after 16 days of head-down tilt. *Am J Physiol Regulatory Integrative Comp Physiol.* 269 (3 Pt 2): R614-620. 1995

Ertl AC. and The Neurolab ANS Team. Sympathetic responses to orthostatic stress is preserved in space (abstract). *Circulation.* 98 Suppl I 471. 1998

Essandoh LK, Duprez DA, Shepherd JT. Postural cardiovascular reflexes: Comparison of responses of forearm and calf resistance vessels. *J Appl Physiol*. 63 (5): 1801-1805. 1987

Fadel PJ, Ogoh S, Watenpaugh DE, Wasmund W, Olivencia-Yurvati A, Smith ML, Raven PB. Carotid baroreflex regulation of sympathetic nerve activity during dynamic exercise in humans. *Am J Physiol Heart Circ Physiol*. 280 (3): H1383-1390. 2001

Ferretti G, Girardis M, Moia C, Antonutto G. Effects of prolonged bed rest on cardiovascular oxygen transport during submaximal exercise in humans. *Eur J Appl Physiol*. 78 (5): 398-402. 1998

Ferretti G, Berg HE, Minetti AE, Moia C, Rampichini S, Narici MV. Maximal instantaneous muscular power after prolonged bed rest in humans. *J Appl Physiol*. 90 (2): 431-435. 2001

Ferretti G, Antonutto G, Denis C, Hoppeler H, Minetti AE, Narici MV, Desplanches D. The interplay of central and peripheral factors in limiting maximal O_2 consumption in man after prolonged bed rest. *J Physiol (Lond)*. 501 (Pt 3): 677-686. 1997

Fitts RH, Riley DR, Widrick JJ. Physiology of a microgravity environment invited review: Microgravity and skeletal muscle. *J Appl Physiol*. 89 (2): 823-839. 2000

Folkow B, Haglund U, Jodal M, Lundgren O. Blood flow in the calf muscle of man during heavy rhythmic exercise. *Acta Physiol Scan*. 81 (2): 157-163. 1971

Fortney SM, Schneider VS, Greenleaf JE. The physiology of bed rest. In: *Handbook of Physiology. Environmental Physiology*, sect 4, vol I, ch 39. American Physiological Society, Bethesda, Md. 1996

Fortney SM, Hyatt KH, Davis JE, Vogel JM. Changes in body fluid compartments during a 28-day bed rest. *Aviat Space Environ Med*. 62 (2): 97-104. 1991

Freyschuss U. Cardiovascular adjustment to somatomotor activation. *Acta Physiol Scan*. Suppl 342 1970

Fritsch JM, Charles JB, Bennett BS, Jones MM, Eckberg DL. Short-duration spaceflight impairs human carotid baroreceptor-cardiac reflex responses. *J Appl Physiol*. 73 (2): 664-671. 1992

Fritsch-Yelle JM, Whitson PA, Bondar RL, Brown TE. Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight. *J Appl Physiol*. 81 (5): 2134-2141. 1996

Fritsch-Yelle JM, Charles JB, Jones MM, Beightol LA, Eckberg DL. Spaceflight alters autonomic regulation of arterial pressure in humans. *J Appl Physiol*. 77 (4): 1776-1783. 1994

Gaffney FA, Buckey JC, Lane LD, Hillebrecht A, Schulz H, Meyer M, Baisch F, Beck L, Heer M, Maass H. The effects of a 10-day period of head-down tilt on the cardiovascular responses to intravenous saline loading. *Acta Physiol Scand Suppl*. 604 121-130. 1992

Gauer OH, Thron HL. Postural changes in the circulation. In: *Handbook of Physiology: Circulation*. Vol. III, Sect 2, Ch. 67. Am. Physiol. Soc., Washington D.C. 1965

Gazenko OG, Shulzhenko EB, Egorov AD. Cardiovascular changes in prolonged space flights. *Acta Physiol Polonica*. 37 (2): 53-68. 1986

Goldstein DS, Vernikos J, Holmes C, Convertino VA. Catecholaminergic effects of prolonged head-down bed rest. *J Appl Physiol*. 78 (3): 1023-1029. 1995

Goldstein MA, Edwards RJ, Schroeter JP. Cardiac morphology after conditions of microgravity during cosmos 2044. *J Appl Physiol*. 73 (2 Suppl): 94S-100S. 1992

Graveline DE, McCally M. Body fluid distribution: Implications for zero gravity. *Aerosp Med*. 33 (11): 1281-1290. 1962

Greenleaf JE, Wade CE, Leftheriotis G. Orthostatic responses following 30-day bed rest deconditioning with isotonic and isokinetic exercise training. *Aviat Space Environ Med.* 60 (6): 537-542. 1989

Greenleaf JE, Bernauer EM, Young HL, Morse JT, Staley RW, Juhos LT, Van Beaumont W. Fluid and electrolyte shifts during bed rest with isometric and isotonic exercise. *J Appl Physiol.* 42 (1): R59-66. 1977

Grigoriev AI. Correction of changes in fluid-electrolyte metabolism in manned space flights. *Aviat Space Environ Med.* 54 (4): 318-323. 1983

Guell A, Braak L, Le Traon AP, Gharib C. Cardiovascular adaptation during simulated microgravity: Lower body negative pressure to counter orthostatic hypotension. *Aviat Space Environ Med.* 62 (4): 331-335. 1991

Halberg F, Cornelissen G, Schwartzkopff O, Syutkina EV, Grigoriev AE, Mitish MD, Yatsyk GV, Studenikin MY, Gubin D, Gubin G, Siegelova J, Fiser B, Dusek J, Homolka P, Watanabe Y, Otsuka K, Perfetto F, Tarquini R, Delmore P. Spin-offs from blood pressure and heart rate studies for health care and space research. *In Vivo.* 13 (1): 67-76. 1999

Hargens AR. Recent bed rest results and countermeasure development at nasa. *Acta Physiol Scand Suppl.* 616 103-114. 1994

Harrison TR. Abuse of rest as a therapeutic measure for patients with cardiovascular disease. *J Am Med Assoc.* 125 1075-1077. 1944

Haruna Y, Suzuki Y. Blood pressure and heart rate responses to sudden change of posture during 20 days of simulated microgravity (-6° head-down tilt). *J Grav Physiol.* 4 (2): 37-38. 1997

Henry WL, Epstein SE, Griffith JM, Goldstein RE, Redwood DR. Effects of prolonged space flight on cardiac functions and dimensions. In: *Biomedical Results from Skylab.* Ch 35. NASA, 1977

Herault S, Fomina G, Alferova I, Kotovskaya A, Poliakov V, Arbeille P. Cardiac, arterial and venous adaptation to weightlessness during 6-month mir spaceflights with and without thigh cuffs (bracelets). *Eur J Appl Physiol.* 81 (5): 384-390. 2000

Humpreys PW, Lind AR. The blood flow through active and inactive muscles of the forearm during sustained hand-grip contractions. *J Physiol (Lond).* 166 120-135. 1963

Hung J, Goldwater D, Convertino VA, McKillop JH, Goris ML, DeBusk RF. Mechanisms for decreased exercise capacity after bed rest in normal middle-aged men. *Am J Cardiol.* 51 (2): 344-348. 1983

Hyatt KH, West DA. Reversal of bedrest-induced orthostatic intolerance by lower body negative pressure and saline. *Aviat Space Environ Med.* 48 (2): 120-124. 1977

Hyatt KH, Kamenetsky LG, Smith WM. Extravascular dehydration as an ethiological factor in post-recumbency orthostatism. *Aerosp Med.* 40 (6): 644-650. 1969

Imholz BP, Settels JJ, van der Meiracker AH, Wesseling KH, Wieling W. Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. *Cardiovasc Res.* 24 (3): 214-221. 1990

Jellema WT, Imholz BP, van Goudoever J, Wesseling KH, van Lieshout JJ. Finger arterial versus intrabrachial pressure and continuous cardiac output during head-up tilt testing in healthy subjects. *Clin Sci (Colch).* 91 (2): 193-200. 1996

Jian BJ, Cotter LA, Emanuel BA, Cass SP, Yates BJ. Effects of bilateral vestibular lesions on orthostatic tolerance in awake cats. *J Appl Physiol.* 86 (5): 1552-1560. 1999

Johansen LB, Gharib C, Allevard AM, Sigaudo D, Christensen NJ, Drummer C, Norsk P. Haematocrit, plasma volume and noradrenaline in humans during simulated weightlessness for 42 days. *Clin Physiol.* 17 (2): 203-210. 1997

Johnson JM, Rowell LB, Niederberger M, Eisman MM. Human splanchnic and forearm vasoconstrictor responses to reductions of right atrial and aortic pressures. *Circ Res.* 34 (4): 515-524. 1974

Kajstura J, Leri A, Finato N, Di Loreto C, Beltrami CA, Anversa P. Myocyte proliferation in end-stage cardiac failure in humans. *PNAS.* 95 (15): 8801-8805. 1998

Kakurin LI, Lobachik VI, Mikhailov VM, Senkevich YA. Antiorthostatic hypokinesia as a method of weightlessness simulation. *Aviat Space Environ Med.* 47 1083-1086. 1976

Kamiya A, Iwase S, Kitazawa H, Mano T, Vinogradova OL, Kharchenko IB. Baroreflex control of muscle sympathetic nerve activity after 120 days of 6 degrees head-down bed rest. *Am J Physiol Regulatory Integrative Comp Physiol.* 278 (2): R445-452. 2000a

Kamiya A, Iwase S, Michikami D, Fu Q, Mano T, Kitaichi K, Takagi K. Increased vasomotor sympathetic nerve activity and decreased plasma nitric oxide release after head-down bed rest in humans: Disappearance of correlation between vasoconstrictor and vasodilator. *Neurosci Lett.* 281 (1): 21-24. 2000b

Kashihara H, Haruna Y, Suzuki Y, Kawakubo K, Takenaka K, Bonde-Petersen F, Gunji A. Effects of mild supine exercise during 20 days bed rest on maximal oxygen uptake rate in young humans. *Acta Physiol Scand Suppl.* 616 19-26. 1994

Katsume H, Furukawa K, Azuma A, Nakamura T, Matsubara K, Ohnishi K, Sugihara H, Asayama J, Nakagawa M. Disuse atrophy of the left ventricle in chronically bedridden elderly people. *Jpn Circ J.* 56 (3): 201-206. 1992

Kent BB, Drane JW, Blumenstein B, Manning JW. A mathematical model to assess changes in the baroreceptor reflex. *Cardiology.* 57 (5): 295-310. 1972

Keys A. Deconditioning and reconditioning in convalescence. *Surg Clin North Am.* 25 442-454. 1945

Kirsch K, Haenel F, Rocker L. Venous pressure in microgravity. *Naturwissenschaften.* 73 (7): 447-449. 1986

Kirsch KA, Rocker L, Gauer OH, Krause R, Leach C, Wicke HJ, Landry R. Venous pressure in man during weightlessness. *Science.* 225 (4658): 218-219. 1984

Koenig SC, Convertino VA, Fanton JW, Reister CA, Gaffney FA, Ludwig DA, Krotov VP, Trambovetsky EV, Latham RD. Evidence for increased cardiac compliance during exposure to simulated microgravity. *Am J Physiol. Regulatory Integrative Comp Physiol.* 275 (4 Pt 2): R1343-1352. 1998

Kubicek WG, From AH, Patterson RP, Witsoe DA, Castaneda A, Lillehei RC, Ersek R. Impedance cardiography as a noninvasive means to monitor cardiac function. *J Assoc Adv Med Instrum.* 4 (2): 79-84. 1970

Lathers CM, Charles JB. Use of lower body negative pressure to counter symptoms of orthostatic intolerance in patients, bed rest subjects, and astronauts. *J Clin Pharmacol.* 33 (11): 1071-1085. 1993

Laughlin MH. Skeletal muscle blood flow capacity: Role of muscle pump in exercise hyperemia. *Am J Physiol Heart Circ Physiol.* 253 (5 Pt 2): H993-1004. 1987

Leach CS, Altchuler SI, Cintron-Trevino NM. The endocrine and metabolic responses to space flight. *Med Sci Sports Exerc*. 15 (5): 432-440. 1983

Lee SM, Bennett BS, Hargens AR, Watenpaugh DE, Ballard RE, Murthy G, Ford SR, Fortney SM. Upright exercise or supine lower body negative pressure exercise maintains exercise responses after bed rest. *Med Sci Sports Exerc*. 29 (7): 892-900. 1997

Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: A nonneural mechanism for orthostatic intolerance. *Circulation*. 96 (2): 517-525. 1997

Levine BD, Lane LD, Watenpaugh DE, Gaffney FA, Buckey JC, Blomqvist CG. Maximal exercise performance after adaptation to microgravity. *J Appl Physiol*. 81 (2): 686-694. 1996

Lind AR, McNicol GW. Circulatory responses to sustained hand-grip contractions performed during other exercise, both rhythmic and static. *J Physiol (Lond)*. 192 (3): 595-607. 1967

Linnarsson D, Tedner B, Lindborg B. Lower leg fluid displacement during a simulated space shuttle launch. *Eur J Appl Physiol*. 78 (1): 65-68. 1998

Linnarsson D, Sundberg CJ, Tedner B, Haruna Y, Karemaker JM, Antonutto G, di Prampero PE. Blood pressure and heart rate responses to sudden changes of gravity during exercise. *Am J Physiol Heart Circ Physiol*. 270 (6 Pt 2): H2132-2142. 1996

Louisy F, Schroiff P, Guell A. Changes in leg vein filling and emptying characteristics and leg volumes during long-term head-down bed rest. *J Appl Physiol*. 82 (6): 1726-1733. 1997

Ludbrook J. The musculovenous pump of the human lower limb. *Am Heart J*. 71 635-641. 1966

Maillet A, Pavy-Le Traon A, Allevard AM, Sigaudo D, Hughson RL, Gharib C, Gauquelin G. Hormone changes induced by 37.5-h head-down tilt (-6 degrees) in humans. *Eur J Appl Physiol*. 68 (6): 497-503. 1994

Mark AL, Victor RG, Nerhed C, Wallin BG. Microneurographic studies of the mechanisms of sympathetic nerve responses to static exercise in humans. *Circ Res*. 57 (3): 461-469. 1985

Maron BJ, Pelliccia A, Spataro A, Granata M. Reduction in left ventricular wall thickness after deconditioning in highly trained olympic athletes. *Br Heart J*. 69 (2): 125-128. 1993

McCloskey DI, Streatfeild KA. Muscular reflex stimuli to the cardiovascular system during isometric contractions of muscle groups of different mass. *J Physiol (Lond)*. 250 (2): 431-441. 1975

Miller PB, Johnson RL, Lamb LE. Effects of four weeks of absolute bed rest on circulatory functions in man. *Aerosp Med*. 35 1194-1200. 1964

Miller PB, Johnson RL, Lamb LE. Effects of moderate physical exercise during four weeks of bed rest on circulatory functions in man. *Aerosp Med*. 36 (11): 1077-1082. 1965

Mitchell JH, Payne FC, Saltin B, Schibye B. The role of muscle mass in the cardiovascular response to static contractions. *J Physiol (Lond)*. 309 45-54. 1980

Montmerle S, Spaak J, Linnarsson D. Lung functions during and after prolonged head-down bed rest. *J Appl Physiol*. 2001 (Accepted)

Moore AD, Jr., Lee SM, Charles JB, Greenisen MC, Schneider SM. Maximal exercise as a countermeasure to orthostatic intolerance after spaceflight. *Med Sci Sports Exerc*. 33 (1): 75-80. 2001

Narula J, Haider N, Virmani R, DiSalvo TG, Kolodgie FD, Hajjar RJ, Schmidt U, Semigran MJ, Dec GW, Khaw BA. Apoptosis in myocytes in end-stage heart failure. [see comments]. *N Engl J Med*. 335 (16): 1182-1189. 1996

Nixon JV, Murray RG, Bryant C, Johnson RL, Jr., Mitchell JH, Holland OB, Gomez-Sanchez C, Vergne-Marini P, Blomqvist CG. Early cardiovascular adaptation to simulated zero gravity. *J Appl Physiol*. 46 (3): R541-548. 1979

Nobrega ACL, Williamson JW, Garcia JA, Mitchell JH. Mechanisms for increasing stroke volume during static exercise with fixed heart rate in humans. *J Appl Physiol*. 83 (3): 712-717. 1997

Olesen HL, Mitchell JH, Friedman DB, Iversen HK, Secher NH. Reduced arterial diameter during static exercise in humans. *Acta Physiol Scan*. 153 (4): 335-341. 1995

Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, Quaini E, Di Loreto C, Beltrami CA, Krajewski S, Reed JC, Anversa P. Apoptosis in the failing human heart. *N Engl J Med*. 336 (16): 1131-1141. 1997

Pannier BM, Lacolley PJ, Gharib C, London GM, Cuche JL, Duchier JL, Levy BI, Safar ME. Twenty-four hours of bed rest with head-down tilt: Venous and arteriolar changes of limbs. *Am J Physiol. Heart Circ Physiol*. 260 (4 Pt 2): H1043-1050. 1991

Papelier Y, Escourrou P, Gauthier JP, Rowell LB. Carotid baroreflex control of blood pressure and heart rate in men during dynamic exercise. *J Appl Physiol*. 77 (2): 502-506. 1994

Pavy-Le Traon A, Louisy F, Vasseur-Clausen P, Guell A, Gharib C. Contributory factors to orthostatic intolerance after simulated weightlessness. *Clin Physiol*. 19 (5): 360-368. 1999

Pavy-Le Traon AP, Sigaudo D, Vasseur P, Maillet A, Fortrat JO, Hughson RL, Gauquelin-Koch G, Gharib C. Cardiovascular responses to orthostatic tests after a 42-day head-down bed-rest. *Eur J Appl Physiol*. 77 (1-2): 50-59. 1998

Pawelczyk JA, Pawelczyk RA, Warberg J, Mitchell JH, Secher NH. Cardiovascular and catecholamine responses to static exercise in partially curarized humans. *Acta Physiol Scan*. 160 (1): 23-28. 1997

Perhonen MA, Zuckerman JH, Levine BD. Deterioration of left ventricular chamber performance after bed rest : "cardiovascular deconditioning" or hypovolemia? *Circulation*. 103 (14): 1851-1857. 2001a

Perhonen MA, Franco F, Lane LD, Buckey JC, Blomqvist CG, Zerwekh JE, Peshock RM, Weatherall PT, Levine BD. Cardiac atrophy after bed rest and spaceflight. *J Appl Physiol*. 91 (2): 645-653. 2001b

Petersen JR, Jensen BV, Drabaek H, Viskum K, Mehlsen J. Electrical impedance measured changes in thoracic fluid content during thoracentesis. *Clin Physiol*. 14 (4): 459-466. 1994

Philpott DE, Popova IA, Kato K, Stevenson J, Miquel J, Sapp W. Morphological and biochemical examination of cosmos 1887 rat heart tissue: Part I--ultrastructure. *FASEB Journal*. 4 (1): 73-78. 1990

Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation*. 101 (3): 336-344. 2000

Potts JT, Shi XR, Raven PB. Carotid baroreflex responsiveness during dynamic exercise in humans. *Am J Physiol Heart Circ Physiol*. 265 (6 Pt 2): H1928-1938. 1993

Purdy RE, Duckles SP, Krause DN, Rubera KM, Sara D. Effect of simulated microgravity on vascular contractility. *J Appl Physiol.* 85 (4): 1307-1315. 1998

Ray CA. Interaction of the vestibular system and baroreflexes on sympathetic nerve activity in humans. *Am J Physiol Heart Circ Physiol.* 279 (5): H2399-2404. 2000

Robotham JL, Mintzner W. A model of the effects of respiration on left ventricular performance. *J Appl Physiol.* 46 (3): R411-418. 1979

Rowell LB. Human cardiovascular control. Oxford University Press, New York. 1996

Rowell LB, O'Leary DS. Reflex control of the circulation during exercise: Chemoreflexes and mechanoreflexes. *J Appl Physiol.* 69 (2): 407-418. 1990

Rowell LB, O'Leary DS, Kellogg JDL. Integration of cardiovascular control systems in dynamic exercise. In: *Handbook of Physiology, Exercise: Regulation and Integration of Multiple Control Systems.* Sect 12. Oxford University Press, New York, Oxford. 1996

Rummel JA, Michel EL, Sawin CF, Buderer MC. Medical experiment M-171: Results from the second manned skylab mission. *Aviat Space Env Med.* 47 (10): 1056-1060. 1976

Russell B, Motlagh D, Ashley WW. Form follows function: How muscle shape is regulated by work. *J Appl Physiol.* 88 (3): 1127-1132. 2000

Sackner MA, Greeneltch D, Heiman MS, Epstein S, Atkins N. Diffusing capacity, membrane diffusing capacity, capillary blood volume, pulmonary tissue volume, and cardiac output measured by a rebreathing technique. *Am Rev Respir Dis.* 111 (2): 157-165. 1975

Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Jr., Wildenthal K, Chapman CB. Response to exercise after bed rest and after training. *Circulation.* 38 (5 Suppl): VII1-78. 1968

Sandler H, Goldwater DJ, Popp RL, Spaccavento L, Harrison DC. Beta blockade in the compensation for bed-rest cardiovascular deconditioning: Physiologic and pharmacologic observations. *Am J Cardiol.* 55 (10): 114D-119D. 1985

Scherrer U, Pryor SL, Bertocci LA, Victor RG. Arterial baroreflex buffering of sympathetic activation during exercise-induced elevations in arterial pressure. *J Clin Invest.* 86 (6): 1855-1861. 1990

Schiefeling M. [influence of simulated weightlessness on blood pressure and heart rate behavior in trained and untrained subjects]. *Pflugers Arch.* 307 (2): R94. 1969

Schlegel TT, Brown TE, Wood SJ, Benavides EW, Bondar RL, Stein F, Moradshahi P, Harm DL, Fritsch-Yelle JM, Low PA. Orthostatic intolerance and motion sickness after parabolic flight. *J Appl Physiol.* 90 (1): 67-82. 2001

Seals DR, Washburn RA, Hanson PG, Painter PL, Nagle FJ. Increased cardiovascular response to static contraction of larger muscle groups. *J Appl Physiol.* 54 (2): R434-437. 1983

Senut B, Pickford M, Gommery D, Mein P, Cheboi K, Coppens Y. First hominid from the miocene (lukeino formation, kenya). *C R Acad Sci Paris.* 332 (2): 137-144. 2001

Shapiro LM, Smith RG. Effect of training on left ventricular structure and function. An echocardiographic study. *Br Heart J.* 50 (6): 534-539. 1983

Sheriff DD, Augustyniak RA, O'Leary DS. Muscle chemoreflex-induced increases in right atrial pressure. *Am J Physiol Heart Circ Physiol.* 275 (3 Pt 2): H767-775. 1998

Shi X, Potts JT, Foresman BH, Raven PB. Carotid baroreflex responsiveness to lower body positive pressure-induced increases in central venous pressure. *Am J Physiol Heart Circ Physiol.* 265 (3 Pt 2): H918-922. 1993

Shoemaker JK, Hogeman CS, Sinoway LI. Contributions of MSNA and stroke volume to orthostatic intolerance following bed rest. *Am J Physiol Regulatory Integrative Comp Physiol.* 277 (4 Pt 2): R1084-1090. 1999

Shoemaker JK, Hogeman CS, Silber DH, Gray K, Herr M, Sinoway LI. Head-down-tilt bed rest alters forearm vasodilator and vasoconstrictor responses. *J Appl Physiol.* 84 (5): 1756-1762. 1998a

Shoemaker JK, Hogeman CS, Leuenberger UA, Herr MD, Gray K, Silber DH, Sinoway LI. Sympathetic discharge and vascular resistance after bed rest. *J Appl Physiol.* 84 (2): 612-617. 1998b

Sieck GC, Regnier M. Plasticity in skeletal, cardiac, and smooth muscle: Invited review: Plasticity and energetic demands of contraction in skeletal and cardiac muscle. *J Appl Physiol.* 90 (3): 1158-1164. 2001

Sigaudo D, Fortrat JO, Allevard AM, Maillet A, Cottet-Emard JM, Vouillarmet A, Hughson RL, Gauquelin-Koch G, Gharib C. Changes in the sympathetic nervous system induced by 42 days of head-down bed rest. *Am J Physiol Heart Circ Physiol.* 274 (6 Pt 2): H1875-1884. 1998

Soubiran C, Harant I, de Glisezinski I, Beauville M, Crampes F, Riviere D, Garrigues M. Cardio-respiratory changes during the onset of head-down tilt. *Aviat Space Environ Med.* 67 (7): 648-653. 1996

Sprangers RL, Wesseling KH, Imholz AL, Imholz BP, Wieling W. Initial blood pressure fall on stand up and exercise explained by changes in total peripheral resistance. *J Appl Physiol.* 70 (2): 523-530. 1991

Stevens PM, Lynch TN, Johnson RL, Lamb LE. Effects of 9-alphaflurohydrocortisone and venous occlusive cuffs on orthostatic deconditioning of prolonged bed rest. *Aerosp Med.* 37 (10): 1049-1056. 1966a

Stevens PM, Miller PB, Gilbert CA, Lynch TN, Johnson RL, Lamb LE. Influence of long-term lower body negative pressure on the circulatory function of man during prolonged bed rest. *Aerosp Med.* 37 (4): 357-367. 1966b

Stevens PM, Miller PB, Lynch TN, Gilbert CA, Johnson RL, Lamb LE. Effects of lower body negative pressure on physiologic changes due to four weeks of hypoxic bed rest. *Aerosp Med.* 37 (5): 466-474. 1966c

Sulzman FM. Life sciences space missions. Overview. *J Appl Physiol.* 81 (1): 3-6. 1996

Sundblad P, Spaak J, Linnarsson D. Haemodynamic and baroreflex responses to whole-body tilting in exercising men before and after 6 weeks of bedrest. *Eur J Appl Physiol.* 82 (5-6): 397-406. 2000a

Sundblad P, Haruna Y, Tedner B, Linnarsson D. Short-term cardiovascular responses to rapid whole-body tilting during exercise. *Eur J Appl Physiol.* 81 (4): 259-270. 2000b

Suzuki Y, Murakami T, Haruna Y, Kawakubo K, Goto S, Makita Y, Ikawa S, Gunji A. Effects of 10 and 20 days bed rest on leg muscle mass and strength in young subjects. *Acta Physiol Scand Suppl.* 616 5-18. 1994

Taylor HL, Erickson L, Henschel A, Keys A. The effect of bed rest on the blood volume of normal young men. *Am J Physiol.* 144 227-232. 1945

Taylor HL, Henschel A, Brozek J, Keys A. Effects of bed rest on cardiovascular function and work performance. *J Appl Physiol.* 5 (2): 223-239. 1949

Thornton WE, Hoffler GW, Rummel J. Anthropometric changes and fluid shifts. In: *Biomedical Results from Skylab.* Ch 32. NASA, 1977

Toska K, Eriksen M. Respiration-synchronous fluctuations in stroke volume, heart rate and arterial pressure in humans. *J Physiol (Lond).* 472 501-512. 1993

Traon AP, Sigaudo D, Vasseur P, Maillet A, Fortrat JO, Hughson RL, Gauquelin-Koch G, Gharib C. Cardiovascular responses to orthostatic tests after a 42-day head-down bed-rest. *Eur J Appl Physiol*. 77 (1-2): 50-59. 1998

Vallbona C, Vogt FB, Cardus D, Spencer WA. The effect of bedrest on various parameters of physiological function. X. The effect of bedrest on the circulatory response to a valsalva maneuver. Nasa CR-180. *NASA Cr*. 1-13. 1967

Verbanck S, Linnarsson D, Prisk GK, Paiva M. Specific ventilation distribution in microgravity. *J Appl Physiol*. 80 (5): 1458-1465. 1996

Vogt FB. Effect of intermittent leg cuff inflation and intermittent exercise on the tilt table response after ten days bed recumbency. *Aerosp Med*. 37 (9): 943-947. 1966

Vogt FB, Cardus D, Vallbona C, Spencer WA. The effect of bedrest on various parameters of physiological function. VI. The effect of the performance of periodic flack maneuvers on preventing cardiovascular deconditioning of bedrest. *NASA CR 176*. 1-37. 1965

Vorobyov EI, Gazenko OG, Genin AM, Egorov AD. Medical results of salyut-6 manned space flights. *Aviat Space Environ Med*. 54 (12 Pt 2): S31-40. 1983

Warner HR, Cox A. A mathematical model of heart rate control by sympathetic and vagus efferent information. *J Appl Physiol*. 17 349-355. 1962

Watenpaugh DE, Hargens AR. The cardiovascular system in microgravity. In: *Handbook of Physiology, Section 4: Environmental physiology I*. Oxford University Press, New York. 1996

Watenpaugh DE, Ballard RE, Schneider SM, Lee SM, Ertl AC, William JM, Boda WL, Hutchinson KJ, Hargens AR. Supine lower body negative pressure exercise during bed rest maintains upright exercise capacity. *J Appl Physiol*. 89 (1): 218-227. 2000

West JB. Physiology in microgravity. *J Appl Physiol*. 89 (1): 379-384. 2000

West JB, Prisk GK. To the editor: Chest volume and shape and intrapleural pressure in microgravity. *J Appl Physiol*. 87 (3): 1240-1241. 1999

White RJ, Blomqvist CG. Central venous pressure and cardiac function during spaceflight. *J Appl Physiol*. 85 (2): 738-746. 1998

Whitson PA, Charles JB, Williams WJ, Cintron NM. Changes in sympathoadrenal response to standing in humans after spaceflight. *J Appl Physiol*. 79 (2): 428-433. 1995

Yamashita-Goto K, Okuyama R, Honda M, Kawasaki K, Fujita K, Yamada T, Nonaka I, Ohira Y, Yoshioka T. Maximal and submaximal forces of slow fibers in human soleus after bed rest. *J Appl Physiol*. 91 (1): 417-424. 2001

Yana K, Saul JP, Berger RD, Perrott MH, Cohen RJ. A time domain approach for the fluctuation analysis of heart rate related to instantaneous lung volume. *IEEE Trans Biomed Eng*. 40 (1): 74-81. 1993

Yang T, Senturia JB, Levy MN. Antecedent sympathetic stimulation alters time course of chronotropic response to vagal stimulation in dogs. *Am J Physiol Heart Circ Physiol*. 266 (4 Pt 2): H1339-1347. 1994

Yates BJ, Kerman IA. Post-spaceflight orthostatic intolerance: Possible relationship to microgravity-induced plasticity in the vestibular system. *Brain Res Rev*. 28 (1-2): 73-82. 1998

Zange J, Muller K, Schuber M, Wackerhage H, Hoffmann U, Gunther RW, Adam G, Neuerburg JM, Sinitsyn VE, Bacharev AO, Belichenko OI. Changes in calf muscle performance, energy metabolism, and muscle volume caused by long-term stay on space station MIR. *Int J Sports Med*. 18 Suppl 4 S308-309. 1997