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Cardiovascular System, Red Blood Cells, and Oxygen Transport in Microgravity

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Preface to the Series

The extraordinary conditions in space, especially microgravity, are utilized today not only for research in the physical and materials sciences—they especially provide a unique tool for research in various areas of the life sciences. The major goal of this research is to uncover the role of gravity with regard to the origin, evolution, and future of life and to the development and orientation of organisms from single cells and protists up to humans. This research only became possible with the advent of manned spaceflight some 50 years ago. With the first experiment having been conducted onboard Apollo 16, the German Space Life Sciences Program celebrated its 40th anniversary in 2012—a fitting occasion for Springer and the DLR (German Aerospace Center) to take stock of the space life sciences achievements made so far.

The DLR is the Federal Republic of Germany's National Aeronautics and Space Research Center. Its extensive research and development activities in aeronautics, space, energy, transport, and security are integrated into national and international cooperative ventures. In addition to its own research, as Germany's space agency the DLR has been charged by the federal government with the task of planning and implementing the German space program. Within the current space program, approved by the German government in November 2010, the overall goal for the life sciences section is to gain scientific knowledge and to reveal new application potentials by means of research under space conditions, especially by utilizing the microgravity environment of the International Space Station ISS.

With regard to the program's implementation, the DLR Space Administration provides the infrastructure and flight opportunities required, contracts the German space industry for the development of innovative research facilities, and provides the necessary research funding for the scientific teams at universities and other research institutes. While so-called small flight opportunities like the drop tower in Bremen, sounding rockets, and parabolic airplane flights are made available within the national program, research on the International Space Station ISS is implemented in the framework of Germany's participation in the ESA Microgravity Program or through bilateral cooperations with other space agencies. Free flyers

such as BION or FOTON satellites are used in cooperation with Russia. The recently started utilization of Chinese spacecraft like Shenzhou has further expanded Germany's spectrum of flight opportunities, and discussions about future cooperation on the planned Chinese Space Station are currently under way.

From the very beginning in the 1970s, Germany has been the driving force for human spaceflight as well as for related research in the life and physical sciences in Europe. It was Germany that initiated the development of Spacelab as the European contribution to the American Space Shuttle System, complemented by setting up a sound national program. And today Germany continues to be the major European contributor to the ESA programs for the ISS and its scientific utilization.

For our series, we have approached leading scientists first and foremost in Germany, but also—since science and research are international and cooperative endeavors—in other countries to provide us with their views and their summaries of the accomplishments in the various fields of space life sciences research. By presenting the current SpringerBriefs on muscle and bone physiology, we start the series with an area that is currently attracting much attention—due in no small part to health problems such as muscle atrophy and osteoporosis in our modern ageing society. Overall, it is interesting to note that the psychophysiological changes that astronauts experience during their spaceflights closely resemble those of ageing people on Earth but progress at a much faster rate. Circulatory and vestibular disorders set in immediately, muscles and bones degenerate within weeks or months, and even the immune system is impaired. Thus, the ageing process as well as certain diseases can be studied at an accelerated pace, yielding valuable insights for the benefit of people on Earth as well. Luckily for the astronauts: these problems slowly disappear after their return to Earth, so that their recovery processes can also be investigated, yielding additional valuable information.

Booklets on nutrition and metabolism, on the immune system, on vestibular and neuroscience, on the cardiovascular and respiratory system, and on psychophysiological human performance will follow. This separation of human physiology and space medicine into the various research areas follows a classical division. It will certainly become evident, however, that space medicine research pursues a highly integrative approach, offering an example that should also be followed in terrestrial research. The series will eventually be rounded out by booklets on gravitational and radiation biology.

We are convinced that this series, starting with its first booklet on muscle and bone physiology in space, will find interested readers and will contribute to the goal of convincing the general public that research in space, especially in the life sciences, has been and will continue to be of concrete benefit to people on Earth.

Bonn, Germany — Günter Ruyters
Bonn, Germany — Markus Braun
July, 2014

DLR Space Administration in Bonn-Oberkassel (DLR)

The International Space Station ISS; photo taken by an astronaut from the space shuttle Discovery, March 7, 2011 (NASA)

Extravehicular activity (EVA) of the German ESA astronaut Hans Schlegel working on the European Columbus lab of ISS, February 13, 2008 (NASA)

Foreword

The cardiovascular as well as the respiratory systems of the human body are challenged—like the vestibular system—immediately after the astronauts enter into the microgravity conditions of space: several liters of fluids are shifted from the lower to the upper part of the human body leading to the well-known phenomenon of bird legs and puffy faces of astronauts. For adaptation to this new environment, a proper regulation of the cardiorespiratory system is mandatory; results from space research on this topic will, therefore, provide new insights into the functioning of this important system not only for astronauts but also for people on Earth.

"The cardiovascular system, red blood cells and oxygen transport in space" is thus the title of the fourth volume in the SpringerBriefs series on Space Life Sciences. In their short introductory chapter, the authors describe the physiological functions of the cardiorespiratory system with special emphasis on basic differences in the functioning of the circulatory and respiratory systems on Earth and in space.

In the second chapter, these changes are described in more detail differentiating between acute or immediate effects and those of long-term adaptation and the problems astronauts encounter upon return to Earth. Results from space experiments are compared with those of terrestrial studies such as bedrest and immersion studies as well as on parabolic airplane flights or incentrifuges.

Changes in red blood cells and oxygen transportation are the focus of the third chapter. It is well known that microgravity leads to significant changes in blood volume, red blood cells, and hemoglobin. The regulation of the hormone erythropoietin (EPO) plays an important role here. Results from spaceflight experiments are compared with those from terrestrial studies; the influence of exercise is also covered.

The lungs are directly affected by microgravity: their shape and the distribution of gas-filled spaces are immediately changed. This makes parabolic airplane flights a suitable tool for research in addition to experiments under real space conditions such as on the ISS (International Space Station). In fact, the authors present results from short-term microgravity on parabolic flights and from space platforms which

were available before the development of the American shuttle system and the Russian MIR station and conclude with data from the ISS. The good news: all in all, the lungs possess highly effective compensation mechanisms against the influence of microgravity.

The booklet presents in its fifth chapter an overview of countermeasures that are either already in use, under development, or discussed for the future and concludes with an outlook on existing or potential terrestrial—e.g., clinical—applications of knowledge and technologies gained from space research in this field. In this sense, it follows nicely after the conclusions of the other booklets in the series that all try to build a bridge between the accomplishments from space experiments and from terrestrial research for the benefit of people on Earth.

DLR, Bonn, Germany Günter Ruyters
March 2016

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Chapter 1
General Introduction

Abstract Microgravity is an extreme environment Astronauts are exposed to when they escape Earth's gravitational field. A different set of stimuli experienced during spaceflight seriously affects all parts of the body. Instantly, the body starts to adapt to the new gravity-free environment; different organs and organ systems do so in different ways and at different rates. The cardiovascular system, for example, no longer needs to work against gravity and extensive mechanisms that maintain cerebral perfusion and prevent lower body edema on Earth become redundant and weaken. As reasonable as those adaptations might be in Space, they become critical upon return to Earth's gravitational field. Therefore, it is important to grant the changes in the cardiovascular system special attention. This chapter briefly outlines physiological functions that are critical for understanding the changes occurring in microgravity, as well as introducing the microgravity environment aboard Space stations.

Keywords Weightlessness • Microgravity • Space • Cardiovascular • Blood • Respiration • Physiology • Astronauts

1.1 The Circulatory System

With over 10^{15} cells and a similar number of microbes on the surface (skin) and in our bodies, it takes a logistic masterpiece (1) to supply every single cell with the necessary nutrients such as oxygen and (2) to keep the necessary barriers between the different cell and tissue compartments intact. Oxygen has to be carried from the lungs to the brain and all the way down along the body to the different organs and organ systems. Moreover, the cardiovascular system protects the body by carrying special blood cells and antibodies that clean up cellular debris and fight pathogens. Hormones are also carried through the body in the blood's plasma. Under resting conditions, about 5 L of blood per minute are pumped through the vascular system of a male adult to ensure homeostasis. Briefly, the cardiovascular system consists of a pump (heart), an infrastructure (vessels), and a transport medium (blood)—a crucial structure developed about 500 million years ago.

As part of the cardiovascular system blood is propelled from the left ventricle of the heart through the arteries and all the way to peripheral organs. A pressure

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induced by the left ventricle oscillates between 0 and 120 mmHg. These pressures and the intermittent flow are converted to a more continuous flow by the physical properties of relatively stiff arteries. The majority of the resistance in the vascular system is in the arterioles, whose changing diameter inversely alters the pressure inside. The exchange of required substances such as nutrients with waste products occurs within about ten billion capillaries in the body. On the venous side—where most of the blood resides (capacitance vessels)—the blood first drains from capillaries into venules, from there into veins and then returns to the heart. Additionally, the lymphatic system is part of the circulatory system and contributes to maintaining homeostasis by circulating lymph.

Arguably, the hardest working component of this delivery system is the heart. In size, this organ is comparable to a fist and beats roughly 100,000 times a day. The heart rate depends on health, fitness level, physical activity, and environmental conditions and is mainly regulated by the autonomic nervous system (ANS) to suffice current physiological needs. While sleeping, the heart rate dips to its lowest level; this is usually around 60 beats/min, but might be less in some cases, for example, in trained athletes. On the other extreme, the heart rate can rise rapidly if required, for example, during exercise, in extreme heat, or in situations of extreme psychological stress. Roughly speaking, the maximum heart rate is around 220 minus the age of the individual [1] or other formulas were used [2]; e.g., Spanaus where gender and body weight in trained subjects is embraced [3]. The vast range of possible heart rates shows how the cardiovascular system responds instantly to given signals in order to adjust to a specific situation.

From an engineering point of view, the cardiovascular system is an automatically electronic driven mechanical pump (the heart) with a closed loop (vascular) system. Several feedback mechanisms (e.g., brain signals) provide information on internal conditions and set off regulatory mechanisms to keep these in equilibrium.

The core body temperature (CBT), for instance, can be regulated by dilating or constricting the vessels beneath the skin. In the case of hyperthermia, higher blood flow is required and the heart rate increases when the body core or skin temperature, respectively, rises above individual set points. While heart frequency and vasodilation occur, more blood volume is transported to the surface of the human body. Superficial skin blood vessels dilate and auxiliary anastomoses open as well (shunt veins between deep and superficial vessels). This improves heat dissipation from the skin surface to the environment. Additionally, humans reduce their core temperatures by sweating on the body's surface (even in the lung). This adjusts the core body temperature even under extreme physical or environmental conditions below deleterious levels (state of hyperthermia higher than 42.0 °C) until the system collapses due to limitations (e.g., dehydration). On the other hand, in a state of hypothermia (CBT below 35.5 °C), the skin blood vessels constrict and blood flow is particularly through the central organs of the body and less heat is lost to the environment over the surface (barrier function).

Another major regulatory task of the cardiovascular system is to maintain a sufficient blood pressure via nerval and hormonal mechanisms. An increased stroke volume or heart rate for instance will pump blood through the system faster and consequently increase blood pressure. Furthermore, a change in peripheral

resistance, for example, by altering vessel radius, will influence the pressure inside—A change in the viscosity will also attenuated the work load for the heart, i.e. higher viscosity—higher work to perform, lower viscosity less work for the heart. Factors which influence the viscosity are vessel diameter, temperature, hematocrit, and blood flow velocity.

One feedback loop for blood pressure involves stretch-sensitive mechanoreceptor neurons called pressoreceptors or baroreceptors located in the vascular system (aortic arch, cervical artery, carotid sinus, and large arteries of the lung). The response is immediate and part of a negative feedback system called the baroreflex. When this reflex is set off, the short-term response is to slow the heart rate, thereby decreasing the blood pressure. If the activation of receptors persists, a long-term response sets in which includes—among others—the release of the atrial natriuretic peptide (ANP), a hormone released from special cells in the atrium of the heart that acts via the kidneys mainly to reduce water and sodium content of the circulatory system, and also brain natriuretic peptide (BNP) which is suppressed from the heart cells by the same mechanism.

1.2 The Circulatory System on Earth

Originally, all transport functions were located within the single cell of unicellular organisms. As organisms developed to vertebrates and mammals, these functions required a system to supply nutrients to all cells. Once this step was complete, different species had to begin coping with gravity. Aquatic animals, that left their home environment, were more exposed to gravity and their own weight impeded movement. Throughout human evolution and especially during the times of an upright gait, our bodies have adapted to the constant stress of gravity. Physiological systems, structures, and mechanisms developed as necessities to overcome the burdens induced by a constant downward pull. Even though we might not realize it, man has developed a multitude of mechanisms and structures that allow bodily functions to continue in spite of (and sometime because of) gravity.

Stabilizing structures of muscles and bones support the assemblage of fluid-filled bags and interconnected tubes belonging to the cardiovascular system. The cardiovascular system in turn supplies the muscles and bones with materials essential to its growth and function. Crudely speaking, the cardiovascular system can be estimated to an array of interlinked vertical columns of blood, in which pressure increases with depth, just as it does in a pool or in the ocean.

While for organisms with a horizontally organized vascular system like a snail or a worm, the pressure difference is negligible; hydrostatic pressures induced in the cardiovascular system of upright animals become significant. An extreme example is a giraffe that has a heart to brain distance of 2.8 m; see Fig. 1.1. A giraffe's heart has to produce a pressure difference of 400 mmHg to pump blood to the brain. In the extinct Jurassic dinosaur *Brachiosaurus brancai*, even higher pressures have to

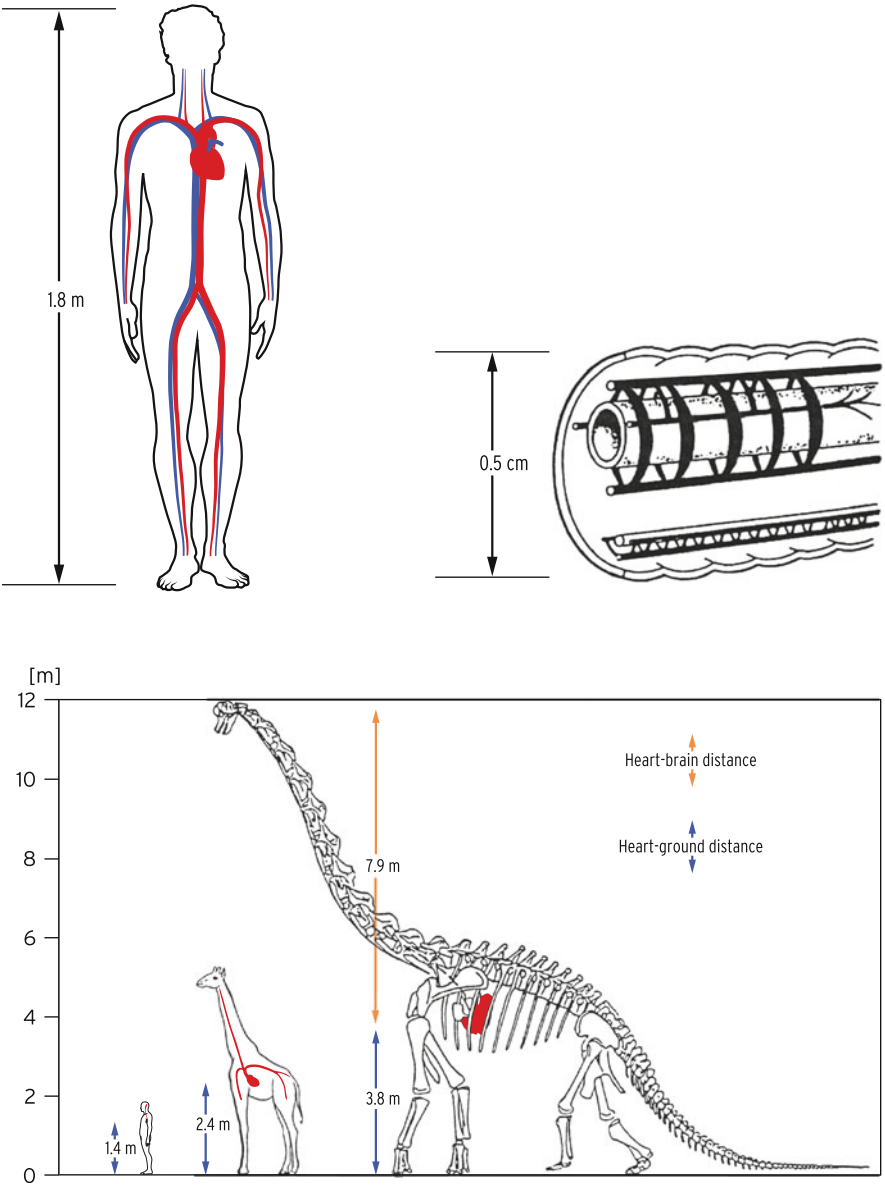

Fig. 1.1 Hydrostatic magnitudes: the vertical size differences of a worm, a human being, a giraffe, and the dinosaur *Brachiosaurus brancai*. The diverse heart to brain distance (0 m, 0.4 m, 2.8 m, and 7.9 m, respectively) induces different hydrostatic pressure differences in the cardiovascular systems (adapted from [4])

be assumed [4]. The human heart has to produce less extreme pressure differences (120 mmHg) to overcome a height difference of 30 to 35 cm to the brain [5].

The average human spends 70 % of his or her day in an upright posture. While standing, there is an induced pressure difference of over 100 mmHg from the level of the heart to the feet. Accordingly, the circulation of blood in the body is therefore strongly influenced by gravity. The heart has to induce adequate pressures to allow cerebral blood flow, whereas converse issues also arises: the movement of oxygenated blood through the arteries into the legs is assisted by gravity, but returning blood to the heart via the veins works against gravity. The low-pressure system (veins) with its distensible walls bears the risk of blood pooling in the lower periphery. If fluid would leak in extent from the vessels into the interstitium, it would accumulate in the legs leading to edema formation. The body has developed mechanisms of the cardiovascular system that aid venous return from the periphery. Constricting muscles in the walls of arterioles in the lower limbs function to withstand the hydrostatic forces when standing. The arterial and venous tone in the lower extremities prevents pooling of blood in the capacitance vessels. Moreover, the legs are equipped with a skeletal-muscle pump—a collection of skeletal muscles that increase venous return to the heart. Increased muscle activity associated with an upright posture and especially during exercise counteracts the loss of intravascular fluid and periodically pushes blood upwards, out of the periphery.

Deep veins in the extremities, specifically in the calves, play a major role in propelling blood toward the heart and operate as non-return valve. The combination of venous valves prohibiting regurgitation (reverse blood flow) and powerful calf muscles that compress the deep veins with every step allow them to carry most of the blood from the legs to the heart, see Fig. 1.2. Muscles, making the return slower,

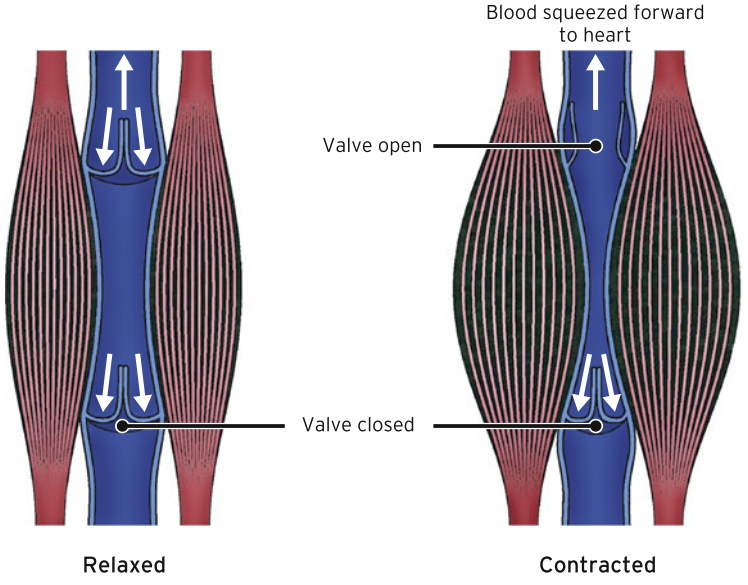

Fig. 1.2 Venous valves: constriction of skeletal muscles around veins aids the venous return, while a backflow is hindered by valves in the veins

do not surround superficial veins. Thus, valves in the superficial veins are aligned not only to support the transportation up to the heart but also concentrically inwards to the deep veins. The rest of the blood fluid (tissue fluid, lymph) is carried back to the heart by the lymphatic system. They have the same transport mechanism as the veins but also a special system: the lymphangions which are regulated by the ANS and work like "a heart" by contraction up to 60 times per minute.

These controlling mechanisms ensure an adequate circulation of the blood under various conditions. The application of these mechanisms depends largely upon the posture of the body. Hydrostatic gradients are largest when the body's z-axis is perpendicular to ground, i.e., standing upright [6]. The reaction to changing from a horizontal to an upright position are not always immediate and can be experienced for instance as dizziness when standing up too quickly. The sudden stress imposed on the cardiovascular system in the case of moving into a supine position in many ways parallels to the return of an Astronaut from Space to Earth.

1.3 The Circulatory System in Space

Evolutionary processes have optimized the human body to cope with and counteract the force of gravity—a stimulus that is completely lost upon injection to Space. Consequences are drastic and must be well understood to assess lingering hazards of microgravity.

Prolonged exposure to microgravity is a topic that gains more relevance as plans for covering greater extraterrestrial distances are made. To travel to Mars for instance, astronauts will spend 9 months in a spacecraft to reach their destination. Hence, it is important to understand and assess the dangers faced along the way and on arrival. Among high doses of radiation and limited food/fuel supply, Space travellers must compensate for the lack of physical stress inherent to weightlessness.

Currently, astronauts on the International Space Station (ISS) already spend extended periods in weightlessness. The space station encircles Earth so rapidly that a day–night cycle lasts only 90 min. The first space stations were placed on orbit in the early 1970s by the USSR and the USA. Among the most successful space stations—in terms of days spent on orbit, number of crew members hosted, and thereby number of experiments carried out—is Russia's Mir station. It was launched in 1986 and stayed on orbit for 15 years. NASA's first space station Skylab was launched in 1973. The ISS—a joint project between the USA, Japan, Canada, Russia, and the European Union—was launched in 1998. Now, already the ISS has spent over 6000 days on orbit and 215 Astronauts/Cosmonauts have visited it. Next to the ISS, there is only one other space station operating at the moment: China's Tiangong 1 station launched in 2011 and should be completed around 2020.

Aboard the ISS, weightlessness is not achieved because Astronauts have escaped the influence of Earth's gravitational field (in fact the influence of gravity is infinite and the gravitational force of Earth does not vanish anywhere in the Universe—it

simply becomes minuscule and is over-powered or cancelled out by the forces of other gravitational sources). Weightlessness is achieved by the orbiting speed of the station; the ISS has a speed "forward" around the Earth (28,000 km/h), completing one orbit in 90 min. This creates a centrifugal force outward, away from the Earth, which cancels the downward pull of gravity. The spacecraft and everything within or on it are in free fall, i.e., floating in weightlessness.

Aboard such a space station, the cardiovascular system is exposed to microgravity, and the mechanisms to cope with the burden of gravity become redundant. Hence, the question arises, what happens to the body when the force of gravity is removed? In fact, the missing impetus has severe consequences on the cardiovascular system, red blood cells, and oxygen transportation, which are outlined in the following chapters.

1.4 The Respiratory System on Earth

The respiratory system consists of the upper and lower airways, the lungs as central organ, the related muscles, which drive inspiration and expiration, as well as, in a wider sense, the related neural centers for respiratory control. The lungs can be characterized as an extremely compliant organ. Gas-filled spaces are embedded into the fluid-rich tissue. As a consequence, weightlessness affects directly geometry and functions of the lungs. Next to original weightlessness effects onto the mass of the organ, acute effects are related to changes in hydrostatic pressure and, therefore, to pressure gradients. Since the lungs have an interface function between environment and the cardiovascular system, these pressure effects are also directly related to changes in the cardiovascular system. Furthermore, the artificial environment in spacecrafts with controlled ambient pressure and O_2- and CO_2-concentrations has further impact on respiratory control.

1.4.1 Anatomic Basics

The lungs are embedded in the thorax, separated from the thoracic wall by the fluid-filled pleural cavity. The lower airways arborize eventually in a dichotomous pattern until the alveolar level. The alveoli in total are a sponge-like mass composed of about 150 million little sacs (alveoli), each with a diameter of 50–300 μm (depending on expiration or inspiration state), representing altogether a gas exchange surface of about 100 m^2. Here, the gas exchange between the gas-filled spaces and blood in the surrounding capillary system takes place across a diffusion border of only 0.5 μm. This diffusion border is composed (from airspace to bloodspace) by the alveolar epithelium, the common basement membrane, and the capillary endothelium. The lungs have elastic mechanical characteristics due to abundant elastic fibers within the organ, resulting in the tendency to collapse. The

surfactant film, however, on the alveolar surface prevents an alveolar collapse. These forces are balanced by outward directed elastic forces of the thorax and the abdominal weight interfaced by the diaphragm. This ensures a certain gas-filled volume in the lungs even if no muscles are active.

The highly compliant characteristics can be compared with the characteristics of a Slinky spring [7]. In upright position, the suspension is located at the upper level of the thorax while the lower end rests on the diaphragm. The stretch of the lungs is decreasing from the upper to the lower part due to its self-weight. In gravity, the buoyancy of gas-filled alveoli influences the gas distribution in the lungs.

Ventilation and aeration are driven by expansion or reduction of the thorax volume. The primary respiratory muscles, namely the diaphragm, scalene muscles, and external intercostal muscles, execute the expansion for inspiration. Expiration is predominantly a passive process due to elasticity of the lungs and the weight of the thorax. Several muscles can support this with a major contribution from the abdominal muscles. Both volume expansion and compression changes the intrapulmonary pressure, which creates the in- and outward gas flow, but also influences pressures in the cardiovascular system.

The structural characteristics and the different forces and pressures have to be recognized to understand lung function in weightlessness:

- Gravitational forces on the thorax and lung tissue, consisting of fluid and gas-filled spaces
- The elastic forces of lungs and thorax
- The hydrostatic pressure along the lung structures, which is obviously also gravity dependent

1.4.2 Respiratory Control

Respiratory control is based on partial pressures of O_2, CO_2 (PO_2/PCO_2), and the pH. Signals from chemo-sensitive cells in the aortic and carotic glomera for all three parameters and from PCO_2-sensitive sensors in the medulla oblongata stimulate respiration. A complex neuronal network is mainly located in the medulla oblongata and in the pons control inspiratory and expiratory activity. Higher neuronal levels, i.e., motor cortex, also modulate autonomous respiratory control with further voluntary influences.

The autonomous control is not directly influenced by gravity. However, muscle activity and other gravity-induced metabolic changes have an impact on respiration.

1.5 The Respiratory System in Space

The cessation of gravity has significant consequences for the lung function. The gravity-dependent forces on the thorax, the lung tissue, and the abdomen disappear. Moreover, hydrostatic pressure gradients are not relevant in Space. The absence of pressure gradients results in a homogenous gas distribution and perfusion of the lung. From the beginning of spaceflight, these effects were studied with classical methods of spirometry. Further development of methods and instrumentation allows sophisticated analysis which is partially adapted to microgravity condition and the special conditions of spaceflight experiments. The results enable the develop of advanced modeling for a better understanding of acute and sustained microgravity effect and, by that, a better understanding of gravitational effects on the respiratory system for health on Earth and other planets.

Acute effects can be studied in parabolic flights with weightlessness exposures of about 20 s. Spaceflights with duration from days to months allow to study the adaptation processes. Analogue test beds on Earth, i.e., bed rest and immersion, are only inadequate simulations in this context, since gravity and, by that, hydrostatic pressure cannot be eliminated. However, data from such experiments may provide important information, especially for the immobilization effects. This may allow to discriminate between adaptations to weightlessness and the resulting immobilization.

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Chapter 2
The Cardiovascular System in Space

Abstract In space the human body and, in particular, the cardiovascular system are exposed to an altered and unfamiliar environment. The new set of stimuli imposes novel challenges on the cardiovascular system. More precisely, a lack of the impeding gravitational force makes some cardiovascular functions more facile. Upon injection to space, extensive mechanisms that have been evolutionarily developed to cope with the burden of gravity become redundant. Next to the skeletal and muscular system, the cardiovascular system is less strained in weightlessness than on Earth and is deconditioned during longer periods spent in space. As far as current experience has shown, this process continues throughout the stay in microgravity and poses severe challenges to astronauts returning to Earth. One must understand the timeframe and severity of all areas of cardiovascular deconditioning in order to evaluate the feasibility of manned missions and ensuring a safe return to a gravitational field—be it Earth, Mars, or another planet. This chapter outlines our current knowledge of cardiovascular deconditioning in microgravity, hypothesized through terrestrial simulations and partly validated by experiments in space.

Keywords Microgravity • Weightlessness • Spaceflight • Cardiovascular system • Fluid shift • Physiology • Terrestrial simulation

2.1 Hypotheses from Terrestrial Experiments

Currently, astronauts spend extended period aboard space stations such as the ISS, where they are continually exposed to microgravity. Their bodies adapt to the new environment and allow us to trace changes induced. But when it comes to investigating the change of the cardiovascular system in weightlessness, in fact, when it comes to any investigation of physical- and life sciences in zero gravity, a major shortcoming is the amount of available data. Extensive physiological experiments are needed to determine the long-term consequences of spaceflight on the cardiovascular system, but several practical considerations limit their feasibility. High cost and limited access are stitched to the fabric of human space flight. Crew members travel to and from the station aboard two annual Soyuz flights. Consequently, the number of available subjects for physiological tests is small. In

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addition, these crew members are in charge of operational and maintenance tasks so their time available for carrying out physiological experiments is limited.

Furthermore, the experiments in space have certain operational demands in terms of the methodological possibilities. The measuring equipment for instance needs to be easy to handle and efficient. During spaceflight, there are only exceptional cases in which researchers themselves can intervene with running onboard experiments.

One way to bridge the gap between large volumes of required data and limited measuring opportunities in space is to include results from ground-based experiments that simulate weightlessness. Such experiments include bed-rest and immersion studies, both of which aim to remove the head to toe gravity vector acting on the body. These experiments attempt to simulate microgravity in order to predict and support the data recorded during spaceflight missions. A third possibility is to use short intervals of weightlessness achieved during parabolic flights to supplement spaceflight data.

2.1.1 Bed Rest Studies

Lying down in a horizontal position substantially relieves bones, muscles, and the cardiovascular system from the strain of an upright posture. Physicians and healers have used this method to treat early phases of injuries and acute diseases for centuries. Exploitable stimuli include a decreased pressure on weight bearing bones, decreased metabolism due to hypokinesia, and changes in hydrostatic pressure. These can amend stresses and alleviate physical pain in some patients.

A renewed interest in bed rest was sparked by growing interest in the possibility of spaceflight, as bed rest decreases gravity's strain on the body. Bed-rest studies date as far back as the 1850s and are still used as ground-based studies to test the effects of weightlessness on the body.

During bed rest, subjects spend weeks to months exclusively in a supine position, in which they must perform all daily tasks including eating, drinking, washing, and exercising. Limited movement, especially through the gravitational field, severely decreases muscular efforts. But bed rest also involves changing strain for the cardiovascular system. When lying down, subjects no longer experience the gravity vector acting from head to toe and pulling fluids into the legs and feet. The horizontal position almost fully removes the hydrostatic pressures within the body so that the fluid redistributes more evenly throughout the body—this also occurs in space.

More specifically, a head-down tilt of -4 to -6° is used to induce a similar cephalic fluid shift as it occurs in space; see Fig. 2.1. Immediately after taking this position, subjects show a marked central shift of intravascular and interstitial fluid. Consequently, venous pressure, cardiac output, and stroke volume increase significantly [1]. A few hours of head-down bed rest are sufficient in triggering dizziness when regaining an upright gait, a state known as orthostatic intolerance. This

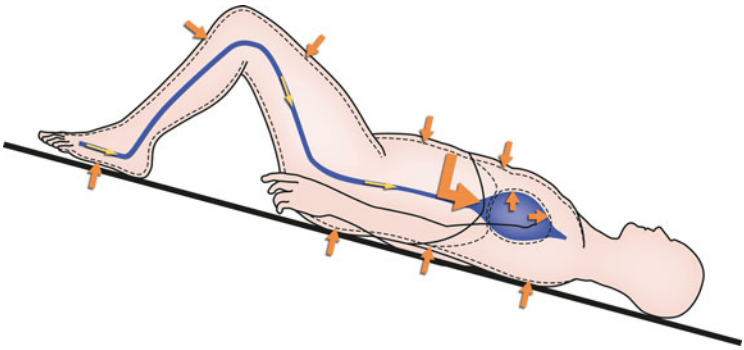

Fig. 2.1 Head-down tilt bed rest. The schematic setup of a head-down tilt bed rest. *Bold arrows* indicate pressures due to gravity and the *slim arrows* indicate the fluid shift to the heart

indicates how quickly the cardiovascular system adapts to the new requirements and stress level.

Subjects that persist in longer bed-rest studies experience changes that show a reduction in plasma volume within the first week. After 20 days in bed rest, the inner layers of the artery in the calf muscles (anterior tibialis) decrease in thickness [2]. Furthermore, arteries in the legs relax and dilate in response to increased shear stress (flow mediated dilation) within 50 days [2]. All of these are indicators of cardiovascular adaptations to the level of extreme disuse.

To achieve maximum stress levels on the cardiovascular system, subjects are usually moved to a vertical position after bed rest with the help of a tilt table. Monitoring the reaction to this sudden reintroduction of head to toe gravity reveals the extent of cardiac and vascular dysfunction imposed by bed rest. Immediately after returning to an upright posture, subjects show an elevated heart rate, decreased central venous pressure, stroke volume, and cardiac output [1]. With such measures, the cardiovascular system is trying to compensate for the movement of fluids back into the periphery. After extended periods of lying in bed, subjects experience difficulties to balance freely and walk without assistance and suffer from orthostatic intolerance.

The stretch receptors in the cardiovascular system are also influenced by the decreased gravitational loads during bed rest. Under normal conditions, these stretch receptors are able to identify changes in the blood pressure or blood volume and set off regulatory mechanisms, such as a change in heart rate, accordingly. After a 2 week head-down tilt bed rest, Iwasaki et al. observed an apparent abnormality in this form of heart rate regulation. Adaptation to sedentary cardiovascular conditions and the concomitant reduction of plasma volume achieved during bed rest may be largely responsible for the described change in cardiac baroreflex control [3]. Already in 1992 Eckberg and Fritsch reported that stretch receptors continuously exposed to pressure—as is the case during bed rest—seem to become less sensitive and responsive [4]. Such an impairment was first indicated by bed rest studies and later diagnosed during spaceflight.

Rehabilitation to the upright gait after bed rest studies mirror the re-adaptation to gravity of astronauts after their return. Therefore, bed-rest studies mirror three phases of spaceflight: the residence in space, the return to Earth, and the rehabilitation upon return. Hence, this ground-based simulation technique is a lush source of physiological information—from cardiovascular deconditioning to the rehabilitation upon return.

Countermeasures against deconditioning have benefits that exceed those involved in space travel—patients bed-ridden because of illness or accidents suffer the same symptoms and can also profit from these studies, see Chap. 5.

Bed-rest studies as a simulation for microgravity portray a range of weaknesses. Gravity is reduced along the z-axis of the body, but still acts to impose hydrostatic pressures in the transverse plane. The subject is in continuous contact with the bed and so mechanoreceptors in the skin are stimulated. These effects may contribute to a difference in physiological adaptations between bed rest and spaceflight.

2.1.2 Immersion Studies

Alike bed rest, water immersion (WI) leads to support unloading and a removal of gravity-induced pressure gradients in the body. But unlike bed rest, WI achieves this by using the hydrostatic pressure of the water; see Fig. 2.2. This leaves the cardiovascular system virtually weightless.

The two predominant forms of immersion are head out of water (‘wet’) immersion and dry immersion where the subject is enclosed by a waterproof lining. Wet immersion cannot exceed 6–12 h so that those studies focus on short-term adjustments. The dry immersion method was first proposed by soviet specialists in space biology and medicine in the 1970s [5] and allows for long-term immersion (longest experiment lasted 56 days [6]. As a comparison, bed-rest studies can continue for over a year (longest study to date lasted for 370 days [7].

Both forms of immersion have three main effects: (1) they create supportlessness because forces act equally from all sides, (2) they induce extensive physical inactivity, and (3) they cause hydrostatic compression of the superficial tissues and vessels. The third effect severely influences the cardiovascular system in that it causes fluid movement from the interstitial to the intravascular space—that is from the tissue into blood vessels. The pressure exerted on the legs by the water decreases the peripheral vascular capacity and leads to a redistribution of fluid from the lower extremities to the upper body. Again, as in bed rest, a marked increase of thoracic blood volume parallels developments in space.

WI increases central blood volume by about 700 mL with a concomitant rise of 200 mL in heart volume [8]. Superficial consequences of this mechanism can be seen in a decreased calf and leg circumference that similarly occurs during WI and in weightlessness. Furthermore, the fluid shift increases venous pressure in the central circulation zones by more than 10 mmHg, as it is expected to do in microgravity [9].

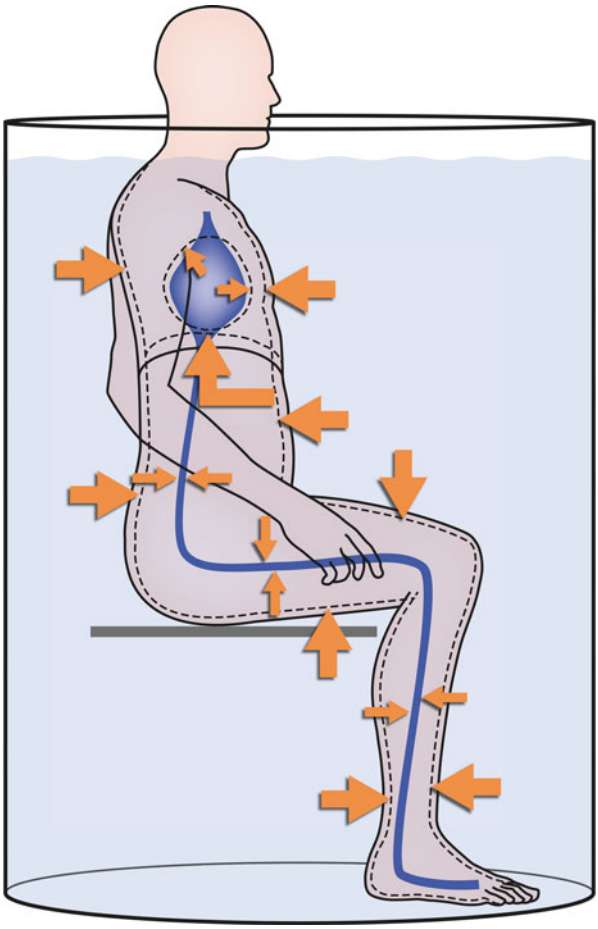

Fig. 2.2 Immersion: schematic setup of head out of water immersion experiments. The body of subjects is fully immersed in water while the head remains above the water. *Hollow arrows* indicate the hydrostatic pressures induced by immersion

The similarity of effects on the cardiovascular system between WI and weightlessness was shown by Norsk et al. in 1999 during an experiment that monitored the influence of 20 s WI and weightlessness during parabola flights [10]. The team measured the stroke volume, cardiac output, and peripheral vascular resistance, all of which changed in the same way and to the same extent during both procedures. Thus, the acute effects of weightlessness on central cardiovascular variables in humans can, at least in some cases, be simulated by WI.

Conflicting examples exists as well. For instance, the central venous pressure was found to increase initially during dry immersion [11], whereas in space a decrease in venous pressure in the periphery and of the central venous pressure has been observed [12]. Furthermore, WI is linked to a high urinary flow induced by the fluid shift [13, 14], whereas a decreased diuresis is observed during space missions [15–17]. Actual weightlessness and simulated weightlessness can,

therefore, not be interchangeably used and the one can simply hypothesize the influence of the other.

Next to hypothesizing the influences of weightlessness, immersion tanks can be used to practice extra-vehicular activity by exploiting neutral buoyancy, for example, in NASA's Weightless Environment Training Facility.

WI is a useful ground-based model to test the influences of prolonged conditions of weightlessness on the cardiovascular system. Especially dry immersion allows subjects to be freely suspended in water so that the consequences of long-term exposure to microgravity can be predicted. Nonetheless, alike bed rest, WI only imitates weightlessness and thereby cannot achieve the full set of adaptations experiences in space. Microgravity, bed rest, and WI all share a marked increase in central blood volume as the most striking event. Nonetheless, the three situations have different primary mechanisms, with which this shift is achieved. Consequently, other variables are peculiar to each situation and the ground-based simulations remain valuable composites, but cannot suffice as a replacement of experiments in space.

2.1.3 Parabolic Flights

The only way to have matter floating in weightlessness; see Fig. 2.3, on Earth is during free fall from a drop tower, in sounding rockets or in aircraft parabolic flights. The latter is the only feasible option to combine with human experiments, making parabolic flights the only way to investigate the true influences of microgravity on the cardiovascular system without travelling to space.

Parabolas are flown in an airbus similar to passenger vehicles, with an interior specially fitted to accommodate experiments. The aircraft begins with horizontal flight and climbs to an angle of 47° during a pull-up phase, before throttling the engine and creating a free-fall interval of 20–25 s; see Fig. 2.4. Thereafter, the aircraft dives back down to a horizontal flight mode and reiterates the process 30 times during one session. This creates subsequent periods of 1, 0, and 2 g levels allowing the study of transient phenomena occurring during the change from high to low gravitational fields and back again. As the intervals of weightlessness last for less than 30 s, the observed changes are expected to occur mainly in the outflow of the autonomic nervous system and can be detected easily by measurable parameters such as heart rate and blood pressure.

The Airbus A300 "Zero-G" has been used since 1997 everywhere in the world. With such a vehicle, ESA alone has conducted over 160 experiments in a total of more than 3000 min of weightlessness, of which every tenth was dedicated to the cardiovascular system [18]. Earlier aircraft that performed parabola flights include NASA's KC-135 and the Russian Ilyushin.

Acute hemodynamic changes in weightlessness were measured onboard NASA's aircraft in 1991, when researchers concluded that cardiac output increased and heart rate decreased when entering microgravity and more so in the standing

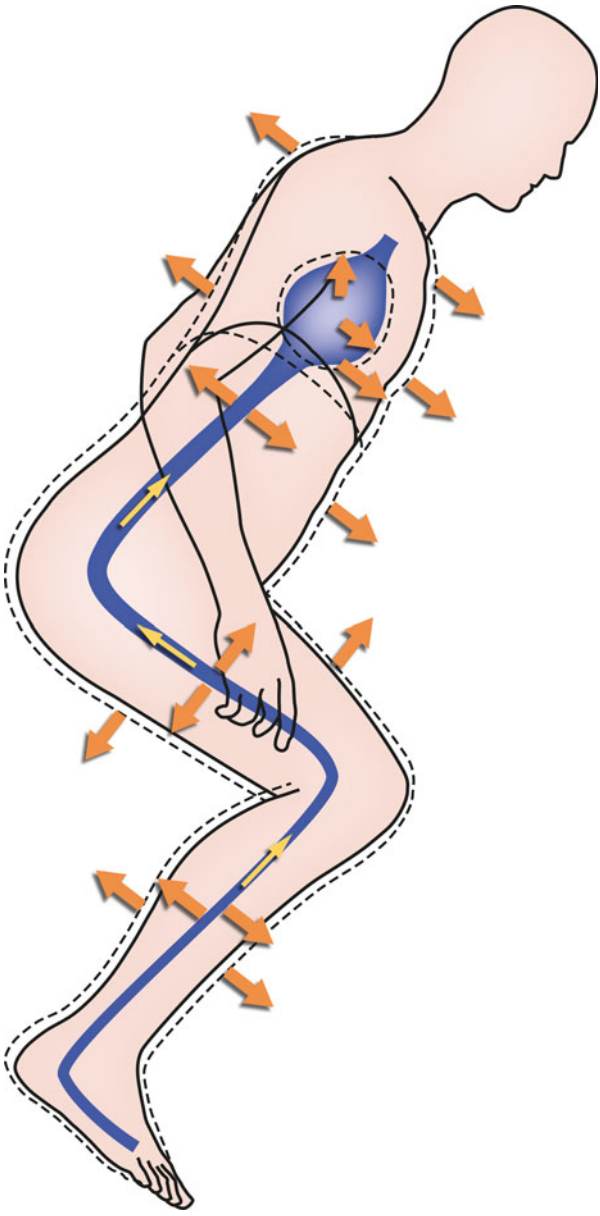

Fig. 2.3 Weightless: during parabolic flight, as in space, forces of gravity no longer act on the body's surface (*bold arrows*). Blood begins to move to the upper body (*slim arrows*)

position [19]. Early campaigns on the Airbus A300 "Zero-G" involved the Advanced Respiratory Monitoring System (ARMS). During this set of experiments, a Danish group showed that hypotensive effects through peripheral vasodilatation might be induced by distention of heart and the associated central vessels [18].

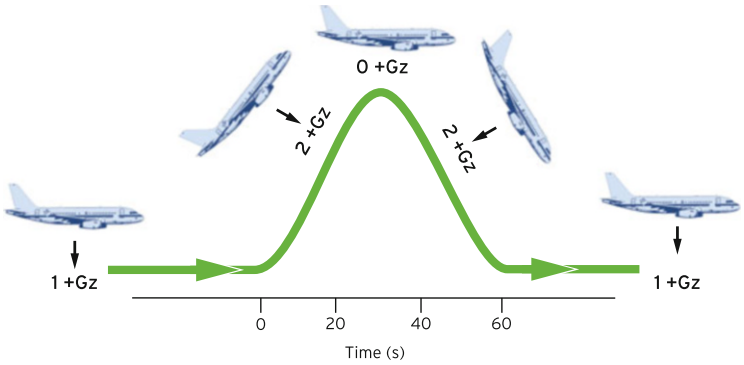

Fig. 2.4 Parabola flight: single sequence flown by an airbus to create weightlessness inside the craft

Another campaign by Aubert et al. investigated the heart-rate variability with standing and supine positions. In later stages, the team tested ISS astronauts and included blood pressure and breathing measurements to compare results from short periods of weightlessness during parabolic flights to longer missions onboard the ISS [18]. They concluded that values of vegal activity and sympathetic activity achieved during parabolic flights are comparable to those of a 10-day stay on the ISS.

In general, parabolic flights have provided a broad range of results regarding changes in the cardiovascular system in microgravity. For instance, a better understanding of orthostatic intolerance and decreased peripheral blood flow suffered by astronauts returning to Earth could be achieved. Parabolic flights have also revealed that variations in the heart size already occur in short periods of weightlessness and that changes in the heart rate resulting from transitions between g-levels depend on the body's orientation with respect to the direction of gravity. All in all, many of the physiological phenomena observed in space such as slowing of heart rate already prevail during the 20–25 s of free fall in a parabolic flight.

As parabolic flights completely remove the density vector in the body, they achieve the same acute effect on the cardiovascular system as spaceflight. However, the intervals of weightlessness do not exceed 30 s, so that only short-term adaptations are exposed and long-term changes remain speculations. This makes parabolic flights a useful composite element of ground-based experiments that predict the consequences of weightlessness on the cardiovascular system, but make experiments in space by no means redundant. Next to physiological investigations, the real value of parabolic flights lies in the testing and validation of equipment and techniques to improve the success rate of experiments taken to space.

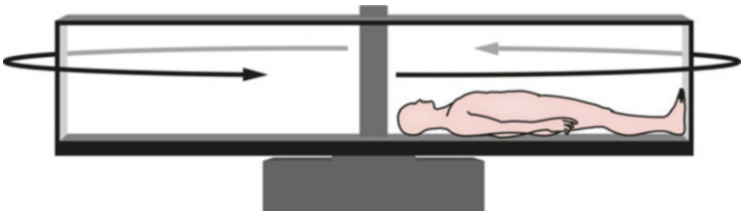

Fig. 2.5 Centrifuge: rotating arms of the centrifuge induce outward forces that can exceed the size of gravity

2.1.4 Centrifuge Experiments

While the experimental setups mentioned above attempt to simulate lower gravitational levels in space, important information can be won from reverse conditions—larger gravitational forces. Such gravitational levels (above 1 g) can be achieved by employing a centrifuge; see Fig. 2.5. The fact that gravity strongly influences the distribution of blood in the body is evident from terrestrial centrifuge experiments. Investigating the reaction of the body to increased gravitational forces can provide indications of how it will react if the changes were opposite, i.e., below 1 g and down to 0 g.

Already in the 1940s, Prof. Otto Gauer experimented with the centrifuge to monitor the influence that gravitational changes had on the physiology in horses, monkeys, and humans. Understanding how the cardiovascular system responds to increased gravitational forces indicates the consequences of weightlessness by means of extrapolation. Gauer and his colleagues made substantial progress in understanding the influence of the gravitational parameter on physiology, especially on the cardiovascular system. With a paper published in 1950 by Gauer and Haber, the researchers demonstrated the increasing interest in manned explorations to microgravity and paved the way to research of the body weightlessness [20].

Such experiments are continually carried out today to better understand the influence of gravity on the cardiovascular system and consequently enhance the understanding of adaptations to lower gravitational levels [21–23].

Furthermore, the effects of high-g play a role during the brief periods of takeoff and before landing. Centrifuge experiments are, therefore, also key to investigate the cardiovascular response and resistance to gravitational stresses experienced in space shuttles.

Another and more substantial application of centrifuges to space travel is its potential as a countermeasure to cardiovascular (and general) deconditioning, see Chap. 5.

The different ground-based methods to investigate the effect of weightlessness provide a solid base to form predictions of what actually happens in space. Although they present a decent indication and often even a valid result, data collection during space missions can be at variance and even in contrast to terrestrial data. Different terrestrial setups may be selectively chosen to mimic certain

effects [24]. Understanding the full extent of the cardiovascular reaction to weightlessness, however, requires data from actual spaceflight.

2.2 Adaptations to Microgravity

The predictions of adaptations to microgravity from ground-based models must be validated by actual spaceflight data. The distinction between the fluid shift itself and the reaction to this shift introduces two timeframes of physiological change. Firstly, the immediate changes induced as a consequence of removing the gravitational force are listed as acute adaptations in the following section. Secondly, concomitant adjustments to these changes will be described as long-term adaptations below.

2.2.1 Acute Adaptations

Influences of spaceflight on the cardiovascular system begin even before liftoff with preparatory measures, such as the preflight posture. Several hours before takeoff, astronauts were in their positions in the shuttle, lying on their backs with a 90° hip and knee flexion; see Fig. 2.6. This supine position prevented blood from pooling in the legs during ascent, which, in extreme cases, could lead to syncope. It also means that a significant blood volume was placed above the heart and fluid begins move from the periphery to the upper body, indicate what will continue to happen in space. Furthermore, astronauts have the option of taking anti-motion-sickness drugs at their own discretion, which can also have an effect on the cardiovascular system.

The stress that comes with the liftoff itself also influences physiological parameters and might perturb the cardiovascular system. These factors deviate measurements made while initially entering space and hinder differentiating between causes

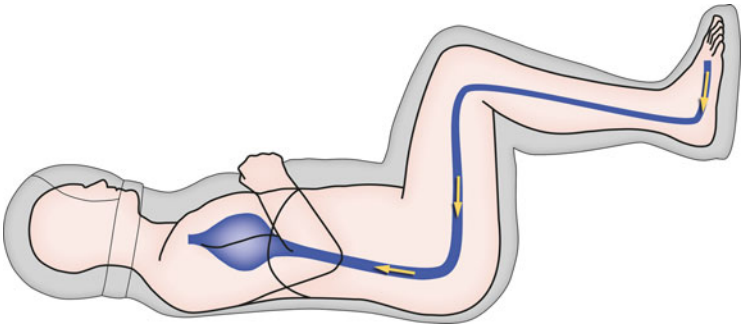

Fig. 2.6 Astronaut prelaunch: this is the position of astronauts in the shuttle before takeoff. Legs are flexed above the heart level, encouraging backflow of blood and a shift of fluid, which is preventive of possible syncope during launch

and the associated outcomes. Furthermore, data vary between individuals, since different subjects react at different rates and in different ways to the new environment.

2.2.1.1 Fluid Shift

Regardless of these difficulties, much effort has been invested to understand the immediate changes of the cardiovascular system in weightlessness. First and foremost, weightlessness induces a fluid shift within the body; see Fig. 2.7. Imagine pouring a free liquid in microgravity—the surface tension will act to hold it in a spheric volume. This is due to the absence of gravity and hence absence of hydrostatic gradients in the liquid. Similarly, the hydrostatic pressures in the cardiovascular system equalize and blood collects in the compliant thoracic area. Gravity no longer acts on the surface of the body. Immediately upon reaching microgravity, this effect kicks in and fluid shifts from the lower extremities to the upper body. Several mechanical reactions within the cardiovascular system follow, many of which are described below.

Upon reaching weightlessness, astronauts immediately feel this fluid shift without relying on visual or physiological indicators. The larger volumes of fluid in the upper body is experienced by a sense of fullness in the head with pressure felt in the

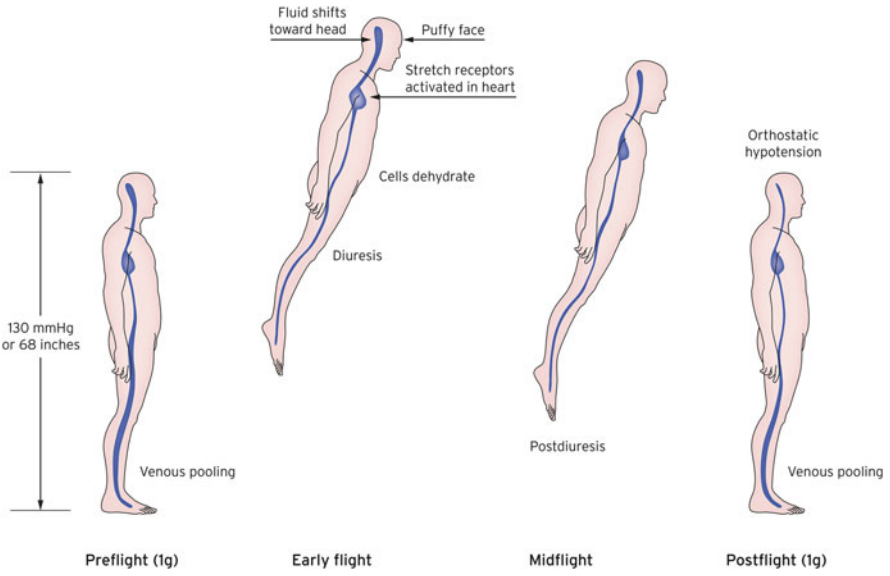

Fig. 2.7 Fluid shift; preflight (*left*) the lower extremities are easily supplied by blood, because of the downward pull of gravity. Early in-flight the blood begins to shift from the lower extremities to the upper body and the blood volume decreases midflight. Postflight (*right*) gravity pulls blood to the legs again, but there is less blood so that the bulk of the volume sinks to the periphery

upper sinuses and eyeballs—a similar sensation to suffering from nasal congestion during a cold. The senses of smell and taste may be weakened too, as they do during illness, and nonverbal communication between subjects will be attenuated because facial expression is hindered.

The fluid shift is easily noticed visually, without regarding physiological parameters. During NASA's Skylab missions, astronauts noted that their faces swelled up especially around the eyes and that the superficial veins on the scalp and neck are engorged, indicating they were full of blood. One astronaut, Dr. Atkov, recounts his first shaving experience aboard the Soviet Salyut 7 flight where he looked in the mirror to find a Mongolian-looking stranger peering back at him.

The cephalad fluid shift increases filtration of plasma water into the interstitium of the facial region, leading to this optical change. Currently several NASA and ESA studies are aiming to evaluate the long-term impact of the cephalad fluid shift on the visual system [25, 26]. The change in the thickness of superficial tissues can be measured to quantify the apparent fluid shift. Accordingly, the thickness in the forehead increased by 7 %, reflecting an increase in fluid of about 2 l in the upper body [27, 28].

The fluid that has accumulated in the upper body and has led to visible changes in the face has left the periphery where, too, visible changes occur. Within the first 4 days in space, the circumference of the legs decreases by up to 30 % to a level that remains this low for the rest of the flight, even 1.5 years later [28, 29].

The decrease in leg girth also indicates that approximately 2 L of fluid are shifted from the lower extremities and must have been accommodated mostly in the intrathoracic circulation areas [30, 31].

The shift from of blood from the legs upward happens within seconds of reaching weightlessness. However, fluid also shifts between compartments, moving from the blood stream into the tissues. This shift is not instantaneous and may occur over a period of a few hours [32]. In general, fluid shift processes occur rapidly and are virtually complete within the first 6–10 h of flight [33].

Fluid shift clearly accounts for the initial decrease in leg girth, especially of the thighs, with continuing decreases in leg volume reflecting additional changes due to loss of leg muscle mass. The visual phenomena reflecting an initial fluid shift are referred to as puffy-face and chicken-leg syndrome and are superficial indications of what is going on in the cardiovascular system.

Even without a closer look at the physiological quantities, it is evident that a restructuring of the cardiovascular system is induced immediately after entering weightlessness. To understand the consequences, however, it is necessary to investigate cardiovascular dynamics and its predicative parameters.

2.2.1.2 Cardiovascular Dynamics

Of all physiological processes in the body, the activity of the circulatory system in weightlessness has gained much, if not most, attention. This is not only because of

the importance of the heart and blood to survival but also because this system relies on mechanical principles strongly influenced by gravity.

The first cardiovascular changes in weightlessness are simply a mechanical or physical reaction to the new gravitational condition rather than chronic adaptations to these changed stimuli. These primary reactions occur as an immediate result of the cephalad fluid shift and are expressed in the form of altered cardiovascular parameters, which are presented in this section.

Heat

The fluid shift leads to changes in heat transfer in space. Since convective and evaporative heat loss are diminished in weightlessness, radiative heat loss in space becomes even more important than our ground. Under terrestrial conditions, over 30 % of heat exchange between the body and environment occurs at the head and neck [34]. A higher blood volume in this part of the body could have consequences on the heat exchange and hence on the cardiovascular system

Blood Pressure

The hydrostatic pressure gradients in the vascular system induced by gravity on Earth are completely removed when entering microgravity. Blood pressure is equalized throughout the body such that blood vessels in regions usually exposed to higher pressures (in the feet and lower legs) are exposed to a lower blood pressure, while the vessels between the heart and head experience a larger pressure than on Earth.

The difference between the two regions of blood circulation—venous and arterial—is independent of gravity and persists in space. The latter is the high pressure system and is quantified by the mean arterial pressure (MAP), which corresponds to the average pressure experienced during one cycle through the arterial loop. The pressure in the venous side of blood circulation is lower because of the high capacitance of these vessels.

MAP is calculated using the systolic and diastolic pressure measurements, but seems to be the least consistent variable among the pool of already inconsistent physiological findings in space. Fritsch-Yelle and Karemaker et al. both observed a decrease in diastolic arterial pressure within the first weeks of flight [35, 36]. In line with these studies, Norsk et al. found that both the systolic and the diastolic pressures are decreased in flight compared to on the ground—and holding for all phases of the daily rhythm [37].

Several other measurements, however, of astronauts during short-term residence in space have displayed no changes or even increases in blood pressure in peripheral vessels [38]. This suggests that the changes in blood pressure are different in different vessel sizes, with the pressure in the branchial artery increasing in short-term spaceflight.

The great variability of MAP in its initial response to weightlessness could be a consequence of a general instability of the blood pressure in early flight and to the different anatomical structures of blood vessels. The cardiovascular system is searching for a new steady state under changed conditions, whereby oscillations of physiological variables such as the MAP are part of a compensatory response to challenge. What is clear, however, is that changes in the MAP do not occur so that there is no evidence for operational threats to the cardiovascular system [39].

Challenges faced when investigating the low-pressure system are of different nature. This time the results do not necessarily fluctuate as those of MAP, but the behavior is quite the opposite of what is expected. Ordinarily, hypervolemia increases venous pressure simply because the vessels are fuller. In space, the situation should be similar; blood volume is shifted to the thorax so that local venous pressure measurements would be expected to elevate.

To characterize the low-pressure side of the blood circulation, one measures the central venous pressure (CVP). The CVP is the pressure in the venae cavae—the veins carrying deoxygenated blood to the heart's right atrium—and is influenced by the blood shift to the upper body. Therefore, the CVP is an indicator of the amount of blood shifted and the rate at which this shift occurs.

Direct measurement of the CVP requires a catheter placed very close to the heart, which bears obvious hazards. An alternative technique used by Dr. Karl Kirsch in the mid-1980s determines the pressure in the veins in the arm. This measurement reflects the CVP at the right atrium under the assumption that all venous valves remain open to create an open circuit between both locations. This technique was applied for the first time during the Spacelab 1 Mission [12] and the D1 Mission [40], measuring the blood pressures in four crew members starting 22 h and 20 min after launch, respectively.

Another indirect technique measures the pressure in the lungs. When blood flow through the vein in the chest cavity stops the pressure in the lung is approximately equal to that in the vein. The lung pressure can then be used as an estimate for the CVP in the right atrium. This noninvasive technique was used on a single crew member onboard the STS 61-C to monitor his CVP during the first 5 days of flight [41]. Both of these measuring techniques have yielded the same surprising result; CVP decreases in weightlessness to a level below prelaunch values. These findings were confirmed by CVP values attained during a Spacelab mission in 1993 using a catheter placed within the inferior vena cava before launch. This experiment portrayed the trend of CVP from before launch, through takeoff, to the period after reaching weightlessness. Already before takeoff, the CVP begins to increase as a result of a rush of fluid to the right atrium in the supine position. The pressure further increases during launch and ascent because the g-forces in the foot to head direction increase the fluid shift as well as compressing the chest area. As in the prior indirect measurements, the CVP decreases to and then below prelaunch values once astronauts are on orbit [42]. This trend was observed in the SLS-1 and SLS-2 missions, both reporting that CVP remains below Earth normal levels during early spaceflight [42, 43]. These results establish a discrepancy between low CVP and high intrathoracic filling volumes. A possible explanation is that the venous blood

vessels in the thorax show a rapid increase in compliance and are able to hold more volume at a lower pressure [32]. To date, the exact spaceflight vasodilatation mechanisms that could enable the decrease in CVP despite higher filling volumes have not been exposed and need to be explored further [37].

Stroke Volume and Cardiac Output

The stroke volume and the cardiac output are two further cardiac variables that are immediately influenced by fluid shift. As hydrostatic effects disappear, the amount of blood in the heart virtually doubles [44]. Venous blood that is no longer pulled into the compliant vessels in the legs and abdomen rushes into the right atrium. This means that the cardiac preload increases, and each heart contraction pumps a larger amount of blood, i.e., the stroke volume increases.

With an increased stroke volume, the cardiac output increases even if the heart rate remains unchanged. This is supported by an increase in central venous pressure observed early on orbit by Norsk [37]. Prisk et al. directly measured an increase in cardiac output by 18 % of 4 astronauts arriving to weightlessness [31]. The elevation prevailed while the cardiovascular system began to adapt to the new environment and values fell towards preflight levels within a few days. The initial increase in SV—similarly to the other short-term changes mentioned above—is merely a physical consequence of fluid shifts in the absence of gravity.

Heart Rate

The heart rate is the physiological parameter that is easiest to measure. Therefore, it can be monitored continuously throughout launch and arrival to space. The heart rate is controlled by the autonomic nervous system, and hence its change is not a mechanical consequence of weightlessness. Nonetheless, it adapts so quickly to the new requirements of changing environments that its response is definitely short-term. A continuous measurement of the heart rate is utile, since it reflects the external stimuli on the body as well as receiving influences from the psychological state of the astronauts.

Fritsch-Yelle et al. [35] performed the first systematic evaluation of basic cardiovascular variables in 1996 monitoring 12 male astronauts for 24 h periods before and during their 5–10 day shuttle trips. The researchers recorded a significant decrease in heart rate in flight, assuming that this was a consequence of increased stroke volume—with a more efficient contraction, the body requires fewer beats to sustain the same blood circulation. To date, studies have reported alternate developments of the heart rate in space, some even reporting on increases [45, 46].

However, one must distinguish between those that record during experimental interventions rather than consistently throughout routine activities. This criterion

grants the study of 1996 high credibility [35]. Furthermore, 24 h measurements on animals have also displayed decreased heart rates in space [47].

A very recent study by Norsk et al. reports that the heart rate of astronauts exposed to microgravity remains constant [37]. Despite ambiguous results from diverse studies, consensus can be reached on the fact that the heart rate does not seem to increase—despite psychological stress.

Another aspect of the heart rate in microgravity, one that seems more certain, is that there is a significant decrease during sleep. Gundel et al. observed a cosmonaut on the Mir space station and found that the decrease in heart rate during sleep is larger than the decrease on the ground [48]. Norsk et al. also observed this trend on the ISS. These observations suggest that the parasympathetic drive to the heart increases in microgravity, possibly due to the fluid shift and increased preload of the heart [37].

From the fluid shift, more blood in the thorax increases the cardiac preload so that each contraction of the heart pumps more blood. Hence, the circulation of blood becomes more efficient so that a lower heart rate will sustain the same supply to the body.

In the study mentioned above, Fritsch-Yelle et al. recorded a reduced diurnal variation and premature ventricular contractions [35]. The heart has to work less hard in space allowing reduced dysrythmia and beat frequency. The team concludes that weightlessness itself does not present a chronic stress to the cardiovascular system. For the residence in space, this is good news. However, once astronauts return to the ground they will suffer from the present "lazy" period—like an athlete returning to training after a long break.

The investigation of possible threats to the cardiovascular system, however, goes beyond the behavior of the heart rate. As astronauts spend extended periods in weightlessness, the body adapts to the new requirements in multiple ways. The ways and the extent to which the cardiovascular system are affected are discussed in the following sections.

2.2.2 Long-Term Adaptations

Immediate mechanical changes in the body are followed by a cascade of mechanisms with which the body reacts to these changes. With suddenly changed stimuli, the cardiovascular system introduces a range of primary reactions to cope with the increased thoracic volume short-term. This rapid reaction involves a decrease in the heart rate, as well as a dilatation of arterioles to decrease peripheral resistance and thereby decrease blood pressure [35].

Thereafter, the body begins to adjust to the changed stimuli by arranging a new set point long-term. The dominant long-term change, which has influences on many other aspects of the cardiovascular system and beyond, is a reduction in fluid volume. The body perceives a fluid overload due to a high thoracic filling, although the total body water and blood volume are normal by terrestrial standards. The

consequence is an induced reduction of blood volume. This is an appropriate measure in adapting to microgravity, but results in a fluid volume that would be considered hypovolemic on Earth [49].

Indications for a fluid reduction are delivered by decreased stroke volumes and reduced plasma ANP levels [50]. The changes correspond to a decrease in plasma volume by about 20 %. Some models to quantify liquid volume reduction are based on simulation models, such as bed rest studies and head-down tilt studies. Johansen conducted a head out of water immersion study and observed that the central blood volume decreased to levels below the pre-intervention level [51].

The way in which the fluid reduction is achieved involves stretch receptors in the intrathoracic vessels and heart [52]. On Earth, the carotid sinuses that are located about 25 cm above the heart set the norm for the stretch receptors. In space, density differences are eliminated, and higher fluid volume in the thorax leads to a higher filling of blood vessels. This triggers the stretch receptors sending the baroreflex into action.

It was first believed that a reduction in blood volume is achieved by increased diuresis as part of a feedback mechanism. This mechanism was first described by the gravitational physiologists Gauer and Henry and is therefore termed the Gauer–Henry Reflex [53]. Thoracic stretch receptors suppress the production of the Antidiuretic Hormone (ADH). This means that less water is reabsorbed in the kidneys and more urine is produced.

However, a corresponding increase in urine production is not detected in the first days of spaceflight [54]. In fact, Spacelab astronauts produced less urine in the initial phase of space flight compared to preflight values [16]. If less liquid is excreted in space, how can this be in accordance with a decrease in blood volume?

The answer is that the body cannot be mapped by a simple liquid container, whose content corresponds directly to how much or how little is micturated. Firstly, the fluid intake plays a role. Astronauts that have a fluid intake below the excretion rate will experience a net fluid reduction. Reports of decreased thirst on arrival to the space station can be part of the answer.

Secondly, we must treat the blood volume separately from the total body water, i.e., the liquid can shift within the body to decrease the filling of one compartment (i.e., intravasal) by increasing another (i.e., interstitial or intracellular volume). Firstly, the lower blood pressure in the legs causes a kind of dehydration of tissues so that there is a decrease in extracellular fluid [49]. Instead, the interstitial water in the legs first moves into the capillaries and the blood stream and then accumulates in the upper body. Here, gravity does not lead to tissue compression and fluid moves from the blood stream to the tissue. This movement leads to the variety of visual changes mentioned above. This will also cause a decrease in blood plasma (the liquid portion of blood).

2.2.2.1 Physiological Parameters

As the changed stimuli prevail, the body adjusts fundamentally to accommodate these.

The immediate increase of diastolic arterial pressure mentioned above is followed by significant decreases in the systolic and mean arterial pressure later in the mission [37]. This is decrease is induced by the reduction in plasma volume.

After an initial rise in cardiac output, it was assumed that the human body would adapt to a lower level throughout a longer residence in weightlessness. There is little direct measurement of cardiac output and stroke volume changes throughout long-duration space flight. Ertl et al. measured a decrease in stroke volume, which is in line with a decreased blood volume and will induce a lower cardiac output provided that the heart rate remains unchanged [50]. Measurements of 26 cosmonauts onboard the Salyut-7 and Mir stations displayed person-specific trends of cardiac output (CO) and stroke volume (SV) in the first 3 months of flight. Thereafter, however, the cosmonauts displayed a unison trend of decreasing SV and CO during 4–6 flight months [55]. Hypovolemia induced by space flight leads to an under-filling of the heart chambers, which decreased the SV and thereby the CO.

However, data on the stroke volume from studies in microgravity are rather ambiguous. Hughson et al. and Hamilton et al. and found no change in stroke volume using the continuous finger blood pressure contour technique and echocardiography, respectively [56, 57]. On the contrary, Herault et al. observed a decrease in stroke volume of 10–16 % in 5–6 months of a long mission aboard the Mir space station [58]. A recent study led by Norsk recorded a significant increase in stroke volume of up to 35 % after 3 months of space travel [37]. Norsk, however, mentions the possible discrepancies resulting from varying reference positions (upright seated, supine, etc.). To resolve the prevailing inter-study ambiguity, more research campaigns involving the long-term changes of cardiac parameters are required.

Shifts in the cardiovascular system could also have an influence on the vision acuity of astronauts. During long-term missions of at least 6 months, crew members report a decrease in their vision acuity and blurred eyesight [59]. So far, there are no indications that prolonged exposure to microgravity could lead to blindness in the near term. A possible cause for the changes in vision is an increase in intracranial pressure—pressure in the skull. The intracranial pressure is directly influenced by the cardiovascular system, in that an increased cardiac output and upper body venous pressure can lead to a chronic increase in intracranial pressure. Over time, this could manifest itself as ocular changes [37]. The change in eyesight of astronauts highlights the possible sphere of influences that the cardiovascular system has. It is important to understand exactly what is changing when in order to quantify concurrent alterations in other parts of the body [26].

2.2.2.2 Where Is the limit?

After about 1.5 months, a new equilibrium is reached, known as "0g set point" that represents a new adaptive state for microgravity [45]. Beyond this point, where crew members are able to work and exercise effectively, there are no reports of further in-flight functional decrements during missions lasting up to a year [39]. Fluctuations in heart rate and blood pressure experienced early in the adaptation phase of the mission, both during exercise and during rest, lessen further into the mission. This further supports the idea that the cardiovascular system reaches a steady state after an initial labile period.

The truncated deconditioning occurs while astronauts perform rigorous daily exercise programs—how the cardiovascular system would change if this countermeasure was omitted is unknown. The unique combination of environmental and psychological changes in space and their exact effect on the cardiovascular system have yet to be understood.

In regard to the cardiovascular system, the changes that occur during a one year mission do not appear to pose severe hazards for their time in microgravity. What happens after that is unknown. What is known, however, is that the return to gravity becomes increasingly stringent after prolonged exposure and adaption of the cardiovascular system to weightlessness.

More research is needed to investigate changes occurring during mission lengths of several years, and our knowledge from preluding long-term studies is still very scanty. Preluding studies are costly, both on time and in an economic sense, but absolutely necessary before we can safely send humans on such missions or define an absolute limit to the possibilities of spaceflight.

2.3 Adaptations Upon Return

The cardiovascular system faces its largest challenges of spaceflight upon return. Concerns regarding instabilities of the cardiovascular function on reentering are relevant as capsules require human piloting and possibly emergency measures by astronauts in the case of a fuel leak or similar [39].

Once astronauts have safely returned to Earth, the consequences of prolonged exposure to microgravity and the adaptation of the cardiovascular system to the lack of gravitational stimuli begin to show. The deconditioned cardiovascular system is characterized by an inability to respond efficiently to challenge [60]. Even a simple upright gait can be a staggering challenge for astronauts returning to Earth. Problems faced during such challenges include dizziness, sweating, pre-syncope, and—above all—orthostatic intolerance.

Orthostatic intolerance is regarded as one of the most serious cardiovascular problems upon return from space to earth weightlessness and is manifested in an elevated heart rate, decreased systolic pressure, as well as an increased tendency to

faint. An obvious cause for this state is the hypovolemia. Astronauts have less blood volume than before their departure and most of the volume remains during up-ward standing in the lower parts of the body (venous pooling). This effect is heightened by the postflight hemodynamic state. Over the course of weightlessness, the arterial vessels below the heart have slackened—the antigravity tone disappears as unneeded. This is even more true for venous hemodynamics that is more sensitive to microgravity [55]. Therefore, the return of venous blood is slow, leg vein capacity is increased, and arterial resistance is reduced [61]. These challenges lead to a greater than normal amount of blood pooling below the hip level [62]. Blood is no longer shifted to the upper body and is missing the heart and brain, leading to a faster heart rate, dizziness, and even fainting.

Postflight exercise performance naturally depends on the state of the muscular system that has deconditioned during a period of disuse in microgravity, but is also influenced by the condition of the cardiovascular system. A decreased mass and size of the left ventricle of the heart has been reported postflight [63, 64], which is part of the deconditioning effect on the cardiovascular system and influences the exercise capacity negatively. Some studies also report on a decreased capacity of blood to carry oxygen; see Chap. 3. Hypovolemic conditions of the cardiovascular system contribute most significantly to a decreased exercise capacity experienced by returning astronauts. Levine et al. measured a postflight exercise capacity that was 22 % worse than before flight. The decrease in VO2max (maximum volume of oxygen that can be used—it is the standard measure for exercise capacity) is a result of a reduced intravascular blood volume and a reduced stroke volume and cardiac output [65]. Results from the second manned Skylab mission similarly reported on a reduced exercise capacity postflight, without such a negative (but rather a positive) change in flight [66].

Both orthostatic intolerance and decreased exercise capacity upon return become more severe for longer missions and require a longer recovery period [67]. According to [68], the recovery of orthostatic tolerance to preflight levels after a 1 month mission is around 1 day. With the use of in-flight exercise programs, however, deconditioning does not worsen linearly with time. Skylab astronauts that had spent 59 days in weightlessness could return to preflight exercise capacities within 5 days [66]. Decreased weight and increased thirst of astronauts is proof of the reduced liquid volume, which the body immediate attempts to reestablish. The quick re-adaptation of the orthostatic status to a 1 g level shows the adaptive nature of previous changes in microgravity.

It is important to note that in-flight deconditioning might be more severe if daily exercise routines would be neglected. With these in-flight programs, and other countermeasures, the space operational medicine department and flight industry attempt to limit challenged face by returning astronauts. The development of countermeasures to cardiovascular deconditioning essential to prolonged space travel bears advantages to areas beyond the spaceflight industry.

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Chapter 3
Red Blood Cells in Space

Abstract The cardiovascular system and the contained red blood cells are the backbone of oxygen transportation in the human body. From an evolutionary point of view, this system is rather ancient and originated approximately 500 million years ago when multicellular organisms had grown so much that transportation of oxygen and nutrients by diffusion had become insufficient. The development of erythrocytes containing hemoglobin to bind oxygen and carbon dioxide reversibly occurred approximately at the same time and marks an important step in the evolution of more complex forms of life. Today, we know that the production and release of erythrocytes from the bone marrow in humans is regulated by a hormone called erythropoietin. In adults, the kidneys are the organ responsible for the production and release of this hormone. Specifically, erythropoietin is stimulating erythropoiesis by increasing the proliferation, differentiation, and maturation of the erythroid precursors. Most remarkably, already during early spaceflight in the 1960s and 1970s, it was realized that blood volume, red blood cells, and haemoglobin concentrations are severely altered in astronauts. This chapter briefly describes the time course, magnitude, and means by which this reduction occurs and what the impact for living and working in space might be.

Keywords Red blood cell regulation • Terrestrial studies • Extreme environments • Space flight

3.1 Red Blood Cells and Erythropoietin

The cardiovascular system and the contained red blood cells are the backbone of oxygen transport in the human body. Figure 3.1 shows different complexities of cardiovascular systems that developed in the early course of evolution. The cardiovascular system had to be developed at an early stage of evolution: approximately 500 million years ago during the Cambrian explosion, in which multicellular organisms grew so much that the transportation of oxygen and nutrients by diffusion had become insufficient. Already in 1929, Hill described the increase in diffusion time with tissue thickness (Fig. 3.2) that makes cardiovascular systems unavoidable for larger organisms. The development of erythrocytes containing

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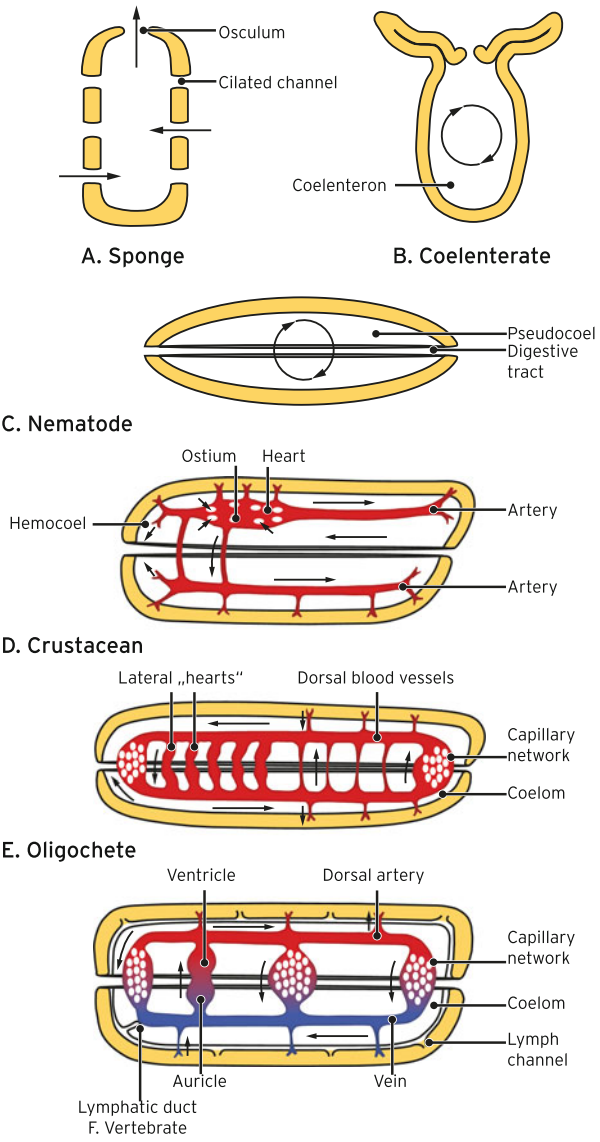

Fig. 3.1 Principle structures of cardiovascular systems in different organisms [1]

hemoglobin to bind oxygen and carbon dioxide reversibly developed approximately at the same time (Fig. 3.3).

During evolution, humans transformed from a quadruped to a bipedal form—from moving on four, to moving on two limbs. In the bipedal form, humans spend a majority of the day upright and most nights supine or prone. The change in posture is likely to have caused physiologic responses, which modulate the effects of gravity on the distribution, volume, and pressure within the vascular space [4]. Microgravity (micro-g) is a unique opportunity to analyze the impact of gravity

Tissue thickness [mm]	Time [sec]
0.007	0.0054
0.7	54.0
10.0	11,100.0

Fig. 3.2 The diffusion of oxygen and lactic acid through tissues [2]

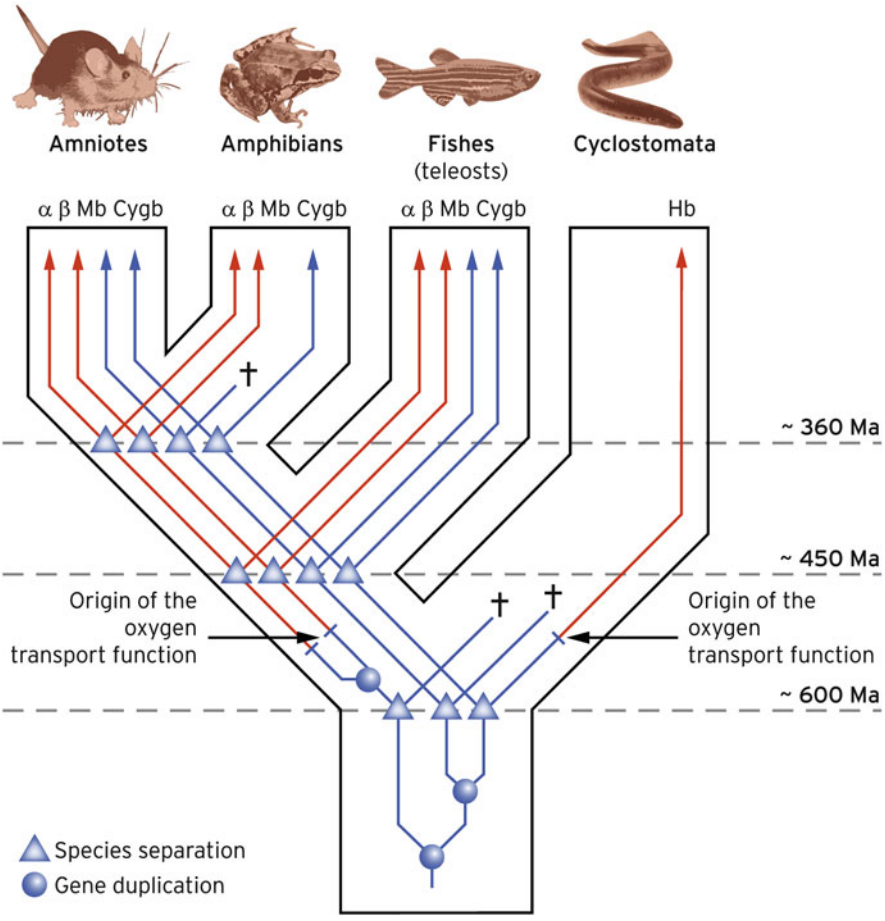

Fig. 3.3 Gene cooption and convergent evolution of oxygen transport hemoglobins in jawed and jawless vertebrates (adapted from [3])

on human evolution and physiology, including human blood volume control mechanisms.

Ever since the very first spaceflights, it is known that micro-g induces pronounced changes in plasma volume, red cell mass, and haemoglobin concentration [4–7]. Studies on the regulation of erythropoietin (EPO) during spaceflight—the

hormone which controls red blood cell production (erythropoiesis) and release from the bone marrow—have only recently shown that fluid shift in micro-g (central hypervolemia) do not only effect the plasma volume but also the cellular (erythrocytes) volume, a process termed neocytolysis [6, 8]. Furthermore, very recent studies at high altitude have shown that this newly discovered mechanism of red cell mass control is not only limited to the micro-g environment but can also occur during plethora under terrestrial conditions [9].

EPO functions and sensors, including some evolutionary aspects, are summarized below to make the complex neocytolysis process comprehensible. Recent studies on EPO regulation under simulated and real micro-g conditions, which have paved the way for a new concept of the control mechanism of the red cell mass in humans, are discussed thereafter.

In adults, the kidneys are the main organ for the production and release of EPO, and enormous efforts were invested during the last decades in the purification, molecular encoding, and description of the EPO gene. Specifically, the hormone stimulates the proliferation, differentiation, and maturation of the erythroid precursors in the bone marrow [10, 11]. Finally, the production of recombinant EPO has led to incredible advances in the understanding of the EPO-feedback-regulation loop at a molecular level, focussing mainly on oxygen-dependent EPO gene expression, a key function in the regulation loop [12]. In a healthy adult, about 120 million erythrocytes are destroyed every minute, mainly in the spleen, liver, and bone marrow [10]. To avoid anemia, a very finely balanced equilibrium between this destruction and the production of new red blood cells has to be ensured. The major humoral factor responsible for maintaining a normal blood erythrocyte count under conditions of constant oxygen availability is the glycoprotein EPO. This hormone is produced in cells located in the renal cortex, probably in the endothelium of peritubular capillaries or interstitial cells such as fibroblasts. Sugar chains on the EPO molecule seem to be important for the life span and structural integrity of the protein component of the molecule. EPO and thrombopoietin are the only hematopoietic growth factors that behave like a hormone: EPO, produced in the kidneys and the liver, interacts with erythroid progenitor cells in the bone marrow to promote their proliferation and maintain their viability. About 500–1000 EPO receptors are present mainly on the surface of purified human erythroid precursor cells, and the production is regulated at the level of its gene mainly by tissue oxygenation [10, 11].

Since hypoxia plays a key role in stimulating EPO production and release, the biochemical mechanisms of oxygen sensing, in general, have been the target of intensive research during the last decades. According to present knowledge, a transcriptional factor, called the hypoxia-inducible factor (HIF), is essential to promoting cellular adaptation to changes in oxygen availability and regulating the hypoxic gene expression [13] (Fig. 3.4). Studies have shown that in oxygenated and iron-repleted cells, the HIF-alpha subunits are rapidly destroyed. This destruction involves ubiquitylation by the von Hippel–Lindau tumor suppressor (pHVL) E3 ligase complex. In contrast, this process is suppressed by hypoxia and iron chelation and a transcriptional activation is induced [13].

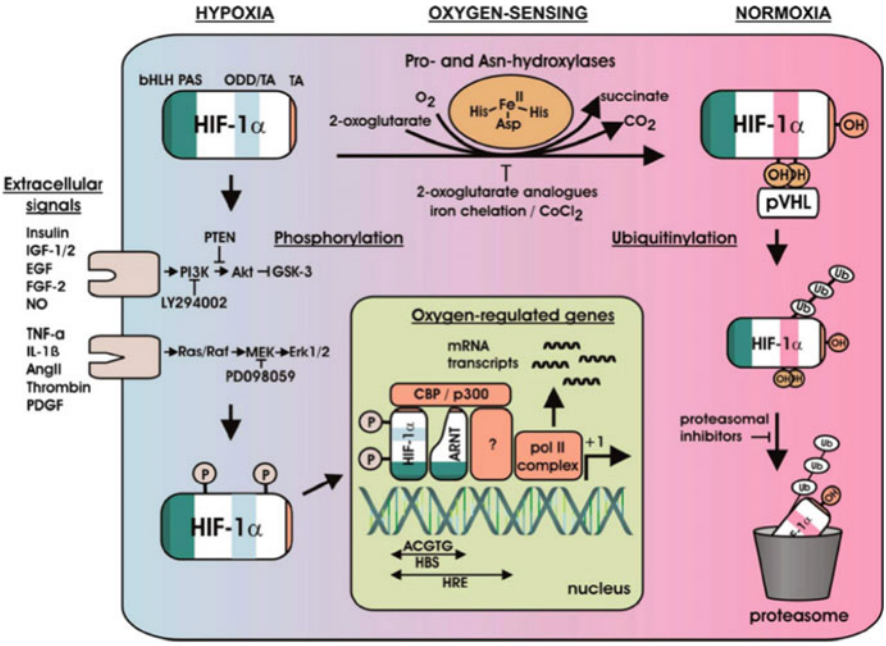

Fig. 3.4 The cellular adaptation to hypoxia according to a scheme given by Wenger [13]

Recently, it could be shown that the interaction between pVHL and a specific domain of the HIF-1alpha subunit is regulated via hydroxylation of a proline residue (HIF-1alpha P564) by an enzyme termed HIF-alpha prolyl-hydroxylase (HIF-PH). This HIF-PH seems to function directly as a cellular oxygen sensor [13, 14]. This regulatory mechanism developed over approximately 450 millions years, when circulatory systems developed to guarantee sufficient oxygen supply to the metabolizing tissues. Accordingly, the most advantageous physiological and biochemical adaptations to acute and acclimating responses (genetic adaptations) prevailed. This evolutionary process is still under way and not yet complete (Fig. 3.5) [15].

To understand and to put the changes observed in space into perspective, we will briefly describe some major studies of EPO regulation under terrestrial conditions and in simulated weightlessness and will then summarize studies on plasma volume, red blood cells, and EPO regulation in space.

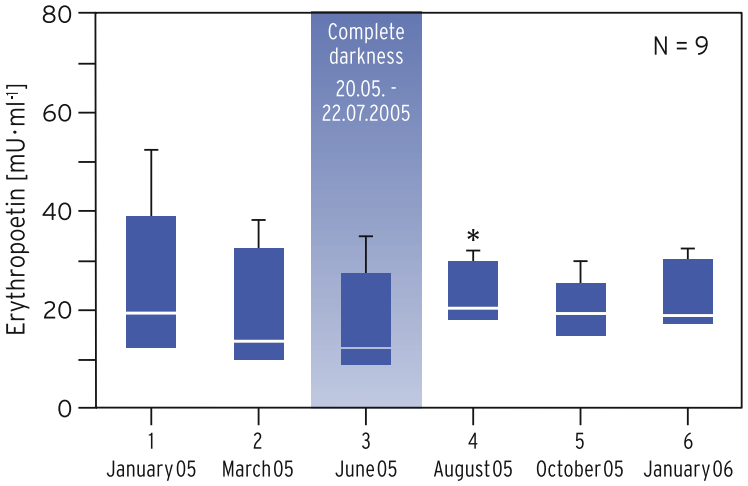

Fig. 3.5 Changes of erythropoietin levels in healthy humans ($N = 9$) during a 1-year stay in Antarctica at sea level (Georg-von-Neumayer-Station, Ekström Shelf Ice, Atka Bay, northeast Weddell Sea, Position: 70°39′S, 08°15′W) (permission by Tiedemann). Values are shown as medians (*horizontal bars inside the box*) with the 25th and 75th percentile (*upper and lower frame of the box*) and the 5th and 95th percentile (*bars*). Outlying mavericks are shown with *circles*. * indicates $p < 0.05$ compared to complete darkness [12]

3.2 Physiological Erythropoietin Regulation under Different Terrestrial Settings

Studies on the circadian rhythm of EPO are still very scanty [12]. So far, these studies show different results. While Cotes and Brozovic [16] and Wide et al. [17, 18] determined pronounced circadian rhythms in EPO, Miller et al. [19] among others observed only minor diurnal variations or even no circadian rhythm at all [20]. Our own results are inline with the latter study [21]. In preparation of a mission to the Mir station, we studied 10 male subjects. These subjects showed only minimal diurnal variations in the overall range (see below Sect. 3.1.1). These different results might be due to the different experimental settings, i.e., ambulatory [18] vs. a strict horizontal bed-rest setting [21]. Currently, this issue on a circadian rhythm of EPO production and release cannot be settled. Long-term studies during isolation and confinement under normobaric–normoxic conditions only show minimal changes (Fig. 3.6) [12, 21]. Further chronobiologic studies on EPO production and release are needed, as it might have an impact on the interpretation of data mentioned below.

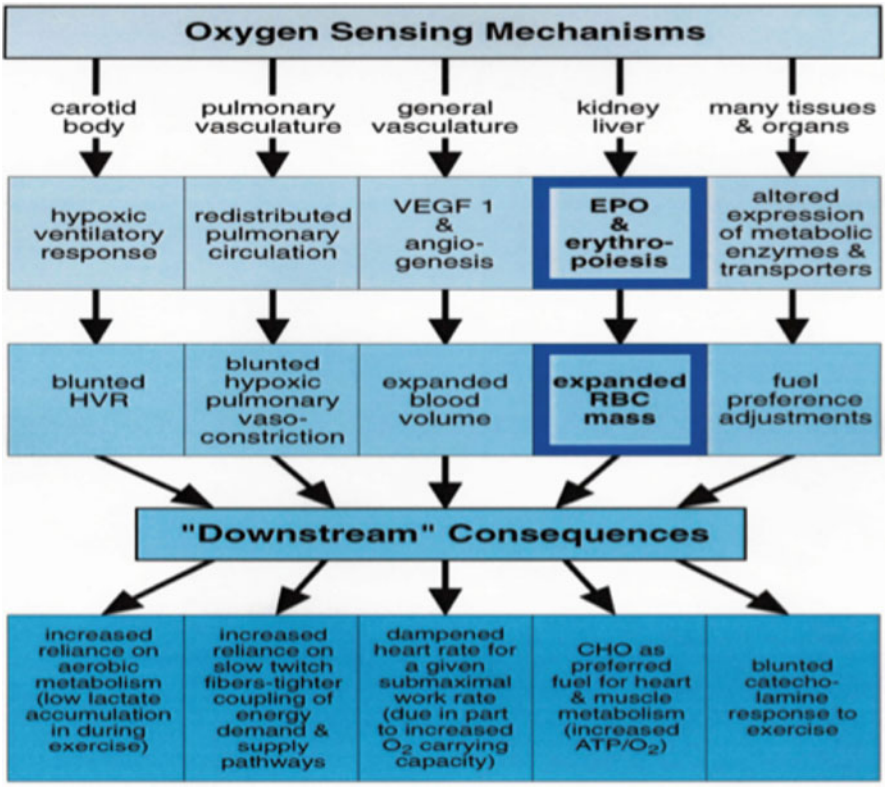

Fig. 3.6 An integrated view of the multiple sensor system throughout the body to monitor oxygen demands of the tissues and adaptations at a cellular and organismic level to increase physical performance (CHO = carbohydrates) [15]

3.3 Short-, Medium-, and Long-term Exercise at Sea Level and Its Impact on Erythropoietin

Next to special muscle fiber types, enzymatic pathways, capillarization, innervation, and the central nervous system, the cardiopulmonary adaptations play a central role in the oxygen transport capacity of the blood. Since the maximal oxygen uptake is mainly related to the cardiac output and arteriovenous oxygen difference (AVD_{O2}), these parameters substantially influence physical performance and mainly depend on total blood volume, in particular erythrocyte volume, hemoglobin affinity for oxygen, and the hemoglobin concentration [Hb].

Several studies have shown that endurance-trained subjects display a very strong correlation between the maximal oxygen uptake and total hemoglobin, but not as close to the [Hb]. An artificial increase in plasma volume has positive effects on exercise at a submaximal level, whereas an increase in the amount of hemoglobin from altitude training, blood-, or EPO doping mainly affects the aerobic capacity.

Therefore, a stimulation of erythropoiesis through exercise at sea level mainly affects the oxygen transport capacities, whereas endurance training improves cardiac output and muscular vascularization, as does blood- or EPO doping [22].

In general, the endurance capacity of the human species relative to the body weight is exceptionally high compared to other mammals. Upright stance (pedal locomotion) leads to an unusual volume distribution [23], and environmental conditions during the early phases of human evolution (increasingly higher and dryer) favored a higher blood volume [15].

In today's textbooks of physiology, the blood volume of a 70-kg man is given as 5 L or 7 % of the body mass. Comparative studies on blood volume in terrestrial quadrupeds have shown that this value is closer to 5 % of the body mass. Recently, Sawka et al. [24] could show that healthy young men have blood volumes (erythrocyte volume, plasma volume) correlating with the lean body mass (LBM, fat-free body mass). They found values of 38–49 mL plasma volume/kg LBM, 24–33 mL erythrocyte volume/kg LBM, and 63–83 mL total blood volume/kg LBM. In females, the values are all in the lower range of mL/kg LBM.

Schmidt [25, 26] compared trained and untrained subjects and found a blood volume of 77 mL/kg, an erythrocyte volume of 30 mL/kg, a plasma volume of 47 mL/kg, and a hematocrit of 45 % of the body mass in untrained subjects. Highly trained endurance sportsmen, in contrast, showed a blood volume of about 107 mL/kg, an erythrocyte volume of 40 mL/kg, a plasma volume of 67 mL/kg, and a hematocrit of about 43 %. The decrease in hematocrit is due to an over-proportional increase in plasma volume in the highly trained subjects. Compared to untrained subjects, the total erythrocyte mass is actually increased by approximately 30 % and the plasma volume by 42 %.

Schwandt et al. [27] observed elevated [EPO] levels 3 h and even 31 h after a marathon race. It is well known that during exercise, a plasma volume decrease of about 20 % can be expected due to fluid shifts from the intravascular to the extravascular compartments because of (1) raised hydrostatic pressures, (2) heightened muscle blood flow (i.e., more filtration surface), (3) increased metabolites in the exercising muscles leading to a rise in the osmotic outward shift from the intravascular towards the intracellular compartments of the muscle cells. Taken together, all this leads to a rapid diminution in blood volume (plasma volume) of about 150–350 mL. Combined with an increased compliance of the venous systems (i.e., increased capacity of the low-pressure system due to the thermal stress from exercise) [28], this leads to a prolonged decrease in central blood volume. As suggested earlier [29], this decrease in central venous pressure might be an adequate stimulus not only for plasma-volume-regulating hormones such as vasopressin (antidiuretic hormone, ADH) [30] but also for EPO production and release from the kidneys. Indeed, studies of dogs could show that solely changes in central venous pressure are involved in modulating EPO production and release from the kidneys [31].

Nevertheless, it is known that two major stimuli for EPO production and release from the kidneys are most important: hypoxia and blood volume loss. When humans are exposed to hypoxia, besides the physiological changes that occur in

the muscular, respiratory, cerebral, cardiovascular, and hormonal systems and in the fluid and electrolyte balance, the oxygen transport capacity is strongly affected. Perhaps this is the reason why the most frequently studied adaptation to high altitude is the increase in red blood cells. As early as 1878, Paul Bert [32] suggested that one of the key adaptations during high altitude adaptation might be a rise in red blood cells and [Hb]. Two factors lead to an increased oxygen transport capacity of the blood to counterbalance the diminished oxygen partial pressure at altitude. In 1890, Viault [33] analyzed the blood samples from high-altitude subjects in South America and found a marked increase in red blood cells. A decade later in 1906, Carnot and Deflandre [34] first postulated that a hormone-like substance might exist, which they named hémopoietine, that stimulates the production of red blood cells, the erythropoiesis.

For a long time, it was thought that altitudes below 3000 m (i.e., ensured saturation of hemoglobin provided a sufficient oxygen supply) would be too low to trigger changes in [EPO]. In a large field study (29 subjects), Gunga et al. [35] studied EPO, thyroid hormones (triiodothyronine, T3; thyroxine, T4), and the thyroid stimulating hormone (TSH) before and several days after an ascent in the Alps from 744 to 2315 m. Surprisingly, a remarkable increases in [EPO] 48 h after the ascent was measured. No significant changes were found in the thyroid hormones, indicating that they, as well as TSH, only play a minor role in the regulation of EPO production and release under mild hypobaric–hypoxic conditions (2315 m). Since then these changes in [EPO] were confirmed by additional studies [36, 37]. Studies at higher altitudes (>3000 m) including hypobaric chambers have been carried out by several groups to form a clear picture of the course and extent of EPO regulation in humans at high altitudes [38].

In addition, short-term exposure also alters EPO production and release as shown in an experimental laboratory study conducted by Eckardt et al. [39]. The undoubted importance of oxygen transport and metabolism for endurance is the reason why altitude training in preparation for competition at sea level has become so popular. But its effect on erythropoiesis and thus the importance for the maximal oxygen uptake are much more complex than had been assumed. This is mainly due to (1) different training modalities/schedules, which are all named "high altitude training," (2) different physiological organ systems in the human body, which react to training at different rates, (3) different magnitudes of change in these various systems, (4) different analytical methodologies, (5) the varying training status of the athletes studied, and last but not least (6) a pure statistical problem due to the low number of subjects.

Appropriate literature is plentiful and we can only mention a negligible subset here. For an extensive review, see Gunga et al. [21]. Wilber [40] summarized the novel approaches and modalities for altitude training, i.e., (1) normobaric hypoxia via nitrogen dilution (hypoxic apartment equivalent to 2000–3000 m; "living high—sleeping high"), (2) supplemental oxygen, (3) hypoxic sleeping devices (simulating altitudes up to 4500 m; "sleeping high—training low"), and (4) intermittent hypoxic exposure. Levine and Stray-Gundersen [41] reviewed this topic and stated that the success of the strategy depends on mainly two key features: (1) living

high enough, for enough hours per day, over a long enough period of time to initiate and sustain an erythropoietic effect of high altitude and (2) training low enough to allow maximal quality of high intensity workouts, requiring high rates of sustained oxidative flux. Such an approach can be achieved using hypoxic apartments. Athletes using these usually live and sleep there for 8–18 h a day, but complete their training at sea level, or at approximate sea-level conditions. Some studies could show that the athletes were thereby able to increase their [EPO], reticulocyte count, and red blood cell mass, leading to improvements in post-altitude endurance, but in other studies researchers failed to demonstrate significant changes in these important hematological parameters [42].

Although the evolutionary strategies of high altitude adaptations are not within the scope of this chapter, we will nonetheless further investigate this topic in respect to hematological adaptations because such observations raise an important question: is EPO expression at altitude of "adaptive" value, or is it only an epiphenomenon associated with hypoxia and altitude exposure? We are convinced that it is not an epiphenomenon; however, there are obvious genetically driven differences between humans in the hematological response to hypobaric–hypoxic exposure. Since altitude adaptation is a multifactorial process and the EPO response and the hematological adaptations are only two parameters in the orchestra of biochemical, physiological, and anatomical potential strategies to improve performance at high altitude adaptations in humans [15] (Fig. 3.5).

However, a specific altitude training effect can only be proven if an equal load (in percent of maximal oxygen uptake) is more effective than during sea-level training. And indeed, a review by Böning [43] shows that only three of 10 investigations with this design significantly improved performance, maximal oxygen uptake, or endurance. When training in hypoxia combined with living in normoxia, two out of four groups improved their performance. Altogether, there is an increasing amount of data which shows that "living high—training low" is more effective than sea-level training alone and that it is important whether subjects are EPO "responders" or "nonresponders." Further studies are necessary to show how these groups can be determined in advance and to help to understand why some individuals react with pronounced EPO production and release whereas others do not. Lastly, future studies should enable and develop strategies for those who could profit from such hypoxic exposures—among them in future astronauts, living for technological constraints under hypobaric–hypoxic conditions in spacecrafts, during extravehicular activities, and/or new habitats in other moons and planets.

3.3.1 Erythropoietin Under Simulated Microgravity Conditions

It is obvious that the most reliable data for increasing our knowledge of physiological adaptations to micro-g and thus of effective countermeasures can be obtained in

space. But, research carried out in space is subject to certain constraints; opportunities are rare; time and energy are limited; standard procedures such as blood drawing and handling samples are more complex than on Earth. Therefore, procedures become time consuming, while the workload of astronauts is high and experimental conditions cannot always be controlled. From the statistical point of view, the amount of data needed to attain appropriate confidence levels requires repeated measurements during several missions. Over the last decade, several terrestrial situations were developed that could simulate micro-g to some extent. The most common space-analogous environments are antiorthostatic horizontal (supine) bed rest, the head-down tilt position (−°6), and wet or dry immersion [44].

3.3.1.1 Bed Rest

Bed rest is the model used most frequently for micro-g simulation. Gunga et al. [21] conducted 24-h bed-rest studies to investigate unresolved question regarding a circadian rhythm of [EPO] and the early adaptation phase of EPO production and release to a micro-g environment. The team then compared these results with those observed during head-down tilt and data from space. Investigations of EPO circadian rhythm are still very scanty and yield conflicting results. Earlier studies found pronounced circadian rhythms in [EPO]. In the Klausen et al. [18] study, for example, the nadir of [EPO] was reached in the morning hours, followed by a 60 % increase to peak concentrations during the late evening and early night. On the other hand, only minimal diurnal variations were observed in ten male subjects by Gunga et al. [21] and in 26 healthy men over a 24-h period in a study by Roberts and Smith [20]. We have to conclude that momentarily the question of whether a pronounced EPO circadian rhythm in humans exists cannot be settled. A preliminary explanation for ambiguous results could be given by the dissimilar test settings. In the Klausen et al. study [18], for example, subjects could move freely during the day, whereas in the Gunga et al. test [21] subjects were restricted to a supine position around the clock. It is reasonable to assume that such differences lead to variable volume distributions in the body and have a decisive impact on the central venous pressure, see below. If we compare these data with findings during real spaceflights (see below), it can be concluded that the short-term bed-rest model (24 h) does not adequately reflect the early changes in EPO production and release observed under real micro-g conditions.

3.3.1.2 Isolation and Confinement

No data were available in the literature on [EPO] alterations in healthy, young humans under long-term isolation and confinement until the EXEMSI‘92 study conducted by the European Space Agency (ESA) ([21]. During 8 weeks of isolation, we found the lowest [EPO] values on the 23rd day ([EPO] Δ −24.2 %) and on the 51st day ([EPO] Δ −25.3 %). The highest [EPO] values were found on the 2nd

and 9th day ([EPO] Δ +4.8 % and Δ +9.5 %, respectively). It is most likely that limited physical activity throughout isolation and confinement, and not the slight hyperbaric pressure (1060 mbar) inside the chambers, led to the reduced [EPO] values [21]. The reduction was not observed until the third week of isolation, whereas experiments under hypoxia have shown that this would induce an immediate EPO suppression [10, 11]. In a one-year isolation in Antarctica, we also found slight changes of the circulating EPO concentrations [12] (Fig. 3.6).

3.3.1.3 Head-Down Tilt (−6°)

Head-down tilt is a simulation model for spaceflights which was introduced by Genin and Kakurin in 1972 [44]. Although prolonged head-down tilt during bed-rest maintains influences of the Earth's gravity and thus cannot be considered equivalent to micro-g effects, this model induces many physiological changes that are similar to those observed in astronauts during spaceflight. Examples include muscle atrophy, bone demineralization, fluid and body mass redistribution, and a decrease in plasma volume and red cell mass. Grigoriev et al. [45] supplied the first data on short- and long-term effects of head-down tilt (−°6) on [EPO] and compared them to results from spaceflight. During a long-term head-down tilt study (42 days), we found [21] that all subjects showed a rapid decrease in [EPO] initially (Fig. 3.7). Lange et al. [46] studied intensively the regulation of hematopoiesis in rats exposed to antiorthostatic, hypokinetic/hypodynamia (suspended rat model) and is mentioned here although results from animal studies and the test setting are slightly different from the head-down tilt test setting for humans. Nonetheless, Dunn et al. [47, 48] made the interesting observation that (1) in both situations the red cell mass was decreased, (2) production of red blood cells was impaired, (3) there was a transient elevation of the hematocrit due to a reduced

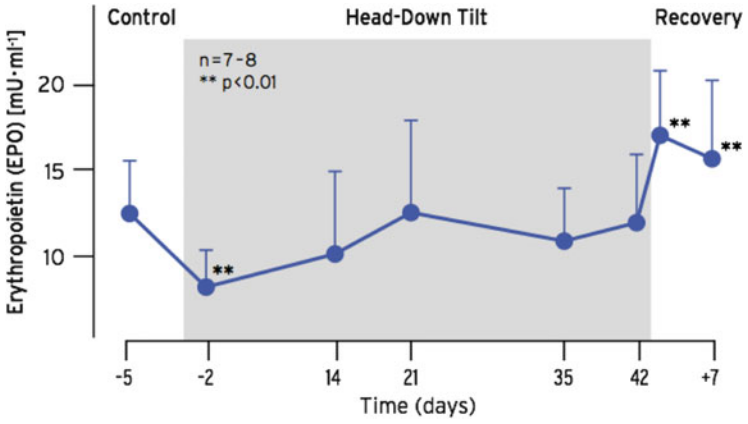

Fig. 3.7 Erythropoietin concentrations during long-term simulated micro-g conditions (head-down tilt (−6°) [21]

plasma volume, and (4) [EPO] were significantly reduced after 24 h of suspension, similar to [EPO] results from human spaceflights. The [EPO] in rats remained diminished during suspension and was then significantly elevated 24 h post-suspension. In this respect, our data support the findings of Lange et al. [46], with the exception of the magnitude of decrease during and the increase post-suspension.

3.4 Erythropoietin in Microgravity

In 2000, the first components of the International Space Station (ISS) were launched, and today several parts of the ISS are in function with three astronauts working there permanently. A central part of future research on board will be dedicated to investigating the effects of microgravity on the human organism. Although the physiological knowledge has grown substantially over the last decades, data concerning hormonal regulation in man under microgravity are still rather scanty, if available at all.

A primary focus of the different research topics during the last decades has been the study of erythropoiesis. The motivation originates in the first space missions, which already indicated a decrease in the number of erythroblastic cells, red cells, and hemoglobin mass in humans and animals [6, 49, 50]. In the review of 39 astronauts in 1981, Cogoli [5] found a reduction in red cell mass of 2−21 % during the initial phase of a spaceflight—approximately 1 % per day. It was assumed that a decreased EPO production in the kidneys as a result of central hypervolemia or relative plethora might be responsible for the reduced red cell mass. Indeed, Leach et al. [49], who first measured EPO during a short-term spaceflight (<10 days), found decreased [EPO]. We could confirm the results some years later (Fig. 3.8) [21]. In an effort to define this phenomenon, Alfrey et al. [6] performed ferrokinetic studies on two shuttle missions. In six astronauts, the red cell production on the second and fourth day inflight was not decreased from that observed preflight. Finally, by using 51Cr labeled erythrocytes, Alfrey et al. [6] was able to show that the young red blood cells were selectively hemolyzed, allowing a rapid adaptation of the erythrocyte volume to a level appropriate for the microgravity environment, a process termed neocytolysis. Red cells older than twelve days had a normal survival rate (Figs. 3.9 and 3.10). Data from mid-term spaceflights showed similar results (<30 days, Fig. 3.11) [51]. Data from long-term missions (>120 days) are still extremely scanty, but their results are of particular interest, since all erythrocytes—which usually have a lifetime of about 100 days—were produced under micro-g conditions. It can then be evaluated, whether the red cells formed in space fulfill their function during the spaceflight and upon return to Earth. Vorob'yev et al. [52] measured red blood cells and hemoglobin concentration in two cosmonauts after a 175-day flight. In one cosmonaut, the team detected only slight changes on the recovery day, but on the 8th day postflight red blood cells and hemoglobin were markedly reduced. Even after 1 month, red blood cell counts and hemoglobin

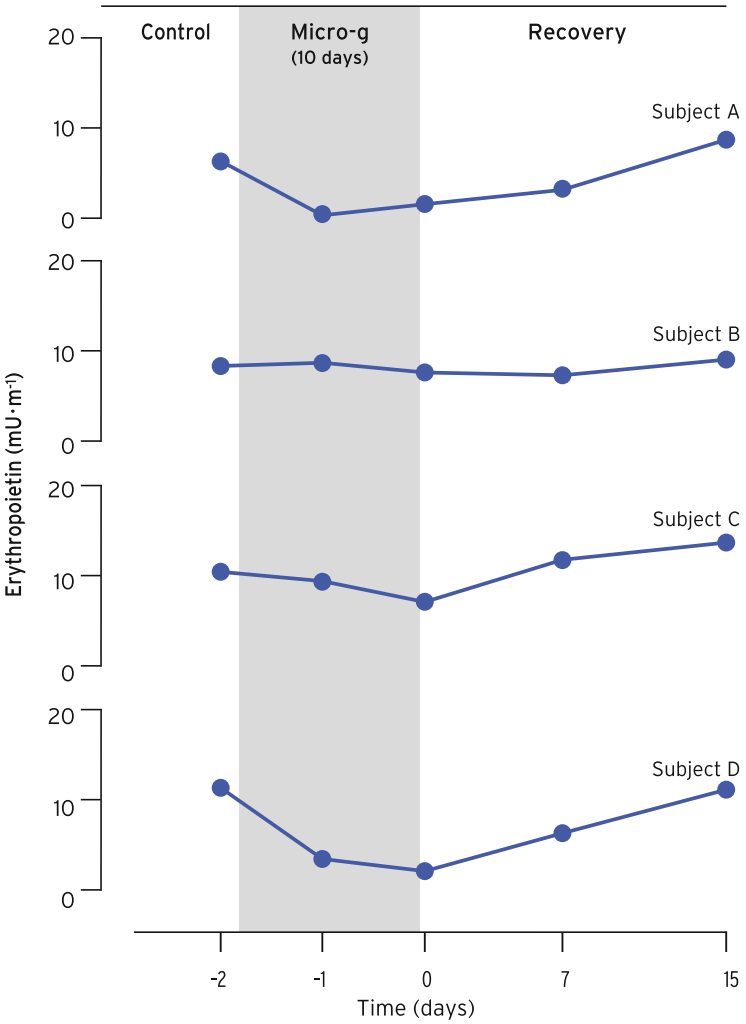

Fig. 3.8 The individual time course of erythropoietin in 4 astronauts before, during, and after a short-term spaceflight (<10 days, Shuttle Flight STS-55, GERMAN D-2 MISSION) [21]

concentrations had not surpassed the control level. Grigoriev et al. were able to get a bone marrow puncture from one cosmonaut, who had been in space for 8 months, 7 h after landing. They found a marked decrease in myelokaryocytes, which suggested inhibition of hemopoiesis. After different Russian space missions lasting from 96 to 185 days, researchers concluded that the hematological parameters recovered within about 1.5 months postflight.

Recognizing that an excess of red cells and a fall in erythropoietin sparks a rapid decrease in young red cells led researchers to study long-term residence at high altitudes with erythrocytosis. The red cell mass decreases rapidly at a rate similar to

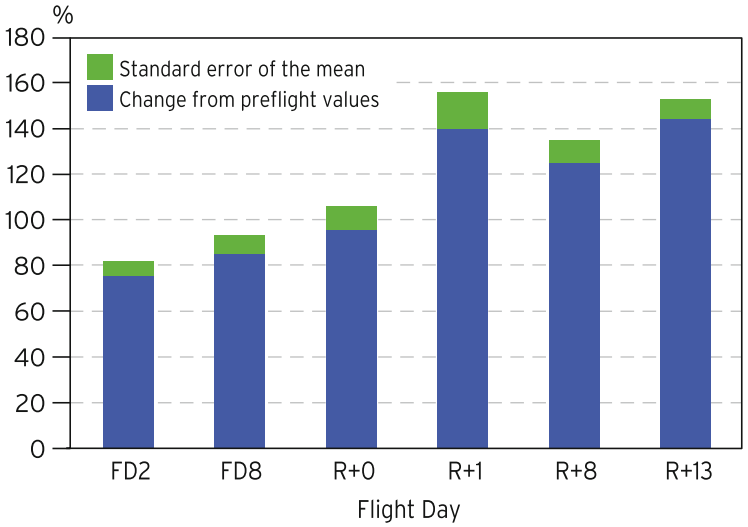

Fig. 3.9 Erythropoietin concentration during and post-shuttle flights adapted from Alfrey et al. [6]

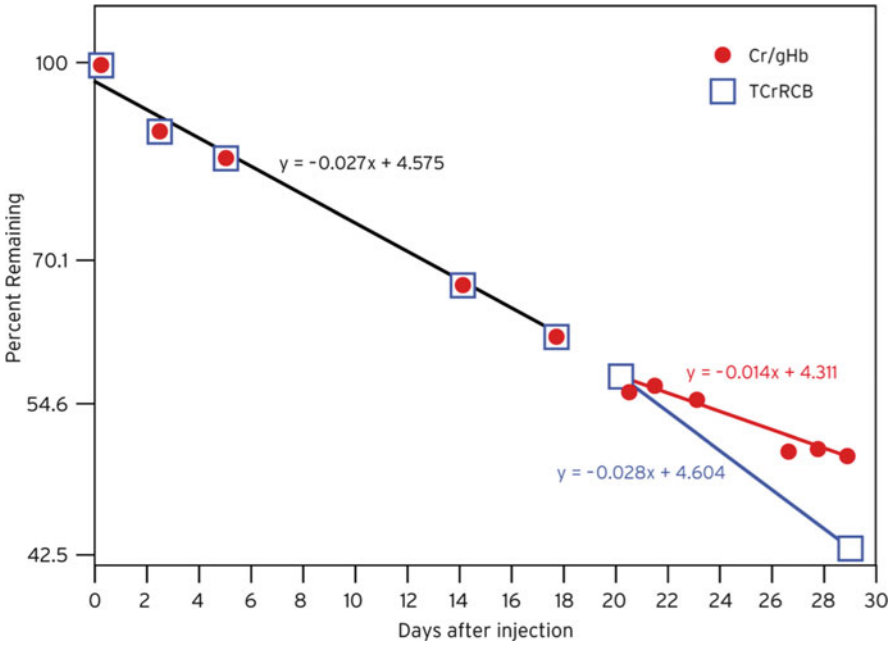

Fig. 3.10 Erythropoietic activity before, during, and after spaceflight adapted from Alfrey et al. [6]

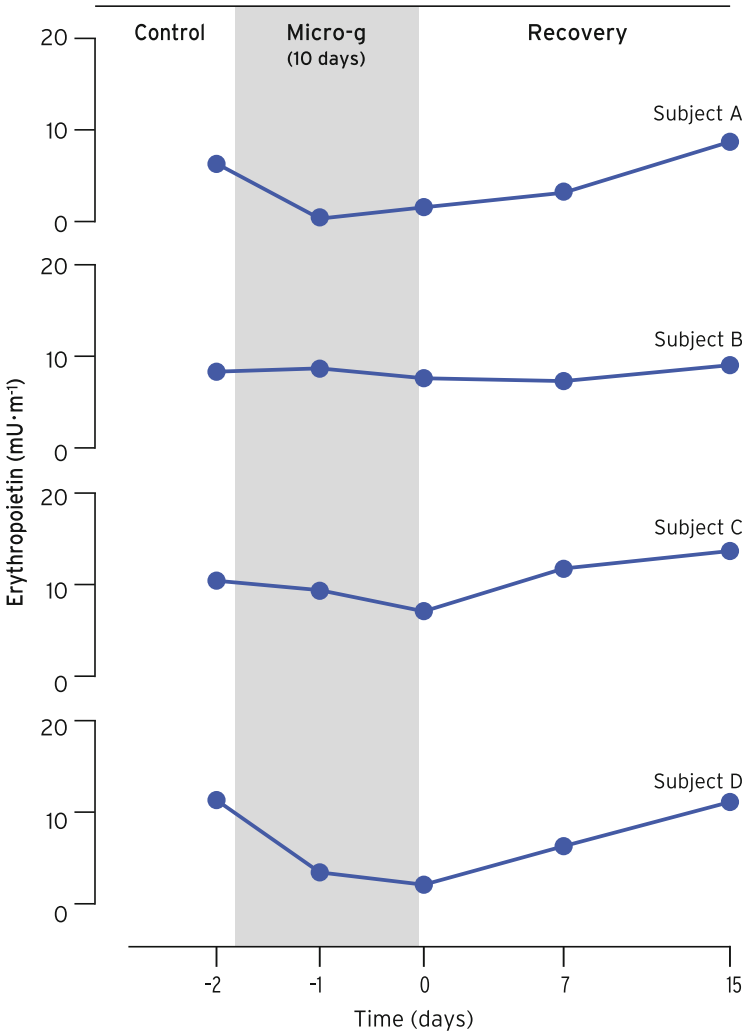

Fig. 3.11 The time course of erythropoietin and transferrin receptors before, during, and after a mid-term spaceflight (21 days, GERMAN MIR'97 MISSION) [51])

that observed in astronauts entering micro-g, and this decrease is blocked by small doses of erythropoietin. Guided by results from space and altitude [8], Trial et al. studied the effects of EPO withdrawal in vitro (similar to shifts from high altitude to sea level—acute plethora and a concomitant decrease in EPO) and again observed a selective hemolysis of young red blood cells [50]. On the basis of these studies, it seems likely that a decrease in [EPO] below a certain threshold initiates neocytolysis by influencing surface-adhesion molecules.

In regard to EPO downregulating erythropoiesis in spaceflight, the diminution in efflux of red cells from the bone marrow requires 1 week. However, anemia manifested by a decrease in hemoglobin or hematocrit concentration does not occur in spaceflight. This is because the decrease in erythropoietin and red cells is preceded by a decrease in plasma volume of up to 25 % in the first 24 h and remains decreased during flight. A decrease in hemoglobin concentration occurs in the first 24 h after returning to Earth as the plasma volume rapidly increases to a vascular volume optimal for the 1-g environment. The resulting anemia is associated with a striking increase in erythropoietin and increase in erythropoiesis.

In conclusion, terrestrial space analogues such as head-down tilt and isolation and confinement studies are very helpful for the preparation, handling, and interpretation of data from research under real micro-g conditions. It can be said that head-down tilt studies in humans and animals to a large extent seem to reflect the changes in EPO and erythropoiesis under micro-g conditions. Isolation and confinement per se contribute to a considerable extent of the diminished [EPO] found in astronauts. Furthermore, EPO seems to be mainly involved in a process called neocytolysis, a newly discovered red cell mass control mechanism, first observed in astronauts and now described in long-term high-altitude dwellers shifting to sea level, as well.

The picture of human physiology in space is not yet complete, so that continuing research in EPO regulation under different physical and environmental conditions is not only essential to ensuring successful missions, but can also be applied to for a general understanding of the relevant factors in blood volume control. In rats, changes in blood volume were much more pronounced than in humans during and after head-down tilt. This is probably due to the fact that the rats being subjected to a larger head-down angle ($-20°$) inducing a rapid temporary increase in central venous pressure. Additionally, it is unlikely that rats have developed the capacity to modulate gravitational changes as well as humans.

Theoretically, intrathoracic central venous pressure receptors [30] could trigger mechanisms which stimulate or suppress EPO production and release in the kidneys via the autonomous nervous system in a similar manner to the control of the antidiuretic hormone (vasopressin). The activation of these receptors depends on the size of the central blood volume and on the vascular compliance. Accordingly, changes in central venous pressures should be inversely related to [EPO] in the blood, i.e., a low central volume should lead to increased [EPO] production and release and vice versa. Since EPO gene expression is unaltered after renal denervation [10], we postulate that next to a nerval component (most likely: intrathoracic low-pressure system receptors transmit signals via the vagus nerve towards the central nervous system), there must be a humoral component acting from the central nervous system (probably hypophysis) on the kidneys.

A former study in dogs has shown that changes in central venous pressure modulate EPO production and release [31]. Therefore, as suggested earlier [29], changes in the central venous pressure might act as a stimulus not only for plasma-volume-regulating hormones such as vasopressin (antidiuretic hormone, [30]) but also for EPO production and release from the kidneys. Accordingly, we propose the following tentative EPO regulatory loop, which includes, besides the well-known

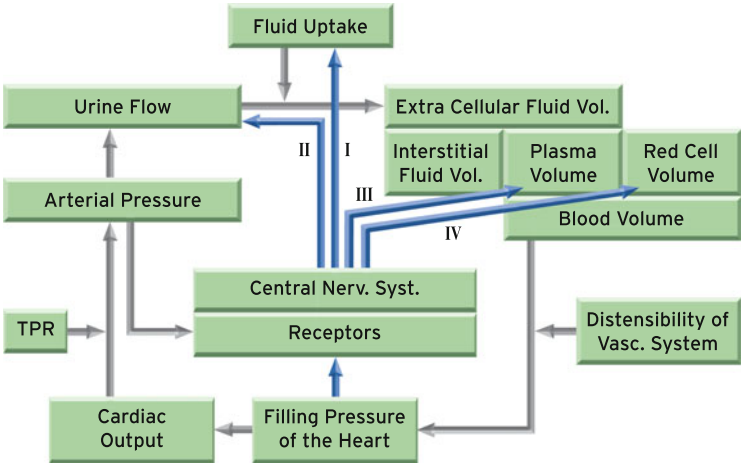

Fig. 3.12 Summary of the proposed regulatory pathways of the central nervous system in total blood volume control: (I) thirst control, (II) urine output, (III) extracellular volume (interstitial and plasma volume), (IV) red cell volume (*TPR*, total peripheral resistance) (modified from [30, 53])

stimuli of EPO production and release, the changes in central venous pressure (Fig. 3.12). The central venous pressure serves as an indicator of the vessel filling and hence the stretching of the walls. Earlier concepts of blood volume regulation in the GAUER–HENRY hypothesis [30] were confined to mechanisms controlling the extracellular fluid volume (pathways I−III) [53].

The fact that the volume of the red cell mass must be integrated to explaining regulatory mechanisms has become an integrative part of the blood volume control mechanisms (pathway IV). In which way this fourth pathway is able to moderate EPO production and release must be investigated further. Such a pathway of EPO modulation would also explain the rapid decrease in EPO production and release after blood transfusions, in which [EPO] was found to be depressed by 62 % one day after the transfusion or the rapidly depressed [EPO] in the -6° head-down tilt position.

3.5 Conclusion

The understanding of EPO regulation at a molecular level has increased substantially over the last decades. But at an organismic/integrated scale, it is still incomplete. Nevertheless, it seems currently clear that the "astronaut's anemia" is mainly due to a lack of erythropoietin production and release under micro-g conditions, which leads to a suppressed erythropoetic activity in the bone marrow, as well as to a process of active destruction of circulating red blood cells in space, i.e., neocytolysis. The altered EPO production and release seems to be induced via a central hypervolemia caused by a fluid shift in micro-g conditions, the same phenomenon that has been discussed in more detail in the previous chapter.

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Chapter 4
Respiration and Respiratory Control

Abstract The lung is directly affected by weightlessness: the disappearance of weight forces on the lung tissue itself and surrounding tissues, and hydrostatic pressure gradient changes lung shape and the distribution of gas-filled space. However, inhomogeneous ventilation and aeration of alveolar volumes can also be detected in weightlessness. In the transient phase immediately after the onset of weightlessness, the lung as an interface between the environment and the cardiovascular system also compensates for temporary misbalances between right and left cardiac stroke volume. Long-term effects directly associated with weightlessness can also be attributed to deconditioning of respiratory muscles.

Effects of other environmental conditions and astronauts' activities may mask the effects of weightlessness. For example, exercise training as countermeasure will also stabilize or improve lung function.

Keywords Weightlessness • Microgravity • Space • Lung • Fluid shift • Physiology • Terrestrial simulation

To study the acute and long-term effects of weightlessness on lung function accurately, subjects must be exposed to a real weightlessness environment. In experimental analogues like bed rest or immersion, lung structure and perfusion are still influenced by gravity. In these analogues, muscle activity has to work against gravity to a certain degree. Hydrostatic and transmural pressure gradients are still present unlike in weightlessness. However, results from analogue studies may allow separating those effects which are not related to weightlessness from others, such as immobilization or increased CO_2 concentrations in the environment which are also present during spaceflight. Most of the comparisons of gravity versus weightlessness refer to upright position in gravity. Obviously, this is the most critical situation with regard to changes in hydrostatic pressure but is also the natural position of individuals in gravity.

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4.1 Short-Term Weightlessness—Results from Parabolic Flight Experiments

From the beginning of spaceflight, no severe problems for lung functions were expected from weightlessness [1]. Short periods of microgravity can be received from trampolining, and the development of military diving aircrafts introduced this phenomenon to aviation physiology [2]. Figure 4.1 illustrates the difference with regard to forces affecting the lungs in gravity and weightlessness in relaxed position: weight of the lungs and the abdominal region, hydrostatic pressure, and elastic forces of the chest and the lung tissue itself.

In weightlessness, all downward directed weight forces disappear. The lung size depends on the balance of elastic forces only. Some extrapolations from investigations of hyper-g exposures in centrifuge experiments but also the knowledge from experiments in different body positions allowed some conclusions for physiological reactions in weightlessness with regard to these forces. As outlined below, this extrapolation is not valid for gas flow into the lungs [3].

Since the lungs are highly perfused, the acute changes in hydrostatic pressure in gravity lead to a transient imbalance of blood in- and outflow to/from the lungs and their different sections, respectively. According to the 3-zone model introduced by West et al. [4], the pressure gradients between the alveolar space and the surrounding capillary network are determinants for the perfusion (Fig. 4.2). Compared to upright standing in gravity, the perfusion of the different zones should become homogenous in weightlessness. Transients after the onset of weightlessness and the new equilibrium of blood and fluid filling of the lungs are directly linked to heart activity.

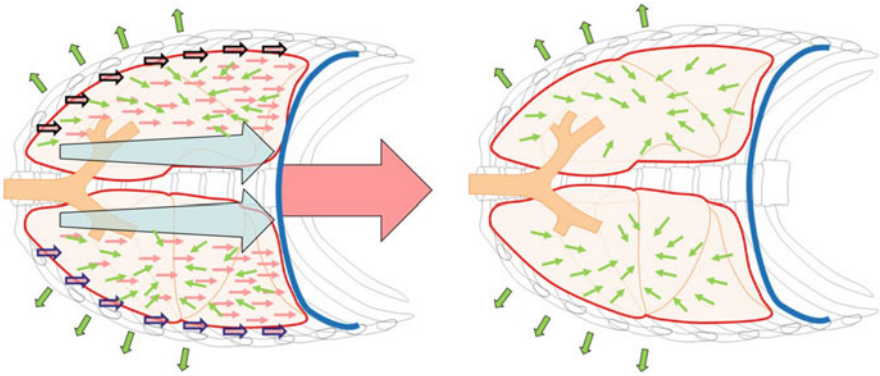

Fig. 4.1 Comparison of forces in gravity in upright position (*left panel*) and weightlessness (*right panel*). *Red arrows*: Gravity forces on lung tissue, chest wall, and abdominal region. Due to higher density, the weight forces in lung tissue are higher in the lower part. *Blue arrows*: hydrostatic pressure. *Green arrows*: elastic forces of the chest wall and lung tissue. Note that under 1 g conditions the lung is only subject to elastic 'forces'

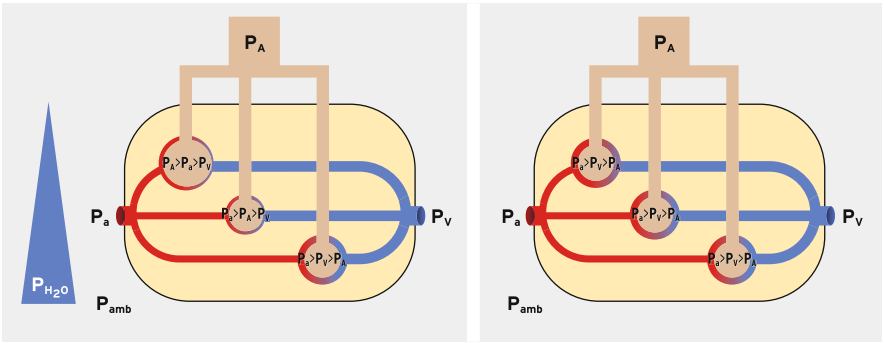

Fig. 4.2 Schematic overview on lung perfusion (*upper, middle, lower parts*) in gravity in upright position (*left panel*) and weightlessness (*right panel*). Due to the increase of hydrostatic pressure in gravity, alveolar gas filling is higher in upper lung sections. In weightlessness, alveolar filling can be assumed homogeneous. Pressure in lung tissue (*light blue area*) is also affected by elastic forces and gravity forces (mod. according to [4])

Figure 4.2 only represents the relaxed position, disregarding pressure oscillations at the arterial side and in the alveolar space. These pressure changes superimpose the pressures of pulmonary arterial (P_a) and venous (P_v) pressure as well as alveolar pressure (P_A). Therefore, the indicated ratios in Fig. 4.2 can be changed by heart rate and breathing frequency. In addition, voluntary breathing maneuvers can be regarded as a further disturbance.

Clearly, the onset of weightlessness alone initiates complex adaptations, which are not easy to predict and are also closely related to adaptations in the cardiovascular system. Acute volume shifts with onset of weightlessness increase right heart stroke volume and temporarily the P_a. In addition, the hydrostatic pressure completely disappears.

The transient effects of weightlessness in the first 20–25 s have been systematically studied in parabolic flight experiments as described in Sect. 2.1.3. This flight maneuver can be summarized as a sequence of 1 g–2 g–0 g–2 g–1 g. In upright position, it can be expected that the gravity changes should affect lung shape and, by acute blood and fluid shifts, functional residual capacity (FRC) during normal breathing. In fact, Michels et al. [5] showed the expected shortening of the lungs in vertical and widening in horizontal directions. This is in line with the Slinky model [6] that has been mentioned in Sect. 1.3.1. Weightlessness immediately results in a homogenous alveolar gas filling (see Fig. 4.2 right panel), which can also be visualized by absolute Electrical Impedance Tomography—EIT [7]. The FRC reduction was confirmed by several studies [8–10]. Controversial results have been reported for vital capacity (VC): While Michels et al. [5] found no systematic changes, Paiva et al. [10] measured in average a decrease for their subjects, Guy et al. [11] reported decreased forced vital capacities in most of their nine subjects,

and Frerichs et al. [12] concluded no change measured by functional Electrical Impedance Tomography.

A detailed volumetric analysis of the thoracic and abdominal cavities showed reduced volumes with regard to the abdominal part [9, 10]. Edyvean et al. [9] who also measured the esophageal pressure in two subjects during parabolic flight demonstrated that this loss of hydrostatic pressure and the cessation of ribcage weight could explain the acute effects on FRC and VC. Most effective should be the absence of the abdominal weight and therefore that of hydrostatic gradients from the abdominal region on the diaphragm must be especially considered in this context.

Fast gas analysis and the application of trigger gases with different densities like argon, helium, and sulfur hexafluoride allow to study the effects of weightlessness on ventilation and alveolar aeration. Single and multiple breath wash-out or multiple breath wash-in maneuvers are appropriate experimental methods to investigate the acute weightlessness effects [13]. In gravity, typical oscillations of gas concentrations can be detected during a prolonged slow expiration. This results from pulsatile cardiac activities. This effect is obviously significantly dampened in acute weightlessness but still present [14]. This and concentration tracings close to residual volume indicate some inconsistencies with regard to homogenous alveolar aeration. The presence of other forces affecting gas distribution in the alveolar space can explain these phenomena. This strongly indicates that extrapolations from hypergravity to weightlessness may be critical [3].

However, the short period of weightlessness in parabolic flight interferes with cardiovascular regulations in response to the preceding sequence of gravity changes. This makes it difficult to identify pure weightlessness effects. Significant results to understand the transient after the onset of weightlessness on lung structures can be obtained. Moreover, the effects of acute blood shifts in cranial direction including cardiovascular regulations can be studied. Further adaptations (beyond 20 s) of fluid shifts and blood volume regulations require longer periods of weightlessness than those possible in parabolic flights. Therefore, the following factors dominate lung function research in spaceflight: role of elastic components of chest and lung tissue as well as blood flow and fluid balance in the lung tissue.

4.2 Results from Spaceflight Before Spacelab and MIR Era

During the era before the Spacelab and Russian's MIR missions, only few data have been reported from inflight situations, although respiratory activity had been measured in the context of health monitoring from the beginning of spaceflight [15]. Comparisons of pre-, in-, and postflight data showed no evidence for pulmonary problems also in Skylab-2/-3 missions [16]. However, indications of potential changes in cardiac function after spaceflight led to a sophisticated instrumentation to monitor gas exchange including a mass spectrometer for gas analysis flown on the Skylab-4 mission. This allowed first detailed respiratory measurements to monitor cardiac function and gas exchange in Space.

For all missions in the 1960s to 1970s, the cabin atmosphere significantly differed from normal atmosphere. Typically, these early missions were performed under hypobaric, normoxic conditions. Little is documented concerning CO_2 concentrations and cabin temperature which might also influence respiratory adaptations.

Sawin et al. [16] reported a decrease in VC of about 10 % from measurements taken during the Skylab 2–4 missions. The reactions in the respiratory system might be the result of the special environment onboard Skylab and should not be discussed here in further detail. However, no significant changes of respiratory parameters were reported from other missions.

4.3 Results from Space Flight in Spacelab, MIR, and ISS Missions

Systematic respiratory physiology experiments started with Spacelab missions, which offered a unique research environment. As part of the Spacelab Life Science missions SLS-1 and SLS-2 (1991, 1993) and the German D-2 mission (1993), numerous experiments were performed focusing on respiratory physiology. These missions allowed in-orbit sojourns of up to 14 days. In this period, extended experiments were also performed on board the Russian MIR Space station. The MIR missions additionally allowed monitoring longer periods in Space but were restricted to a lower number of subjects (e.g., [17]). With the activation of the International Space Station (ISS), further experimental opportunities were offered. Obviously, the design of experimental instrumentation and procedures benefits from the experiences from the Space Shuttle and MIR missions. However, the effects of longer mission duration on lung function may also result from adaptations to generally low physical activity. If physical training as a countermeasure fails to stabilize physical fitness, some of the changes in lung function could simply regarded as a detraining (deconditioning) effect.

As results of the experiments in the mentioned missions in 1990s, Guy et al. [18] and Verbanck et al. [19] confirmed the gravity-independent inhomogeneity of ventilation and airway closure. Prisk [3] attributed this to the elasticity of the lung structure. Furthermore, it has been shown that a VC reduction found in parabolic flights is only a temporary effect [20] at least after a first acute adaptation. During further adaptation of blood and fluid volumes, obviously the effect of the displacement of abdominal volumes is compensated nonetheless with regard to these static parameters. However, some controversial data can be found in the literature regarding VC changes in long-duration missions. Prisk et al. [21] reported only small VC decreases, while from MIR missions [22, 23] and earlier missions [16] significant VC decreases had been reported. This seems to be a typical example inherent to the field-like research situation during Space missions: Influences from environmental conditions (e.g., ambient pressure, O_2 partial pressure) and the

efficiency of physical training during the mission must be regarded as potentially confounding factors influencing some results. Therefore, the results from Prisk et al. [21] refer to data from high quality standardization of environmental conditions and an optimized physical training.

In contrast to the recovering VC, the effect on FRC at rest remains constant during the exposure to weightlessness. Obviously, the absence of abdominal weight is not compensated and has a permanent effect, simply associated with gravity.

The question about consequences of the fluid shift in cranial direction on diffusion characteristics requires weightlessness for some hours or days. Short periods of weightlessness like in parabolic flight mainly allow investigating the blood shift effects, while extravasal fluids require longer periods of mobilization due to diffusion mechanism, which is only possible in spaceflights. The instrumentation available in the missions mentioned above allowed this kind of sophisticated investigation. Several experiments were dedicated to study diffusion capacity and related indicators such as pulmonary tissue volume (V_{ti}) (e.g., [24, 25]). Carbon monoxide (CO) with high affinity to hemoglobin allows to calculate cardiac output (Q') as well as CO diffusing capacity. The observed improvement of CO diffusing capacity in the first days of Space missions obviously stabilized for following mission days. This indicates the absence of problems from fluid shift.

With the cessation of gravity, the subject only has to work against the elastic component of lungs and chest for inspiration. As already mentioned, abdominal contribution to tidal volume at rest is increased [10]. It can be concluded that at least muscles involved in inspiration should show signs of detraining after long-duration weightlessness. In fact, Tikhonov et al. [26] reported decreases of peak flow at forced inspiration and expiration after Space missions lasting 113–366 days. The changes were found in a similar range as after a 370 days bed-rest period. However, Prisk et al. [21] reported no degradation of forced respiratory flows over the stay on the ISS with a period of 130–196 days. As already mentioned, a comprehensive physical training is applied during the stay on ISS, which is subject to permanent optimization. This training aims to avoid deconditioning of the cardiovascular system, muscles, and bones. However, this training also affects the respiratory system. Strenuous breathing maneuvers during weight training as well as high ventilation in response to exercise should also exert some training effect for respiratory muscles.

No direct effects can be expected for respiratory control. However, Prisk et al. [24] reported a reduced tidal volume which was not completely compensated by breathing frequency. The decrease in tidal volume was confirmed by data from ISS missions [21], although the increase in breathing frequency was not established. In parallel, slight increases in end-tidal CO_2 partial pressure were found. It remains an open question whether or not this also leads to an increased arterial CO_2 level. In this context, some adaptations are discussed with regard to slightly elevated CO_2 concentrations during the missions [27, 28]. Such temporary and local elevations inside Space Shuttle, in MIR, as well as in ISS seem to be uncritical with regard to physiological adaptations.

Further effects on respiratory control may also be related to potential changes in aerobic exercise capacity [27, 29].

4.4 Immersion and Bed Rest Studies Do Not Mimic µg Effects on the Respiratory System

Head-out immersion is traditionally regarded as an analogue to weightlessness. This might be true for some aspects concerning the cardiovascular system and the resulting fluid regulations [30]. However, the hydrostatic pressure gradient is still effective in the alveolar membrane, since the intrapulmonary pressure oscillates around the surface pressure. Therefore, this analogue is not qualified to study the effects of weightlessness at the lungs. As illustrated in Fig. 4.2, the P_A is given by the pressure at the surface, while ambient pressure Pamb varies with depth of immersion.

Bed-rest studies to simulate weightlessness are typically performed in a 6 degree head-down tilt (−6° HDT) position (see also Chap. 2). Even in this position, a hydrostatic pressure gradient is effective. However, [31] found decreased diffusion capacities after 120 d −6° HDT in contradiction to the results from weightlessness. This indicates a heterogenic lung perfusion due to the effective gravity. Results from such bed rest studies are only qualified to understand the consequences of immobilization in gravity on lung function.

These results from bed rest and immersion experiments as analogues cannot represent and reflect exactly the real field conditions. Therefore, the results could be used to find new criteria for the interpretation of data investigated in weightlessness, but could not be used as a one-to-one transfer for individuals in Space.

4.5 Conclusions

Although gravity has a significant influence on lung function, the compensation mechanisms seem to be effective in a way that gas exchange is not significantly impaired. A major problem for long-duration flight can be considered the lowered chronic metabolic demands for respiratory muscles. This problem, however, can easily be overcome by physical training in general but also by specific training of respiratory muscles and specific gymnastic exercises.

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Chapter 5
Countermeasures

Abstract The changes and adaptations to microgravity and its implications for the return to Earth have not yet been fully understood. Hence, the development of countermeasures is important, but have only been partly successful in reducing, for example, orthostatic intolerance experienced by returning astronauts, especially after long-duration flights. This chapter concludes the adaptation of the cardiovascular system to weightlessness by presenting a range of countermeasures that are currently used, in development for implementation and have been proposed for the future. These countermeasures are divided into those that require active engagement of the subject—i.e., exercise—and passive techniques, such as lower body negative pressure and penguin suits . Furthermore, a brief outlook on future developments and possible applications of knowledge gained from space experiments to terrestrial situational such as clinical applications is given in this chapter.

Keywords Weightlessness • Microgravity • Spaceflight • Cardiovascular system • Physiology • Simulation • Countermeasures

5.1 Exercise Pre-, During-, and Post-mission

Physical exercise is one of the most obvious countermeasures to prevent orthostatic instability upon return, due to its positive cardiovascular implications. Among these are increased exercise capacity, better regulation of the autonomic nervous system, and higher endurance. Future astronauts follow an exercise program on Earth to maintain their fitness level and prepare for injection to space. The preflight exercise schedule includes two or three weekly sessions of aerobic activity and weight training. The space environment per se is not physically challenging to astronauts; however, a high fitness level can be beneficial during liftoff, possible emergency evacuation, and extravehicular activity. Furthermore, regular exercise is a preventive measure against cardiovascular events—one of the most significant effects that can occur during launch. Nonetheless, the most important physical exercise sessions follow during space flight.

Physical exercise is a major component of an astronaut's routine during flight. The crew of the ISS spends between 2 and 3 h per day exercising. Setting aside such

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a substantial amount interval from the scarce working time of the astronauts shows the necessity of employing countermeasures to micro-g-induced deconditioning. Onboard, the ISS astronauts have a range of equipment for exercise. A detached treadmill, to which the astronaut is harnessed, floats about within the station. The option to use an ergometer and a restitive exercise device aims to prevent muscle atrophy during their disuse in weightlessness. Primarily, onboard exercise aims to maintain strain on the muscular and skeletal system. However, the cardiovascular system also benefits from these daily sessions [1]. Through exercise, subjects train their heart, as well as causing an increased blood flow to the muscles in use, for example, the legs. This way the cardiovascular system circulates blood to the lower extremities—the part of the body that is neglected in space, but essential on Earth. Acute maximal exercise in flight has been proven to decrease orthostatic intolerance upon return [2, 3], as well as restoring blood volume [4] and baroreflex function [5]. Physical activity in flight is applied as a countermeasure against several microgravity-induced disturbances such as muscle impairment but also has positive effects on the cardiovascular system and can aid to reduce orthostatic instability upon return.

Walking and running against artificial gravity in space with the help of the treadmill trains the kind movement that will seem unfamiliar upon return to Earth and is increasingly used close to return. Despite heavy in-flight exercise routines mitigating negative effects and deconditioning, currently they cannot negate them. Thus, physical rehabilitation and training continues postflight. Once safely landed on Earth, astronauts begin rehabilitation exercise at much lower intensities to bring their antigravity function back to par. Recovery of the initial orthostatic stability in 1-G does not take a long time, suggesting the adaptive nature of changes in microgravity.

5.2 Passive Countermeasures

5.2.1 Lower Body Negative Pressure

Lower body negative pressure (LBNP) creates hydrostatic load bearing of the lower body. The setup of such a system is such that the lower half of the body is fitted inside an airtight tube-like box, in which negative pressure is achieved with the help of a vacuum pump; see Fig. 5.1. Negative pressure around tissues induces a shift of blood to the lower periphery and hence creates a fluid redistribution as if on Earth. This provides orthostatic challenge to the cardiovascular system, and the venous return can be modulated by varying the level of vacuum. The large advantage of this device is that it can do so independent of gravity.

During terrestrial experiments, the effectiveness of using daily LBNP sessions to counteract orthostatic instability following cardiovascular disuse (such as during bed-rest) was tested. Furthermore, the effect of LBNP during the short phase of

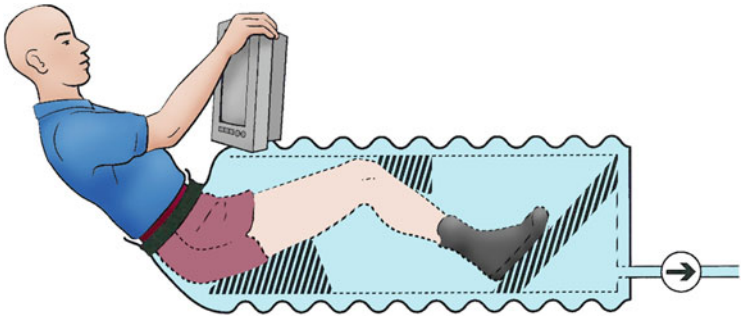

Fig. 5.1 Lower body negative pressure: the setup is such that the lower body is fitted inside an airtight tube-like box, in which negative pressure is achieved with the help of a vacuum pump

microgravity has been tested during parabolic flights. However, in both instances, LBNP has failed to counteract subsequent orthostatic instability [6, 7], as the duration and frequency of LBNP required to make it efficient countermeasure is not operationally feasible.

A more sophisticated approach that is of exceptional interest are those methods, which combine LBNP with exercise modules such as a treadmill. Exercising within LBNP is a desirable concept as induced blood pressures in combination with weight bearing generate simulated gravity conditions [8]. The ideal case would be to be able to perform Earth-like exercise sessions in space, to prevent cardiovascular deconditioning from causing problems upon return.

5.2.2 Gravity Suits

Gravity suits refer to devices that can be worn by subjects to influence fluid distribution in the body and artificially induce gravity-like strain. Examples are compression garments such as thigh compression cuffs called Braslets that are used by Russian cosmonauts. These aim to limit the fluid shift induced by space flight. However, a trial during a 6 month Mir mission showed that the cuffs compensated only partially for the cardiovascular changes in microgravity, but were unsuccessful in interfering with deconditioning [9]. A modified version of the Braslet is tested by ISS crew members to show that the cuff is effective in keeping more blood in the legs and diminishing headward fluid shifts.

Another Russian initiative to develop a wearable device to implement gravitational-like strain is the Penguin suit, also known as the Adeli suit. The original anti-zero-G suit tested in 1975 looked like a standard blue in-flight suit, but had additional elastic band and pulleys that created a force against which the body need to work; see Fig. 5.2.

Researchers have been attempting to develop new skin suits made of lightweight elastic material to better mimic gravity and that are more comfortable to wear. It

Fig. 5.2 Penguin suit: the anti-zero-G suit looks like standard Russian in-flight suit, but had additional elastic band and pulleys that created a force against which the body need to work

applies pressure around the abdomen and lower extremities in a way that gravity would. Developing a piece of wearable equipment counteracting adaptations to micro-g and thereby limiting issues upon return would be a major achievement for space flight. In that case, the need for in-flight exercise would decrease and astronauts could dedicate more time to other important tasks such as in-flight experiments.

5.2.3 Fluid Loading and Pharmaceuticals

An obvious approach to counteract the problems cause by hypovolemia is to increase the blood volume before returning to Earth. This can be achieved by an increased intake of salt and fluids approximately 2 h before reentry [10]. All astronauts returning from space either take in a portion of broth or salt tablets with water. The intake of salt leads to a retention of water, such that the fluid volume is increased while maintaining a constant electrolyte concentration. By increasing the fluid volume in the body, astronauts will suffer less from orthostatic intolerance immediately upon return. Bungo et al. [11] researched the efficacy of this countermeasure in 1985 and saw that heart rate and blood pressure were improved for subjects that had performed fluid loading. However, the plasma volume that has been decreased during space flight cannot be entirely restored by increased fluid intake before reentry.

A similar effect can be induced by the intake of pharmaceuticals. For example, Florinef causes the kidneys to retain sodium and enables the body to restore its plasma volume. Florinef has shown to reduce the post-bed-rest syncope rate, however, has not proven to be a successful countermeasure for orthostatic intolerance for returning astronauts [12]. Another possibility is Midodrine, a pharmaceutical which decreases venous capacity and prevents venous pooling as well as in some cases increasing total peripheral resistance. This has positive impacts on the orthostatic state of subjects. The intake of Midodrine has proven successful in keeping head-down tilt bed-rest subjects from presyncope [13]. On the downside, Midodrine has provoked and increased akathisia response when consumed with certain motion sickness drugs (promethazine) [14]. Florinef and Midodrine are not the only candidates for pharmacological interventions. Other substances such as Octreotide have potential to alleviate postflight orthostatic instability and are being tested. Nonetheless, concerns with the unintended side effects of these medications may limit their use.

Approaching the issue of a reduced amount of body water by artificially increasing the liquid content is merely a transient solution, masking the problem rather than solving it. Therefore, despite fluid loading or certain pharmaceuticals potentially alleviating orthostatic symptoms post-return, they do not suffice as a countermeasure to cardiovascular deconditioning in microgravity.

5.2.4 *Artificial Gravity*

Artificial gravity bears high potential in diminishing unwanted adaptations to weightlessness—not only of the cardiovascular system. However, this approach still faces severe technical challenges. Artificial gravity could be created by short radius centrifugation (setup see Chap. 2). Astronauts could spend certain intervals during the day in an onboard centrifuge and hence be exposed to gravity-like forces. This idea is not new; however, the ideal combination of centrifuge size and rotational speed, and interval length to counteract multiple-system deconditioning, has not yet been determined. Ground-based studies investigate the efficacy of centrifugation to alleviate post-bed-rest orthostatic instability. Vernikos [15] showed that 2 h of daily passive standing via centrifugation is sufficient to prevent post-bed-rest hypotension, whereas plasma volume losses are only prevented with 4 h of passive standing. The ideal duration, magnitude, and type of artificial gravity as a countermeasure for cardiovascular deconditioning have yet to be elucidated.

An alternative to having a centrifuge on board is turning the space station as a whole into a centrifuge. If a cylindrical space station spins around its axis, the centrifugal force outward would cause the sensation of a gravitational pull toward the outside. This would create a "floor" that bends up, back into itself—a theoretical approach that has been implemented in several science fiction movies, such as *Interstellar*. However, centrifuge-induced artificial gravity of entire space stations remains a theoretical approach for now due to exorbitant quantities of energy required to keep the a station spinning for now.

5.3 Outlook and Broader Applications

Space physiology has led to a reconsideration of the role played by gravity in living systems in general, and particularly in the human cardiovascular system. Attention has been drawn by comparative physiology, in which many examples were able to show that gravity has deeply shaped both the form and function of the cardiovascular system. However, the understanding of complex physiological mechanisms and their reaction to microgravity is far from complete. The limited scope is particularly evident when regarding the development of countermeasures, which has only been successful to a certain extent. Ongoing research is determined to make advancements in these fields, but limitations discussed in previous chapters make this progress rather slow. There is much need for continuing physiological investigations in space, with benefits stretching out far beyond the spaceflight industry.

Elucidation of the mechanisms behind the effects of weightlessness on the cardiovascular system may help shed light on clinical, non-spaceflight related issues, such as high blood pressure and heart failure. The design and application of new technologies in fields such as geriatrics or psycho-physiology are the

tangible outcome of our research efforts in space. For example, the thigh cuff countermeasure has been considered as a device that could prevent fluid build up in the lungs. The Adeli suit, on the other hand, is used to treat children with physical disabilities resulting from neurological conditions such as cerebral palsy and patients suffering from neurogenic orthostatic hypotension [16]. But the list does not stop there. The European Space Agency (ESA) has developed 3D scanners to determine change in bone mass during spaceflight. Patients suffering from osteoporosis could benefit from such a technological development.

A specific example that parallels cardiovascular adaptations and the fluid shift in space are dialysis patients. These patients are unable to excrete fluids via the kidney and store about 50 % of their water in the superficial tissues. Fluid accumulation of this nature is paralleled by thoracic hypervolemia in astronauts. Hence, space methods can also be applied in clinical medicine on Earth on a vast spectrum.

Looking beyond applications of space physiology to the medical sector reveals that space physiology has benefits even on a political level. International organizations frequently join forces to achieve united research goals. Europeans have already learned to cooperate closely with their neighbors in space physiology and medicine in order to be competitive in the race to live and work in space, both now and in the more distant future.

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