Lehrstuhl für Anästhesiologie II der Universität Witten/Herdecke

Cardiopulmonary and Circulatory Interactions During Gravity Transitions in Parabolic Flight
- Joint Approach of Gravitational Physiology and Anaesthesiology -

Inaugural Dissertation

Zur

Erlangung des Grades eines Doktors der Medizin

der Universität Witten/Herdecke

Fakultät für Gesundheit

Vorgelegt von Klaus Ulrich Limper

aus Bergisch Gladbach

2014

Dekan: Herr Prof. Dr. med. Stefan Wirth

Mentor: Herr Prof. Dr. med. Frank Wappler

Externer Mentor: Herr Dr. Luis. E. J. Beck

Zweitgutachter: Herr PD Dr. med. Christian Weinand

Externer Gutachter: Herr Prof. Dr. med. Alexander Choukèr

Tag der Disputation: 25. Februar 2015

Meinen Eltern und meiner Großmutter gewidmet

Contents

Preface

You are an anesthesiologist; why do you perform experiments in space flight-related conditions? What is the benefit of research in those extreme environments for humans on Earth? I have been asked these excellent questions repeatedly. To answer these questions and to justify the research of this thesis, I have to go into greater detail. First, I would like to underpin the development of the anesthetist from a pure anesthesia provider to a qualified perioperative physician (1) who takes care of the patient receiving major surgery during all phases of his hospital stay. This development requires a detailed and global understanding of human physiology and pathophysiology not only in the context of the operation theatre but also in the context of pre-anesthesia care and post-surgical intensive care medicine. Fortunately, the anesthetist works under particular and unique conditions that allow him to observe many of the physiological key reactions of the human body. This work is possible because an anesthetist routinely handles inotropic drugs and fluids and provides artificial ventilation, enabling him to immediately follow the responses of the patient's body during these interventions. This ability makes the anesthetist an experienced applied integrative physiologist and patho-physiologist and makes him interested in applied physiological research. Furthermore, an anesthetist becomes aware of numerous physiological and operational questions and issues during his daily work, e.g., what is normovolemia, how is cardiac output regulated, and how can I measure cardiac output invasively and, even better, non-invasively? It seems intuitive to answer these questions directly in the situations in which they arise, meaning in patients receiving anesthesia or intensive care. However, the cardiovascular system of individuals in these situations is maintained at a steady state by the carefully treating anesthetist. Thus, for a better understanding of human cardiovascular physiology and of the reliability and validity of cardiovascular monitoring methods, it is helpful to investigate the human cardiovascular system under environmental conditions, pushing the system to its limits, e.g., high or low gravity, cold, heat or hypoxia.

The field of research of this thesis is "Extreme Environment Physiology", which is a part of the "Integrative Physiology" approach (2). This area of physiological research integrates research, among others, in high altitude, in space flight, in high performance flight, during high performance tasks, in confinement, in cold and heat and in diving. In these environments, the ambient conditions are challenging and in some cases even hostile for the human body and include hypobaric hypoxia, hyperbaric pressure, weightlessness and hypergravity, isolation, other types of psychological stress and extreme temperatures. Extreme environmental physiology tries to determine the impact of those environments and stressors on the human body, each stress on its own or in combination with others (3). Many of our physiological systems are affected by extreme environments: the cardiovascular system; the lungs; the kidneys and the fluid regulation system; the brain, bones and muscles; the immune system; and the blood coagulation system. Challenging

our human physiological systems by exposing them to extreme environmental conditions not only allows us to learn how these systems work under these particular conditions, but extreme environments can serve as a reasonable model for aging and for several diseases. Astronauts on long-term space missions aboard the International Space Station (ISS), for example, suffer from a loss of bone and skeletal muscle mass (4) and from cardiac atrophy (5), which allowed scientists some decades ago to use astronauts during and after spaceflight as a model for the process of aging of the human body. Furthermore, many astronauts suffer from circulatory weakness and pre-syncopes, known as postflight orthostatic intolerance (POI), when they return to Earth. That is why astronauts are used as an in vivo model to better understand dysautonomias (6), which can be observed in patients suffering from Parkinson's disease, diabetes mellitus, spinal cord injury or from severe brain trauma and which play a significant role in the work of an anesthetist (7). Again, astronauts show a decreased arterial blood pressure in space although their sympathetic nervous system is up-regulated at the same time (8), leading to the paradox of systemic vasodilatation and sympathetic nervous stimulation in space (9). The anesthetist faces a similar paradox in patients suffering from liver cirrhosis and from hepatorenal syndrome, which combines systemic vasodilatation and increased systemic and renal sympathetic tone with renal vascular constriction (10, 11).

Therefore, many research projects have been performed by anesthetists in extreme environments to better understand the patho-physiology of critically ill patients starting from Mount Everest (12, 13), the Capanna Margherita in the Suisse Alps (14) and Antarctica (15) to the International Space Station (16) and parabolic flights (17, 18). On the other hand, many of the results of space flight-related research performed by non-anesthetists have become influential for anesthesiology. The surprising behavior of the central venous pressure (CVP) in space, which is lower in weightlessness than on the ground despite the central blood volume shift in space, make it clear that CVP is far from understood (19). A complete understanding of CVP and of its value for anesthesiology is still lacking. A further physiological concept according to J. West with importance for anesthesiology is the zoning of the perfusion of the lungs into three sections depending on gravity (20). Parabolic flights, among other scientific approaches, provided the unique environment to show that the *West concept* is not telling the full story and that gravity seems not to be the main factor regarding blood flow distribution in the lungs. In fact, the structure of the pulmonary vascular tree itself seems to be the primary determinant of regional lung perfusion (21). A final example benefitting anesthesia care that emerged from space flight-related research is a new understanding of sodium physiology. The classical concept of sodium and body fluid regulation tells us that sodium is osmotically active and therefore that sodium and body fluid regulation are always linked. From space flight experiments, however, we know that sodium can also be stored osmotically inactivated in tissues, and that sodium homeostasis is linked to the immune system. The great number of critically ill patients suffering from a coupling of dysnatremia and immune

system dysregulation (22, 23) makes it clear that this new mechanism of sodium and fluid regulation in humans may gain importance for the treatment of the critically ill.

In addition to the symbiosis of anesthesiology and extreme environment physiology in the context of joint (patho-) physiological research hypotheses, there is also an interdisciplinary affinity within the meaning of joint medical-technical challenges. After the era of the American space shuttle, with its short space flight missions lasting no longer than two weeks and undertaking mainly research missions, the era of the International Space Station (ISS), with its long-duration space missions, appeared. A new medical issue emerged, namely the need to protect the astronauts' health against the deconditioning of the physiological systems as triggered by chronic weightlessness. Thus, astronaut health monitoring has gained importance. The challenges of astronaut health monitoring, e.g., of the cardiovascular system, became clear considering the extreme environment of the ISS. Due to a lack of medical support in this isolated place, monitoring techniques should be safe, non-invasive, reliable and easy to handle. These requirements make non-invasive finger blood pressure measurement, impedance cardiography and inert gas re-breathing techniques the methods of choice. However, these methods perform best only when the cardiovascular system is in a so-called steady state, which is not the case during the most important phases of a space flight mission, i.e., the launch and transition into weightlessness; the early phase in weightlessness; the reentry; and the hours after landing. Establishing high-performing, non-invasive methods of cardiovascular monitoring in clinical practice is therefore a common goal in space medicine and in anesthesiology and intensive care medicine. However, methods such as non-invasive pulse contour analysis and impedance cardiography have failed to demonstrate their reliability in unstable individuals, such as sepsis or trauma patients.

Returning to the introductory question of this preamble, it makes sense to look ahead as well. Although a future manned flight to Mars or to near-earth asteroids seems to be far away at this stage and although access to the ISS is limited to only a few highly trained astronauts, a fundamental investigation of the human physiological systems is mandatory for long-duration space missions and for the future exploration of other orbs. Thus, anesthetists, among physicians from other disciplines, are eligible and predestined to perform such research because of their deep understanding of applied physiology.

In conclusion, this thesis tends to increase knowledge of the human cardiovascular system and about the performance of non-invasive cardiovascular monitoring methods under severe cardiovascular stress. This thesis tends furthermore to transfer this knowledge from the space flight-related field into the applied field of anesthesiology and intensive care medicine.

Cologne, September 2014

References

1. Grocott MP, Pearse RM. Perioperative medicine: the future of anaesthesia? British journal of anaesthesia. 2012;108(5):723-6.
2. Edwards LM, Thiele I. Applying systems biology methods to the study of human physiology in extreme environments. Extreme physiology & medicine. 2013;2(1):8.
3. Tipton M. A case for combined environmental stressor studies. Extreme physiology & medicine. 2012;1(1):7.
4. Stein TP. Weight, muscle and bone loss during space flight: another perspective. European journal of applied physiology. 2013;113(9):2171-81.
5. Perhonen MA, Franco F, Lane LD, Buckey JC, Blomqvist CG, Zerwekh JE, et al. Cardiac atrophy after bed rest and spaceflight. Journal of applied physiology. 2001;91(2):645-53.
6. Meck JV, Waters WW, Ziegler MG, deBlock HF, Mills PJ, Robertson D, et al. Mechanisms of postspaceflight orthostatic hypotension: low alpha1-adrenergic receptor responses before flight and central autonomic dysregulation postflight. American journal of physiology Heart and circulatory physiology. 2004;286(4):H1486-95.
7. McGrane S, Atria NP, Barwise JA. Perioperative implications of the patient with autonomic dysfunction. Current opinion in anaesthesiology. 2014;27(3):365-70.
8. Ertl AC, Diedrich A, Biaggioni I, Levine BD, Robertson RM, Cox JF, et al. Human muscle sympathetic nerve activity and plasma noradrenaline kinetics in space. The Journal of physiology. 2002;538(Pt 1):321-9.
9. Norsk P, Christensen NJ. The paradox of systemic vasodilatation and sympathetic nervous stimulation in space. Respiratory physiology & neurobiology. 2009;169 Suppl 1:S26-9.
10. Huschak G, Kaisers UX, Laudi S. [Hepatorenal syndrome]. Der Anaesthesist. 2013;62(7):571-82.
11. Trevisani F, Sica G, Mainqua P, Santese G, De Notariis S, Caraceni P, et al. Autonomic dysfunction and hyperdynamic circulation in cirrhosis with ascites. Hepatology (Baltimore, Md). 1999;30(6):1387-92.
12. Hornbein TF, Townes BD, Schoene RB, Sutton JR, Houston CS. The cost to the central nervous system of climbing to extremely high altitude. The New England journal of medicine. 1989;321(25):1714-9.
13. Siervo M, Riley HL, Fernandez BO, Leckstrom CA, Martin DS, Mitchell K, et al. Effects of prolonged exposure to hypobaric hypoxia on oxidative stress, inflammation and gluco-insular regulation: the not-so-sweet price for good regulation. PloS one. 2014;9(4):e94915.
14. Faoro V, Fink B, Taudorf S, Dehnert C, Berger MM, Swenson ER, et al. Acute in vitro hypoxia and high-altitude (4,559 m) exposure decreases leukocyte oxygen consumption. American journal of physiology Regulatory, integrative and comparative physiology. 2011;300(1):R32-9.
15. Simpson A, Maynard V. A longitudinal study of the effect of Antarctic residence on energy dynamics and aerobic fitness. International journal of circumpolar health. 2012;71:17227.
16. Strewe C, Feuerecker M, Nichiporuk I, Kaufmann I, Hauer D, Morukov B, et al. Effects of parabolic flight and spaceflight on the endocannabinoid system in humans. Reviews in the neurosciences. 2012;23(5-6):673-80.
17. Frerichs I, Dudykevych T, Hinz J, Bodenstein M, Hahn G, Hellige G. Gravity effects on regional lung ventilation determined by functional EIT during parabolic flights. J Appl Physiol (1985). 2001;91(1):39-50.
18. Groemer GE, Brimacombe J, Haas T, de Negueruela C, Soucek A, Thomsen M, et al. The feasibility of laryngoscope-guided tracheal intubation in microgravity during parabolic flight: a comparison of two techniques. Anesthesia and analgesia. 2005;101(5):1533-5.
19. Buckey JC, Gaffney FA, Lane LD, Levine BD, Watenpaugh DE, Blomqvist CG. Central venous pressure in space. The New England journal of medicine. 1993;328(25):1853-4.
20. West JB. Respiratory physiology : the essentials. 9th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012. viii, 200 p. p.
21. Glenny RW, Lamm WJ, Bernard SL, An D, Chornuk M, Pool SL, et al. Selected contribution: redistribution of pulmonary perfusion during weightlessness and increased gravity. J Appl Physiol (1985). 2000;89(3):1239-48.
22. Wild U, Trautmann J, Wappler F, Sakka S. Differentialdiagnostik der Serumhyperosmolalität. Anästh Intensivmed. 2013;54:274-83.
23. Titze J. Sodium balance is not just a renal affair. Current opinion in nephrology and hypertension. 2014;23(2):101-5.

Chapter One

1 General introduction and outline of this thesis

This thesis addresses the cardiovascular system under alternating gravitational stress and how to measure cardiovascular indices noninvasively in this particular environment. Gravitational stress and dynamic exercise require probably the most complex control mechanisms of our cardiovascular system; therefore, investigating the circulation under these circumstances provides the greatest insight into the way this system works. Thus, this thesis uses the former stress to gain new insight into the human cardiovascular system.

1.1 The physiology of the human body under gravitational stress

1.1.1 Human orthostatic control

The human cardiovascular system is not well equipped to perform in upright posture under the influence of the gravity of our planet Earth. The physiologist L. Rowell put it in a nutshell in his book *Cardiovascular Control* when he wrote the following: “The human circulation was not well “designed” for being positioned upright with its pump high above a system of compliant tubes, which are highly susceptible to effects of gravity” (1). That our brain is provided with adequate blood perfusion in almost any body position however demonstrates that evolution generated efficient countermeasures to fight against the trend of the blood to shift away from the brain to the dependent parts of our upright body. However, an understanding in greater detail of the human cardiovascular system under gravitational stress is mandatory to understand the results of this thesis. Gravity is omnipresent and acts continuously on the human body everywhere on the planet Earth. Most quadrupeds, e.g. dogs, withstand gravity well while they stand on their four feet because approximately 70% of their blood volume is arranged at or above their hearts, which again try to pump it to their brains. Thus, venous return to the heart is well maintained when quadrupeds walk on their four feet. However, when our ancestors increased their bodies and developed the ability to stand and to walk upright on two feet, also referred to as orthostasis, gravity became a real threat for the human body because, in an upright body position, it pulls blood away from the heart and the brain toward the dependent parts of the body, such as the legs and the splanchnic vascular beds (fig. 1.1). Orthostatic blood pooling in the splanchnic system in particular is often neglected in orthostatic research, although approximately 25% of the human blood volume is stored in the viscera, which are therefore important blood reservoirs (2). Two thirds of this blood volume can be autotransfused into the systemic circulation within seconds. This autotransfusion works because sympatoadrenal stimulation leads to active splanchnic venoconstriction via alpha-adrenoceptors (2). Again, in an upright stance, the venous return of blood to the heart drops and cardiac output and brain perfusion thereby decrease. Without the physiological countermeasures of the cardiovascular system, so-called orthostatic reflexes, humans would faint in an upright body position. In the upright human body, 70% of the blood volume is situated below the heart level.

This downward blood volume shift opposes the efforts of the human heart to pump blood up to the brain, which sits in an upright body position approximately 30 cm above the heart. The driving force of this downward blood volume shift is the hydrostatic pressure of the blood column together with the fact that the veins of the human body are compliant and not made out of resistant tubes that could withstand the hydrostatic pressure of the blood column in standing position.

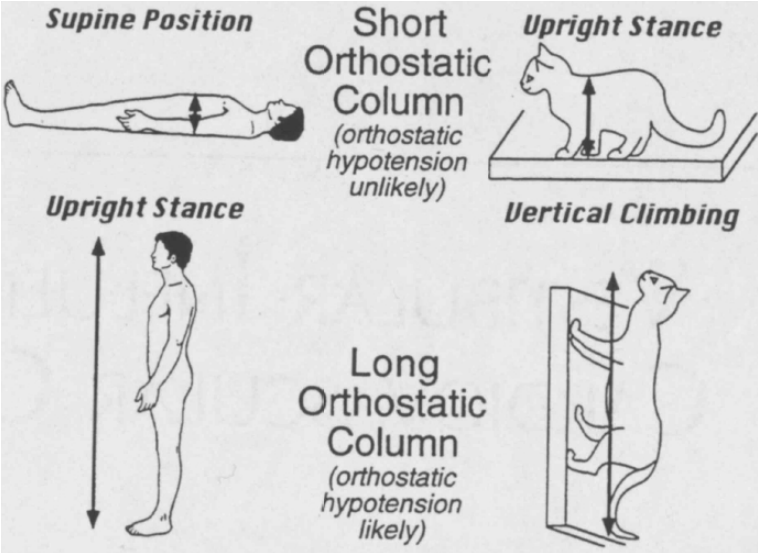

Figure 1.1: Comparative presentation of the (biped) human body and the body of a quadruped under gravitational stress. The blood volume distribution in the human body in the supine position is similar to that of a quadruped walking on its four feet. Standing on two feet induces a downward blood volume shift in both the human and the quadruped body, making orthostatic hypotension likely in both creatures. Adapted from (3).

Therefore, approximately 75% of the blood volume is in those compliant veins. The hydrostatic pressure of a fluid column, similar to the blood in the vascular system, refers to $\rho \bullet g \bullet h$, where p is the fluid density, g is the acceleration due to gravity, and h is the height of the hydrostatic column. This formula clearly shows that the hydrostatic pressure of a fluid column is correlated with acceleration due to gravity. If acceleration is doubled, the hydrostatic pressure is doubled correspondingly, and if acceleration becomes zero, the hydrostatic pressure becomes zero as well. Therefore, the blood volume shift from the thorax to the dependent parts of our body is greater in hypergravity than in normo-gravity and does not exist in weightlessness. Thus, when a human stands up under 1 G_z, 500 to 1000 ml of blood drains off the thorax into the lower parts of the body (4). This drainage suggests that venous return is one of the main if not the most important variable during orthostatic stress. Without potent countermeasures, our body would develop presyncope or syncope immediately after rising. The body fights orthostatic intolerance through two main mechanisms. The first mechanism is the baroreceptor reflex, briefly baroreflex. The arterial baroreceptors are so-called high pressure receptors that are located in the carotid arteries and in the aortic arch. In the supine position, these receptors sense the same mean arterial pressure as that at the level of the heart. When the human body is raised, the baroreceptors are suddenly

located 10-20 cm above the level of the heart. Due to the changed hydrostatic pressure at the baroreceptor side and to a decreasing cardiac output, the mean arterial pressure at the level of the baroreceptors drops by 10-15 mmHg after standing up. The baroreceptors now send a changed neuronal signal to the brain stem, which leads to a depression of the vagal nerve at the heart and to an activation of the sympathetic innervation of the heart and of the resistance vessels. This modulation of the autonomic innervation of the heart and the vessels leads to an increased heart rate and inotropy and to arterial and venous vasoconstriction. Thus, cardiac preload, afterload and force increase. To further recover the dropped venous return or rather the preload of the heart, the body activates the muscle and respiratory pumps.

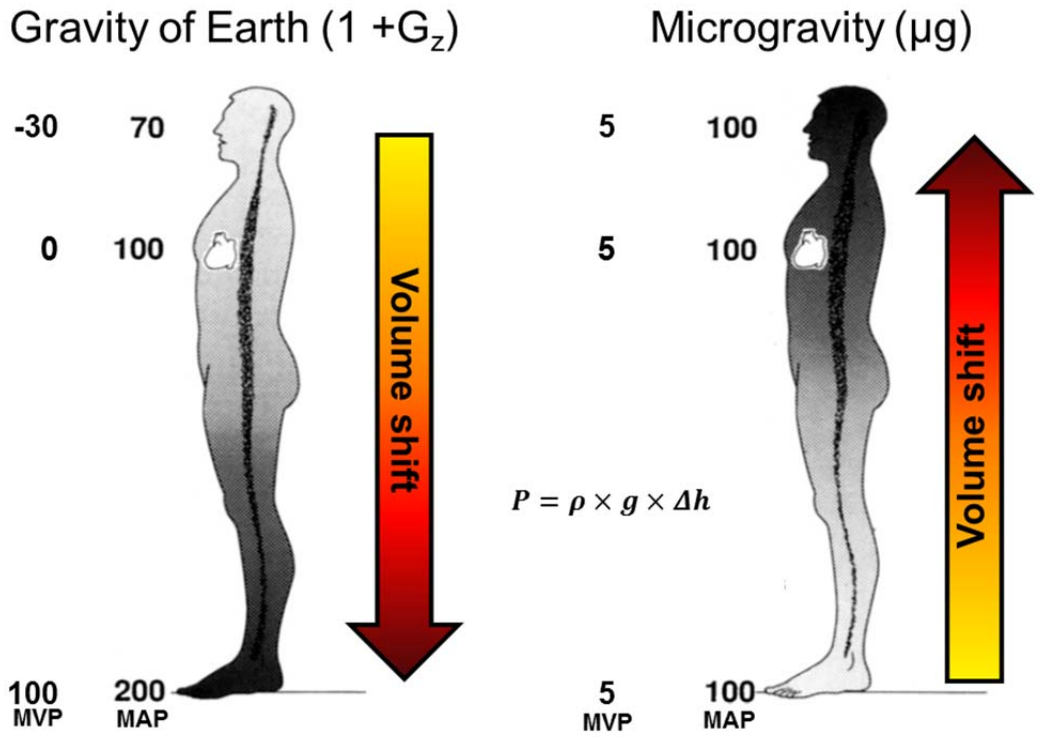

Figure 1.2: The central volume shift and the particular changes of the hydrostatic pressure in weightlessness are shown with respect to the standing human body in 1 G_z. MVP (mmHg), mean venous pressure; MAP (mmHg), mean arterial pressure. The formula for hydrostatic pressure is given as P=ρ*g*Δh. P, pressure (kPa); ρ, volumetric mass density (kg*m^{-3}); g, Earth gravity (m*s^{-2}); Δh, height of the hydrostatic column (m). Adapted from (5).

1.1.2 The lungs under gravitational stress

The lungs are a blood reservoir that plays an important role in human orthostasis (6). In addition, the lungs function as the central gas exchange organ of the human body. In this thesis, the lungs play a particular role as the key organ for cardiac output determination by the inert gas rebreathing method. Therefore, the impact of hyper- and microgravity on the lungs seems to be important, and it is clear that gravity influences the blood flow distribution and the ventilation of the lungs. The lungs contain approximately 300 ml of blood, of which 25% is in the pulmonary capillaries (7). The classical concept that describes a dependency on gravity of the lungs' blood and ventilation

distribution is the *West zones* of the lungs (8). This concept says that in a standing human, both ventilation and perfusion of the lungs increase from top to bottom due to gravity. The uneven distribution of blood flow can be explained by the hydrostatic pressure differences within the pulmonary blood vessels. The uneven distribution of ventilation can be attributed to the weight of the lungs, which makes the intrapleural pressure less negative at the bottom than at the apex of the lungs. As a consequence, the basal lung is relatively compressed but expands more on inspiration than the apex (8). However, when the human is in the supine position, these differences in ventilation and perfusion disappear with the result that basal and apical ventilation and perfusion become more uniform. This effect of gravity-driven ventilation/perfusion equalization is even pronounced in healthy human lungs in the prone position with respect to the supine position (9). This finding helps the anesthetist understand why patients with respiratory distress syndrome may benefit from being transferred to a prone position for ventilation. Similar changes appear in weightlessness. Ventilation and perfusion of the lungs become more uniform. Additionally and attributed to the cephalic blood volume shift in microgravity, the pulmonary blood volume increases, leading to a slightly improved diffusion capacity. Furthermore, the functional residual capacity (FRC) is reduced in weightlessness (10). Nevertheless, gas exchange in microgravity is seemingly no more efficient than that on Earth (11). Reciprocal changes are observed as gravity is increased to more than twofold of that on Earth (12). However, the classical concept of J. West became controversial at some point. Glenny et al. (13) showed that perfusion inequalities of the lungs depend mainly on the vascular tree and not only on gravity. This dependence was demonstrated in pigs in parabolic flights (13). Parabolic flights contributed therefore to a broader understanding of a central physiological matter. That these findings of gravitational physiology are of interest for anesthetists and are transferable to intensive care medicine, and anesthesia care is proven by several excellent reviews in the context of critical illness (14, 15).

1.1.3 Human cardiovascular control in parabolic flight

In addition to the vestibular system, the cardiopulmonary and vascular system has been investigated the most of all human macro-physiological systems in parabolic flight. How the cardiovascular system responds to the parabolic maneuver depends on the body position and on the fluid status of the subject. A standing or sitting body position is required to investigate the orthostatic system. Thus, in this section, the upright standing body position is referred to if not otherwise stated. The fluid status of subjects has not been controlled in any of the human cardiovascular parabolic flight studies but has been controlled for in one study of baboons (16). Parabolic flights generate rapid gravity transitions ranging from twofold of the gravity of the earth to near weightlessness. The two dominating effects on the human cardiovascular system are, first, a rapidly changing cardiac pre-load due to blood volume shift within the veins (fig. 1.2) and, second, rapid change of the hydrostatic pressure component of the arterial blood pressure with an impact on the baroreceptors in the carotid arteries (fig. 1.2). The arterial baroreceptor reflex, briefly baroreflex, and the Frank Starling mechanism are the two dominating mechanisms in controlling

the cardiovascular system in parabolic flight. To a lesser degree, the Bainbridge reflex is involved in cardiovascular regulation in parabolic flight as well (17). The baroreflex and the Bainbridge reflex are neural feedback loops that regulate cardiac function and vascular tone. These reflexes are composed of a sensory (afferent) arm, an integration center in the medulla oblongata in the central nervous system and an efferent motor arm.

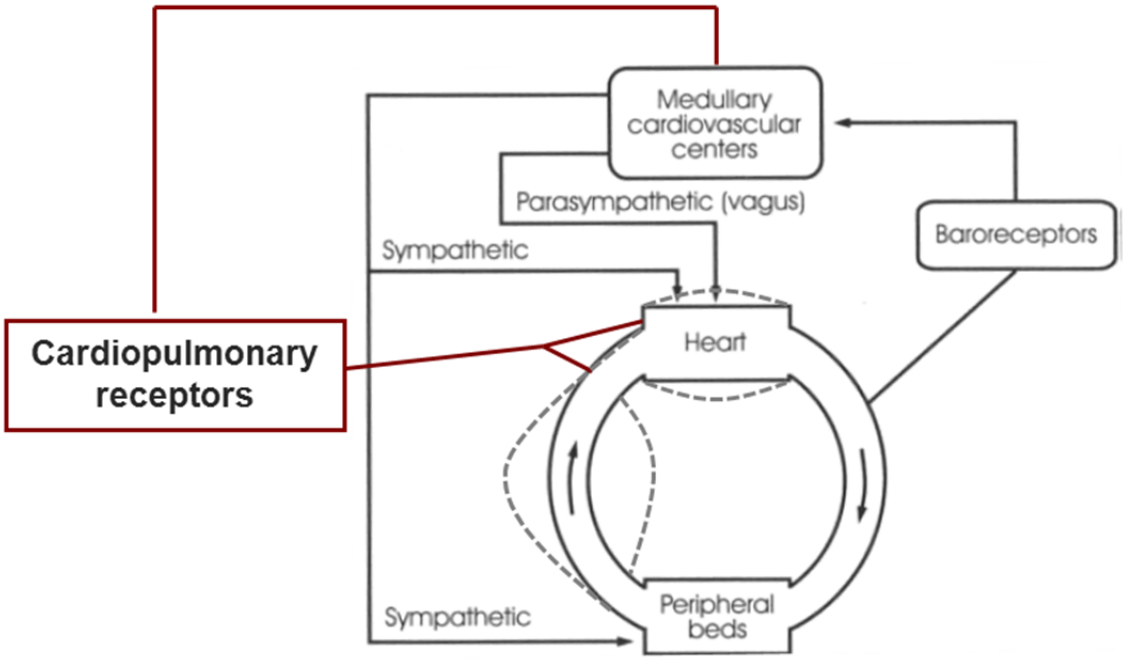

Figure 1.3: Simplified diagram of the reflex control of the human cardiovascular system in parabolic flight. The dashed gray boundaries of the venous part of the circulation represent potential blood pooling in the veins in an upright body position due to the huge compliance of the veins with respect to the arterial tree. The dashed gray contours of the heart represent the Frank Starling mechanism due to an increased ventricular filling in weightlessness. The two major cardiovascular reflexes, the high-pressure baroreflex on the arterial side and the low-pressure Bainbridge reflex on the venous side with its circuitries in the medulla oblongata and their efferent autonomic limbs are shown. The main effector organs of these reflexes are basically the heart and the resistance vessels. Modified from (18).

The third of the major human cardiovascular reflexes, the Bezold-Jarisch reflex, plays no or only a marginal role in cardiovascular regulation in parabolic flights. The baroreceptors are high-pressure stretch receptors and are located in the vessel walls of the carotid sinus and the aortic arch. These receptors respond to changes in the dynamic and hydrostatic component of the arterial blood pressure. The information is transmitted via the vagus nerves to the medulla oblongata. After processing the information, the efferent signals control cardiac output and systemic vascular resistance via the autonomic nervous system (18). The Bainbridge reflex originates from low-pressure stretch receptors at the vena cava, the right atrium and the pulmonary veins. This reflex responds to changes in the blood volume of the thoracic compartment and transmits its neural information via the vagus nerves. The vagal outflow to the heart is inhibited, and the sympathetic outflow is enhanced by increased pre-load leading to tachycardia (19). These reflexes taken

together lead to a classical response pattern of the autonomic nervous system in parabolic flight. The activity of the sympathetic nervous system is nearly doubled in the initial hypergravity phase, leading to tachycardia and a stable mean arterial pressure despite decreased cardiac pre-load due to further blood volume shift to the dependent parts of the body with respect to 1 G_z standing position. Then, after transition into weightlessness, the sympathetic nervous system activity decreases but is still 80% of its 1 G_z activity. The suppression of the sympathetic nerve lasts however only approximately 10 seconds, after which its activity becomes enhanced still in microgravity. During the second hypergravity phase, another strong sympathetic activation occurs (20). An initial baroreflex-mediated vagal heart rate response leads to a bradycardia immediately after transition into weightlessness. This bradycardia is followed by a gradual heart rate recovery during the remaining seconds of the microgravity phase due to parasympathetic withdrawal (21).

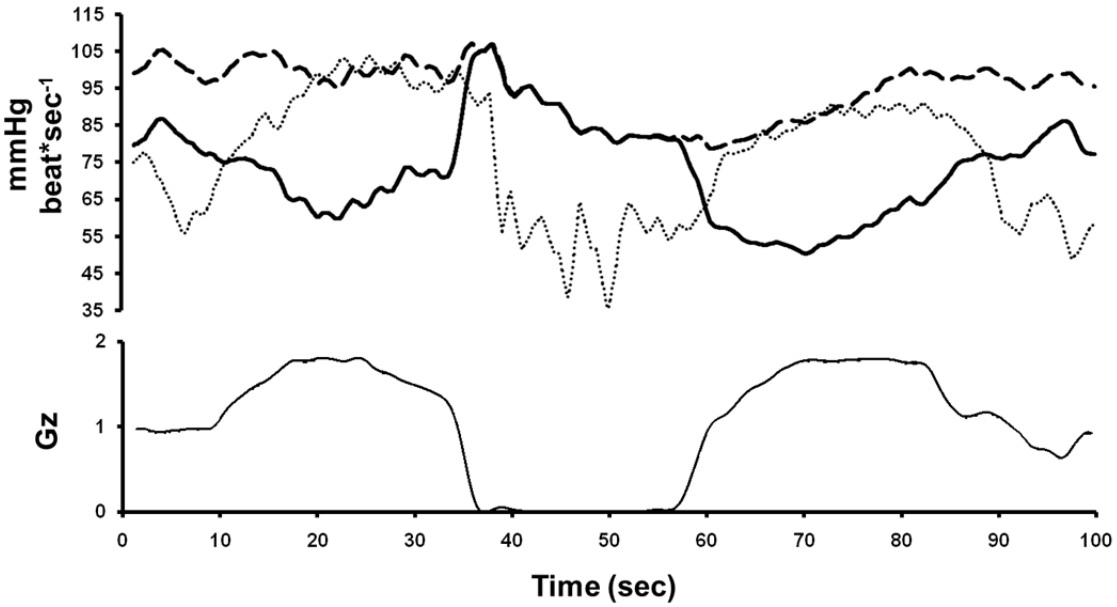

Figure 1.4: The arterial pressure and heart rate dynamics in a representative subject in standing position during a parabola are shown. The graphs of the upper diagram represent the following: dotted line, heart rate; dashed line, mean arterial pressure at the heart level; and continuous black line, calculated mean arterial pressure at the level of the carotid baroreceptors. The lower diagram shows acceleration dynamics in the head-to-toe direction. Particular attention should be paid to the course of the mean arterial pressure at the level of the baroreceptors because this pressure is the central trigger for the responses of the autonomic nervous system. Furthermore, it must be emphasized that heart rate regulation based on an activation of the parasympathetic system occurs within one heartbeat. On the other hand, any regulations that are based on sympathetic nerve activation or parasympathetic withdrawal appear delayed.

Both the baroreflex and the Bainbridge reflex are important for the anesthetist to know. Their interactions may explain a multitude of bradycardia episodes that are observed frequently after induction of spinal anesthesia especially in the parturient (22). The Frank Starling mechanism contributes additionally to the cardiac output increase in weightlessness. The cephalic blood volume shift leads to an increase in ventricular filling, which on the other hand promotes an

increase in the developed cardiac pressure (23, 24). This increase in inotropy cannot be explained by only changes in cardiac muscle filament overlap but must have molecular mechanisms as well (25). These mechanisms include an increase in the calcium release from the sarcoplasmic reticulum, an increased calcium sensitivity and the phosphorylation of contractile filaments (26). However, it is difficult to separate the regulation of cardiac function in intrinsic (Frank Starling mechanism) and extrinsic (autonomic nervous system) control mechanisms (25). As previously indicated, not only the veins of the legs but also the splanchnic circulation play a key role in gravity-dependent volume shift. The importance of the splanchnic circulation for venous return was demonstrated by a parabolic flight experiment by measuring the cardiac output after transition to weightlessness in an upright body position once with and once without the venous tourniquet of the legs. The result of the experiment was that the cephalic volume shift originated one half each from the legs and from the splanchnic circulation (17).

All of these complex control mechanisms of the cardiovascular system are in a fragile balance and can easily become disequilibrated, which has been demonstrated in previously orthostatic tolerant subjects after parabolic flights. Even the short periods of changing gravity of a parabolic flight increased orthostatic intolerance in half of the tested flight subjects (27). Interestingly, this was mainly the case in subjects who showed augmented hyperventilation, which led to hypocapnia and cerebral vasoconstriction (28). This important observation shows that the human brain is not an orthostatically passive organ that only receives its blood perfusion depending on the performance of the remaining cardiovascular system but has an active and regulating role in orthostasis in general (29).

1.1.4 The heart in parabolic flight

Cardiac output is regulated by the preload, contractility, heart rate and afterload (2). Cardiac output during rest in 1 G_z in the supine and standing positions is approximately 5-10 and 4-6 $L*min^{-1}$, respectively, whereas that during exercise is approximately 15-21 $L*min^{-1}$ in the supine and 16-18 $L*min^{-1}$ in the standing position, respectively (30). The cardiac output during rest in the supine position and during rest in weightlessness is comparable but it can increase after transition in a resting standing position into weightlessness to up to 16 $L*min^{-1}$ without exercise stress (31). The blood volume shift that occurs in an upright stance in the parabolic maneuver allows the heart to first drain out blood, then receives a huge amount of blood and finally drains out blood again in just 60 seconds. This drainage leads to the activation and deactivation of the sympathetic and vagal nervous system in rapid sequence. Furthermore, the chambers of the heart are dilated but only to shrink again a couple of seconds later (23). Thus it is not surprising that the human heart responds with arrhythmias to parabolic maneuvers in some cases. Supraventricular arrhythmias and premature ventricular contractions have been observed (32) (fig. 1.5). However, cardiac arrhythmias appear under hypergravity conditions as found in acrobatic flights and in centrifuges

as well (33). Furthermore, arrhythmic risk increases during long-duration weightlessness simulation by head-down tilt bed rest experiments (34).

In actual weightlessness, premature ventricular contractions can appear in astronauts. One astronaut developed a short period of a ventricular tachycardia (35), and the Russian medical community reported more than 75 abnormal ECG recordings in flight in cosmonauts during the last 10 years of the space station MIR (36). One cosmonaut had premature ventricular contractions before his first space flight. He finally flew without complications after the exclusion of morphological heart disease with beta blockers and calcium channel blocker medication (37).

Figure 1.5: The upper graph shows a lead-II ECG tracing in a test subject who was exposed to a parabolic flight maneuver in the standing position. The lower graph shows acceleration in the head-to-toe direction. The subject received 175 µg of scopolamine before the flight. Premature monomorphic ventricular beats appeared repeatedly after transition to weightlessness and disappeared immediately after transition into the second hypergravity phase. Adapted from (32).

1.1.5 The central venous blood pressure in parabolic flight and in space

The intramural and transmural central venous pressure (CVP) plays a key role in the human circulatory regulation because it is one of the main determinants of ventricular filling, respectively pre-load, of the right and left heart. CVP depends on the relationship between cardiac output and venous return (38). The venous return, on the other hand, depends mainly on the mean systemic filling pressure, the stressed volume of the veins and the venous resistance (38). Before CVP had been measured in parabolic flight and in space for the first time, it was expected to increase in weightlessness above 1 G_z standing values because of the shift of 1-2 liters of blood from the dependent to the central compartments of the body. The first studies of CVP in baboons in parabolic flight showed a decrease in the CVP after transition to weightlessness if the baboon was volume depleted and an increased CVP if the baboon was volume replete (16). In humans in parabolic flight, the CVP was measured by Videbaek and Norsk, who showed a decreased CVP in weightlessness with respect to the 1 G_z supine position (39). In space, CVP was finally found to be lower than its value in the sitting position before launch (40, 41). These findings surprised the involved scientists, and a watertight explanation of these findings is still lacking. An increased cardiac output, an increased intrathoracic volume, a decreased intrapleural pressure and a

decreased weight of soft tissues are responsible for the CVP dynamics. These factors together lead to an increase in transmural pressure of the heart, which in turn increases cardiac output via the Frank-Starling mechanism (42, 43). However, the current knowledge on the CVP paradox in weightlessness makes clear that the CVP in space lacks a simple explanation, closing the circle to clinical medicine where CVP lost its significance for cardiovascular monitoring in critically ill patients and patients receiving anesthesia. This loss of significance occurred because CVP failed to demonstrate its validity in the determination of the fluid status of a patient and its ability to detect patients with fluid responsiveness (44, 45). However, the importance of an adequate CVP for cardiovascular function makes it not surprising that CVP remains unchanged despite very serious circulatory stress.

The venous side of the circulation is difficult to access; therefore, parameters of this part of the vascular system are difficult to evaluate. Parameters, such as stressed and unstressed volume and mean systemic filling pressure, are crucial to understanding the venous and central venous system but are not part of the regularly measured parameters in patients receiving intensive care, although they could be of benefit for the treatment of the patient and for the understanding of hypovolemia (46, 47). Furthermore, these parameters have been measured in only patients receiving mechanical ventilation. To better understand the issue of the CVP in weightlessness and in critical care medicine, it must be emphasized that an increase in cardiac output leads to a decrease in the central venous pressure (1). Thus, cardiac output controls the central venous pressure when circulation is in the steady state and not vice versa. Cardiac output increases after transition into weightlessness (21, 48), and a decreased CVP therefore seems to be a logical physiological reaction. This response has led to much of confusion because right arterial pressure is often misinterpreted as the control variable of cardiac output (49, 50). However, there is a particular pathological type of circulation in which central venous pressure and systemic venous pressure together with pulmonary vascular resistance are the key determinants of cardiac output – the Fontane circulation (51, 52). In this single heart circulation control of central venous pressure is the monitoring method of choice for the anesthetist to avoid cardiac failure due to hypovolemia (53).

1.1.6 Interactions of the cardiovascular, vestibular, visual and the postural systems

The shift of blood in the vascular tree and the unloading of baroreceptors are not the only triggers of reflexes of the human body in parabolic flight. Further physiological systems that are highly challenged are the vestibular system, the visual system, the postural system and the viscera. The vestibular system is directly connected to the autonomic nervous system, which is called the vestibulosympathetic reflex (54). This reflex plays an important role in the control of blood pressure during gravitational stress (55, 56). The postural system, that guarantees the stance of the human body in three dimensions works therefore together with the cardiovascular system to maintain orthostasis under orthostatic challenge (57). The visual system (58), proprioceptors in axial and limb muscles and mechanoreceptors in the skin send further inputs to the vestibular nuclei in the central nervous system (59). These nuclei again send their afferents to regions of the brainstem

that regulate circulation and respiration. Furthermore, projections from visceral receptors modulate the circulatory and respiratory centers in the brainstem during gravitational stress (59).

1.2 Methods

1.2.1 The parabolic flight

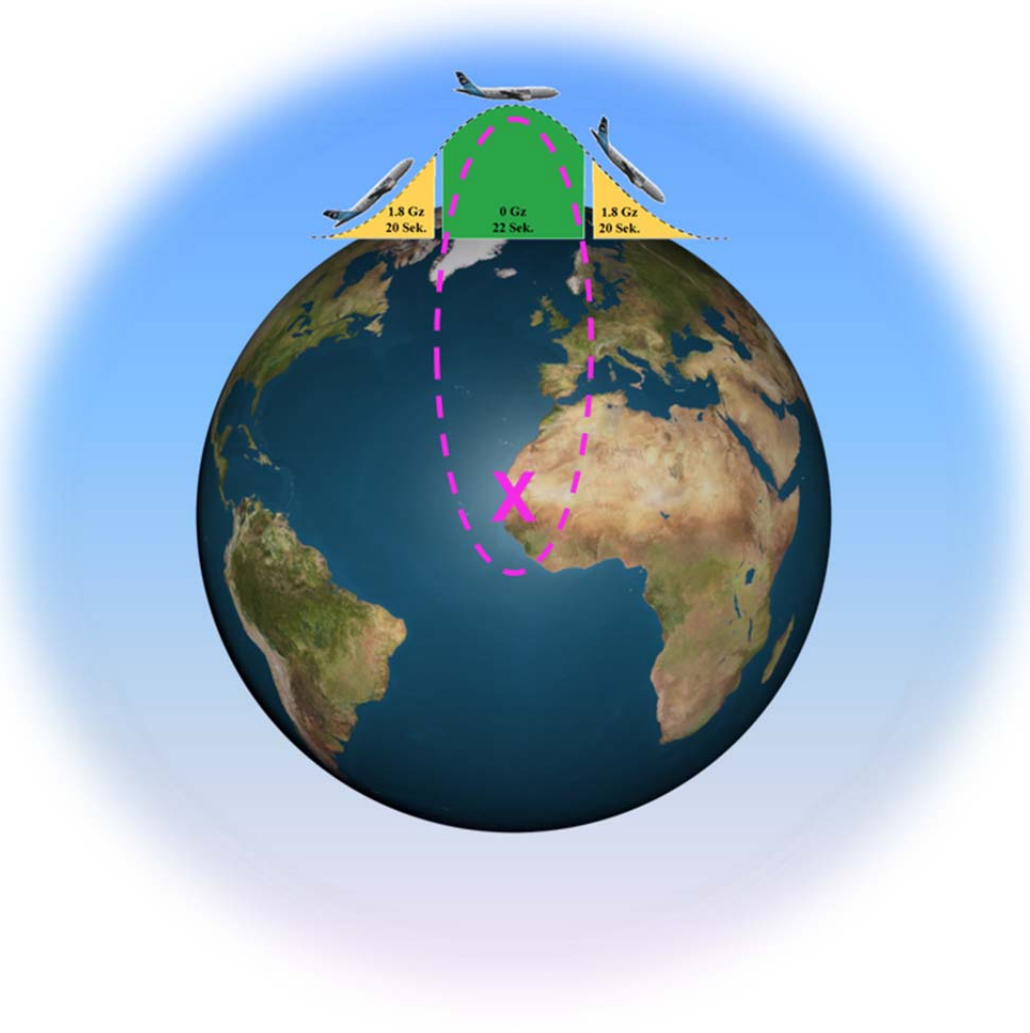

Figure 1.6: The Earth with its center of mass, X, and a theoretical orbit around this center is shown as dashed ellipse. A parabolic flight trajectory creates, from a physical point of view, the identical "weightlessness" that astronauts experience in space. At the peak segment of the parabola, the airplane follows the theoretical orbit around the center of mass of the Earth with an orbital period of approximately 30 min. Adapted from (60).

Parabolic flights using modified passenger airplanes have been performed for decades for scientific reasons and for astronaut training (60). Early reports of medical experiments performed during parabolic trajectories date back to the 1950s (61). The possibility of cheating gravity on earth by creating short phases of weightlessness by following a particular parabolic-shaped trajectory in an airplane was first systematically described by F. and H. Haber in 1950 (62). Based

on this concept, F. Haber later developed the roller-coaster flight pattern of the US parabolic flights for training the Apollo astronauts. In the same year, and before the first man entered space, the German physiologist Otto Gauer wrote a theoretical article on the potential effects of weightlessness on the human body (63), in which he correctly predicted some of the effects of weightlessness on the human inner ear. In addition to these scientific flights, touristic parabolic flights have become increasingly popular in recent years and will gain further importance as a training environment for costumers of the upcoming suborbital commercial space flights.

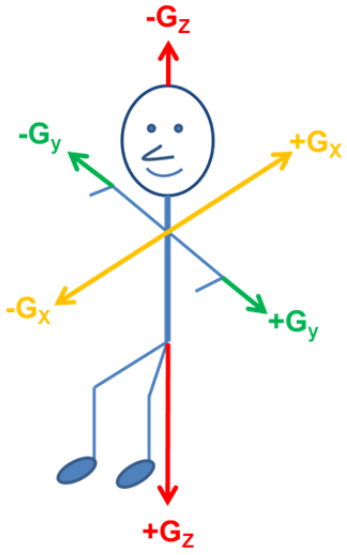

Figure 1.7: Inertial force vectors acting on the body. Attention should be paid to the fact that accelerative force acts in an opposite direction to the inertial force. $-G_z$, footward acceleration; $+G_z$, headward acceleration; $-G_y$, left lateral acceleration; $+G_y$, right lateral acceleration; $-G_x$, backward acceleration; $+G_x$, forward acceleration. Adapted from (64).

1.2.2 Design of a European parabolic flight campaign

During a scientific European parabolic flight consisting of 31 parabolas, the participants experience approximately 11 minutes of weightlessness and approximately 21 minutes of hypergravity (1.8 G_z). Two contiguous parabolas are separated by a phase of steady flight of one minute. Three flight days represent a scientific parabolic flight campaign, meaning that during a flight campaign, approximately 33 minutes of weightlessness and 63 minutes of hypergravity are produced.

Since 2013, there have been touristic parabolic flight campaigns available in Europe. These campaigns contain a single flight day with 15 parabolas. These touristic flights will gain importance as training flights for the upcoming commercial suborbital space flights. Incidentally the suborbital flights follow a parabolic flight path and are therefore also parabolic flights, which, however, leave the atmosphere and enter space.

Much of parabolic flight research is performed in the USA using different types of parabolic flight airplanes, e.g., a KC 135 and a Boeing 727. The US campaigns differ from the European campaigns by the flight profile and the number of parabolas that are flown per flight day. Additionally, the cabin atmosphere in the US parabolic airplanes is different from that of the

European Airbus A300 Zero-G. These differences are important to consider when the research results of US and European experiments are interpreted together. Parabolic flight research is also performed by the Japanese aerospace association using a Gulfstream II.

1.2.3 The flight trajectory

In aviation and gravitation medicine, inertial and accelerative forces are a pivotal concern. Newton's third law of motion states that the inertial force of the body is equal to and opposite of the applied accelerative force. Thus, the headward acceleration of the parabolic airplane produces a footward inertial force, which becomes visible in the downward blood volume shift. The body axis in which the inertial force acts is referred to as either x, y, or z (fig. 1.7) (64). During a parabolic flight, accelerative forces in the x- and y-axes are negligible. The desired accelerative forces in the z-axis of 1.8 and 0 G_z are leveled by the pilots in the narrow range of ± 0.05 G_z.

A single parabola consists of an initial hypergravity phase lasting approximately 20 seconds, followed by the actual microgravity phase of 22 seconds and completed by the second hypergravity phase of again 20 seconds (fig. 1.8).

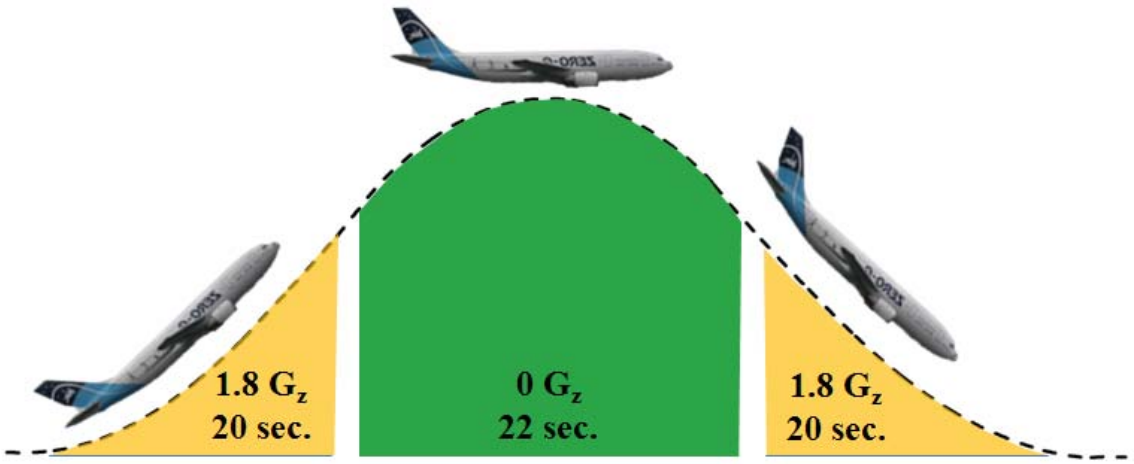

Figure 1.8: Parabolic flight profile with a hypergravity phase at the beginning and at the end of the parabola and the microgravity phase in the middle. The microgravity phase already starts when the airplane is climbing. Adapted from (32).

1.2.4 The airplane

The airplane that is used for the European parabolic flights is one of the first ever built Airbus aircrafts. This aircraft is an A300 B2-C1 with the serial number 003 and was built in 1973. Between 1973 and 1996, this aircraft was used by the Airbus Company for flight testing. In 1996, it was then modified to serve as a parabolic flight test airplane, and the first European parabolic flight campaign with this aircraft was flown in 1997. This airplane is owned by the French Novespace company and is located at the Bordeaux Merignac airport in France. The parabolic flight campaigns are performed by test pilots and test flight engineers of the French test flight center *Centre d'Essais en Vol* (CEV). The parabolic flights are usually flown in a protected airspace over

Brittany or the Mediterranean Sea close to Corsica. In the middle sector of the airplane, there is a 100-m^2 experimentation zone without seats that offers space for 12-15 experiments per flight (60).

1.2.5 The cabin atmosphere

The European A300 Zero-G performs its flights at an altitude of 6.000 – 9.000 a. m. s. l. The cabin atmosphere during the flight is very dry, the humidity is approximately 15%, and the environment is slightly hypobaric and hypoxic. The ambient pressure of the cabin in flight is 825-830 mbar, which is equivalent to an altitude of approximately 1650 a. m. s. l. This hypobaric hypoxia makes the A300 an excellent simulation facility for space flight (tab. 1.1).

Location or facility	Altitude (m.a.s.l.)	Ambient pressure (hPa)	FiO_2	pO_2 (ATP)	pO_2 (BTPS)	pH_2O (hPa)	RQ	$pACO_2$ (hPa)	pAO_2 (hPa)
Sea level	0	1013	0.21	213	200	62.5	0.8	47.9	142
Cabin Space Shuttle (65)	0	703	0.26	183	167	62.5	0.8	47.9	109
Int. Space Station (66)	0	1013	0.21	213	200	62.5	0.8	47.9	142
Cabin A300 Zero-G#	1650	830	0.21	**173**	**160**	62.5	0.8	47.9	**102**
Zugspitze Schneeferner Haus	2650	714	0.21	150	137	62.5	0.8	40	89
Summit of Mt. Everest (67)	8848	253	0.21	53	40	62.5	0.8	17	21
Capanna Margherita (68)	4554	592	0.21	124	111	62.5	0.8	30	76
Concordia Antarctic Station (69)	3233	645	0.21	135	122	62.5	0.8	35	81
Mars/Lunar habitat (65)	4877	552	0.32	**177**	**157**	62.5	0.8	47.9	**99**
Space suit (65)	4877	552	1.0	552	490	62.5	0.8	47.9	432
Scuba diving (20 m)	-20	3039	0.21	638	625	62.5	0.8	47.9	567
PlanHab (70)	900	951	0.15	143	133	62.5	0.8	47.9	75
Hyperbaric oxygen therapy (71)	0	2026	1.0	2026	1964	62.5	0.8	47.9	1906

Table 1.1: The ambient pressure, oxygen fraction and oxygen partial pressures of relevant research facilities are given. Hypoxia in the A300 cabin is similar to theoretical hypoxia in Martian habitats. #, own measurements.

Special consideration should be given to the atmosphere of the A300 with respect to the atmosphere of planned future lunar and Martian habitats. The habitats on the moon and Mars will most likely have an atmospheric pressure that is equivalent to an altitude of approximately 5000 a. m. s. l. and an oxygen fraction of 32% (65). The result of this particular atmosphere would be an only slightly lower partial oxygen pressure than that in the cabin of the A300. However, considering that the partial pressure of water vapor does not depend on the ambient pressure but on the ambient temperature, it becomes clear that this pressure is always 62.5 hPa at 37°C in the lungs. The consequence is that the water vapor pressure would decrease the alveolar oxygen partial pressure more under the conditions of a future lunar and Martian habitat than it does under the conditions of the A300 cabin atmosphere. The result of these considerations is that the level of hypoxia of the A300 cabin and future habitats is comparable, making the A300 an effective

approach to investigate human physiology not only under the gravity conditions of a space flight but also under atmospheric conditions.

1.2.6 Flight medication

The participants of the European parabolic flights aboard the A300 Zero-G receive scopolamine hydrobromide injected subcutaneously before their flight as anti-motion sickness prophylaxis (women: 125 µg; men: 175 µg). Scopolamine has extensively demonstrated its capability in avoiding motion sickness (72). In case of severe in flight motion sickness, certain flight participants receive a second shot during the flight by the flight surgeon. Scopolamine or Hyoscine is an anticholinergic alkaloid drug with muscarinergic antagonistic effects. Except for dry mouth and eyes and slight dizziness, no serious side effects of the drug on the test subjects were observed in the context of this thesis. In particular, there was no distinct tachycardia, and all of the subjects showed a competent orthostatic regulation during their flight.

Figure 1.9: The in-flight experiment setup of the parabolic flight experiment that led to the results of chapters three and four is shown. The experiment team consists of five individuals. The experiment leader is sitting in front of the experiment rack strapped to the ground and triggers the rebreathing maneuvers of the two subjects in weightlessness. The two subjects are free-floating and performing rebreathing maneuvers via a face mask and are only slightly assisted by the two operators behind them. The experiment rack includes two rebreathing devices, two laptops for data storage, two finger blood pressure devices and two ECG and ICG BIOPAC devices. The test tubes for blood sampling are fixed at the front sides of the rack. In the left lower corner, the cooler for blood sampling storage is visible.

1.2.7 Medical considerations of parabolic flights

Participating in a parabolic flight requires a medical checkup before the flights. This checkup can be performed by a specialized flight surgeon or by the family doctor of the participant with the support of the parabolic flight authorities. The checkup is equivalent to a JAR III medical license, which is mandatory for private pilots. Several diseases prevent parabolic flight candidates from participating. Table 1.2 presents an overview about the absolute and relative disease states that complicate or prevent participation.

Exclusion criteria	Expertise of a cardiologist is required	Re-evaluation at a later date
Heart failure	Coronary artery disease	Recently started or changed therapy of arterial hypertension
Myocardial infarction or coronary bypass surgery < 6 months ago	Any type of cardiac arrhythmia and conduction disorder	
Major heart valve anomaly	Any „abnormal“ ECG	
Poorly controlled arterial hypertension	Myocardial infarction or coronary bypass surgery > 6 months ago	
Non-cardioselective β-blockers	Minor heart valve anomaly	
Insulin-dependent diabetes mellitus I° or II°	Accumulation of cardiac risk factors	

Table 1.2: Summary of the medical regulations of the Novespace company (73).

1.3 Ground-based facilities and measurement techniques

Each method that was applied for this thesis is described in detail in later chapters. However, this section aims to bring the methods in line with the medical and clinical context and the medical literature.

1.3.1 The hypobaric chamber at the DLR

The hypobaric chamber (fig. 1.10) at the DLR Institute of Aerospace Medicine in Cologne is a cylindrical tube that is 2.8 meters long and 2 meters high.

Figure 1.10: The hypobaric chamber at the Institute of Aerospace Medicine of the German Aerospace Center in Cologne.

Suction pumps decompress the chamber to create an ambient pressure that is equivalent to any desired altitude. Thus, the chamber is adequate for investigating the effects of short de- and re-compression on the human body, making the chamber essential for medical research in aeronautics and mountaineering. The chamber provides seats for up to 6 people, and experiments can be performed in the sitting and standing positions. Equipment can still be transferred into and out of the chamber during the decompression phase via an air lock. For the experiments of this thesis, the subjects stayed in the chamber for four hours, with three hours of air pressure reduced to 830 mbar.

1.3.2 Blood volume determination by carbon monoxide rebreathing (CORB)

Traditional blood volume determination, based only on hematocrit and hemoglobin values, could not demonstrate its equality in terms of reliability with respect to dye dilution techniques. In particular, the widely used method of Dill and Costill (74) showed an underestimation of blood volume changes of up to 50% during antiorthostatic maneuvers (75). Therefore, the optimized carbon monoxide rebreathing method (CORB) (76) was used for plasma and blood volume determination within the framework of this thesis. This method uses small amounts of carboxy-hemoglobin (COHb) as its dye to determine the total hemoglobin mass (tHb). Carbon monoxide is taken up by the subjects via the lungs by carbon monoxide rebreathing. Measurements of the COHb fraction are performed before and after the carbon monoxide rebreathings via the Radiometer ABL 725 blood gas analyzer (Diamond Diagnostics, MA, USA), which has demonstrated its feasibility for COHb determination (77). For this thesis, a maximal 2-month interval between the CORB procedure and the actual experiments in parabolic flight and hypobaric chamber was met and seemed adequate because the individual total Hb mass is very stable over time. Eastwood and colleagues found a variation in the total Hb mass of only less than 2% over 100 days (78). By assuming the same total hemoglobin mass during the flights and hypobaric chamber runs as that during the actual rebreathing procedure, the intravascular volumes could be calculated from venous blood counts, which were drawn during the flights and the chamber runs. The actual total hemoglobin mass was corrected considering Hb mass loss due to the 16 ml of blood that was drawn at each sampling using the following equation:

$$\left[\mathrm{tHb(g)} - \left(16(\mathrm{ml}) * \mathrm{Hb}\left(\frac{\mathrm{g}}{\mathrm{dl}}\right)\right)\right]$$

The CORB method has demonstrated its feasibility in sports medicine and altitude training physiology predominantly (79, 80). CORB is safe, and carbon monoxide rebreathing has been successfully applied to animals (81) and critical ill patients receiving mechanical ventilation therapy (82, 83). Patients with critical illness in particular suffer from anemia regularly, but an actual threshold below which these patients would benefit from blood transfusion is still lacking. However, in their recent review on anemia in the critically ill, Astin and Puthucheary reported that measuring the total hemoglobin mass (tHb) could be useful for assessing more accurately the transfusion

needs of patients receiving intensive care (84). These authors hypothesized a so-called neocytolysis, a programmed destruction of new red cells, in critically ill patients. Neocytolysis has been demonstrated in astronauts returning to earth and in high-altitude climbers returning to the plain, leading to a reduction in red cell mass in these individuals (85, 86).

1.3.3 Biochemical analyses of parabolic flight and hypobaric chamber blood samples

The blood osmolality was determined in serum by the freezing point depression method (OM 801, Vogel GmbH, Giessen, Germany). In this method, 280–300 mosmol/kg was given by the executing laboratory as a normal range. Albumin was determined in the blood serum by a BCG dye-binding assay (ADVIA 1800, ADVIA Chemistry Systems, Siemens Health Care Diagnostics GmbH, Eschborn, Germany). The albumin normal range was stated as 35.0 – 52.0 g/L. The blood cortisol concentration was determined from the serum by an ELISA assay, with 4.3 – 22.4 µg/dl as the normal range (Siemens ADVIA Centaur Cortisol, Siemens AG, Munich, Germany). The direct renin activity (DRA) measurement was performed in EDTA plasma by a chemiluminescence immuno assay (LIAISON Direct Renin, DiaSorin S.p.A., Saluggia, Italy) (87). The normal range for DRA was set for the upright body position at 2.46 – 25.8 pg/ml. The blood aldosterone concentrations were measured in serum by an ELISA assay (DB 52001, IBL International GmbH, Hamburg, Germany). The aldosterone normal range in the upright body position was given as 40.0 – 310.0 pg/ml. To measure the behavior of arginine vasopressin (AVP) during the parabolic flight and hypobaric chamber tests, we determined the concentration of the C-terminal part of the AVP precursor (copeptin) in the blood serum via an immunofluorescent assay (B·R·A·H·M·S Copeptin us KRYPTOR, B·R·A·H·M·S GmbH, Hennigsdorf, Germany). The normal range of copeptin depends on the blood osmolality. For a blood osmolality between 291 and 300 mosmol/kg, the normal range of copeptin is 2.3 – 28.2 pmol/L. Morgenthaler et al. reported the high stability of copeptin in serum, unlike mature AVP, which can be considered the most relevant advantage of the copeptin assay (88). NT-proBNP, as a stable surrogate of BNP, was determined by a chemiluminescent immunometric assay in the EDTA blood plasma (IMMULITE 2000 systems, Siemens AG, Munich, Germany). The cut-off value for heart failure was set by the laboratory at 125 pg/ml.

1.3.4 Cardiac output determination via inert gas rebreathing

The method of cardiac output determination by inert gas rebreathing was applied in flight and in the hypobaric chamber. For this thesis, the Innocor® device from Innovision® was used, which is a spin-off of the pulmonary function system that is used aboard of the International Space Station. This device is a closed breathing system that uses nitrous oxide (N_2O) as a test gas. The subject inhales and exhales a particular gas mixture from and to a rubber bag. N_2O is taken up by the pulmonary blood flow, the blood flowing through the lungs (fig. 1.9). The amount of N_2O remaining in the exhaled air is measured by a photoacoustic sensor. The amount of N_2O uptake is proportional to the pulmonary blood flow, which is, in turn and in the absence of any significant pulmonary shunt, equivalent to the cardiac output. The bag volume and breathing frequency do not

influence the reliability of the method in a wide range (89, 90). The test subjects performed the rebreathing procedure with a respiratory rate of 20 breaths per minute in approximately 15 seconds. Thus, rebreathing maneuvers form in the limits with least effects on CO, as postulated by Damgaard and Norsk (90). The stroke volume (SV_{rb}) was calculated afterward by dividing the pulmonary blood flow (PBF) by the heart rate (HR) from ECG. The HR determined by Innocor from a finger pulse oxymeter plethysmogram could not be used because Innocor uses the average HR value from a 30-second interval just before the actual rebreathing (personal communication of Innovision). The cardiac index (CI_{rb}) and stroke index (SI_{rb}) were then obtained by dividing the CO_{rb} and SV_{rb} by the body surface area, which was calculated automatically by Innocor using the formula of Du Bois and Du Bois (91).

The very first uptake of N_2O during the first inhalation of a rebreathing is not driven by the pulmonary blood flow but by its rapid uptake into the pulmonary tissues. A similar effect is known in anesthesiology as the *concentration effect* (92). This effect can therefore be used to quantify the volume of the pulmonary tissues. The combined lung tissue volume and capillary blood volume (Vti,c), hence the volume of solvent, are calculated by the Innocor device based on the initial decrease in N_2O concentration (93). Again, it is assumed that the volume of N_2O that is absorbed by the lung is measured during the midinspiratory time of the first inhalation from the bag before the gas is taken up in significant amounts by the capillary blood flow (93-95). Furthermore, the alveolar oxygen consumption (VO_2) is determined by Innocor during rebreathings assuming that the slope of the disappearance curve for O_2 is proportional to the oxygen uptake (93, 96).

In clinical medicine, the method of cardiac output determination by nitrous oxide rebreathing is established in exercise function testing in patients suffering from heart failure or severe lung disease (97, 98). Furthermore, the first attempts have been performed to use the nitrous oxide rebreathing technique for cardiac output determination in critically ill patients receiving mechanical ventilation (99-101). In these cases, a mass spectrometer has been used. In patients with severe lung failure who were treated with artificial ventilation in the prone position, this method was able to identify responders to the prone position by measuring the pulmonary blood flow (102). The Innocor device, as a bedside device, has not yet been adapted for measurements in ventilated patients but has successfully been tested in ventilated dogs (103).

1.3.5 Cardiac output determination via impedance cardiography

Impedance cardiography, a non-invasive and continuous approach, measures the flow changes in the aorta and was developed nearly 50 years ago by WG Kubicek (104, 105). This technique is based on the application of a small alternating current of, for example, 1 mA and 100 kHz via electrodes to the chest. Via further electrodes, the electrical resistance of the thorax is measured. Usually, the electrical current flows along the path of the smallest electrical resistance. Within the chest, the heart and the aorta have the smallest electrical resistance of all of the structures because they contain blood with a very low specific electrical resistance. Therefore, changes in the stroke volume and flow in the aortic arch are related to changes in the thoracic impedance. Based

on the law of Ohm, which states that $U = R \times I$, where U, R and I stand for voltage, resistance and current, respectively, thoracic impedance can be calculated by $R = \frac{U}{I}$. Unfortunately, R is named Z in the context of bioimpedance. As a first basic measure, the first derivate of Z is calculated (dZ/dt). The area under the dZ/dt curve correlates with the cardiac stroke volume (106). Different algorithms exist to determine the actual stroke volume from the bioimpedance signal. For this thesis, the formula of Kubicek was used, which is based on a simplified single cylinder model of the human thorax (105). Kubicek's formula states (107) the following:

$$SV = \rho \times \frac{L^2}{Z_0^2} \times \frac{dZ}{dt_{max}} \times LVET$$

where SV is stroke volume (ml), ρ the resistivity of blood (Ω • cm), L the distance between the voltage measuring electrodes (cm), Z_0 the basic thoracic impedance (Ω), dZ/dt_{max} the maximal impedance change (Ω/s) and LVET the left ventricular ejection time (s). The main determinants of SV are the left ventricular ejection time (LVET) and dZ/dt (108), which lead to a major problem of impedance cardiography, namely the unreliability of the LVET determination. This is shown in figure 1.11.

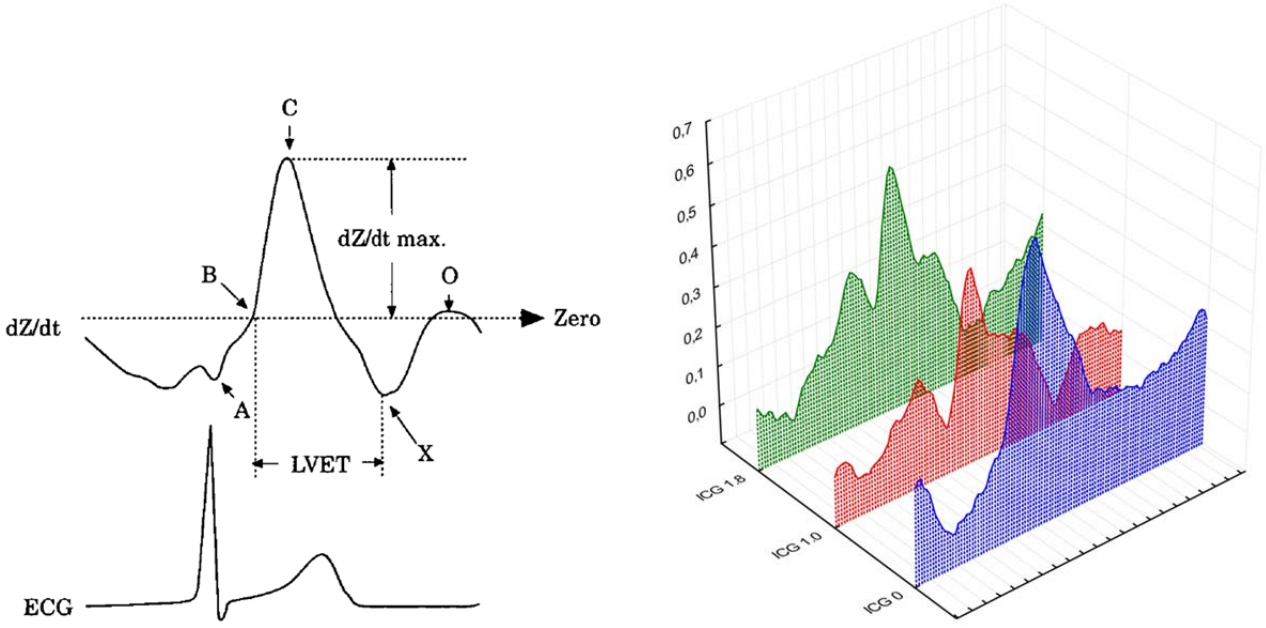

Figure 1.11: The left graph shows the first derivate of the thoracic impedance and a simultaneous ECG recording during a single heartbeat. The B and X points taken as LVET identifier are shown among others. Adapted from (107). The right graph provides a representative recording of the first derivate of the thoracic impedance during a single heart beat in one of the parabolic flight subjects in the standing position in 1.8 G_z (ICG 1.8), 1.0 G_z (ICG 1.0) and microgravity (ICG 0). The change in shape of the curves is clearly visible.

The shape of the first derivate of the thoracic impedance has a certain analogy with the arterial pulse curve. The B and X points determine the ejection period of the left heart chamber. However, the exact location of the X point in particular is usually difficult to detect, and uncertainty in locating

the X point leads to an incorrect ejection period and thus to an incorrect stroke volume. Therefore, bioimpedance has failed to demonstrate its accuracy in cardiac output determination in intensive care patients (109), although its advantages are obvious. In addition to cardiac output, bioimpedance provides information on the heart on a beat-to-beat basis, including systolic time intervals, which are not assessable by other non- or minimally invasive cardiac output monitoring systems (110).

1.3.6 Cardiac output determination via pulse contour analysis

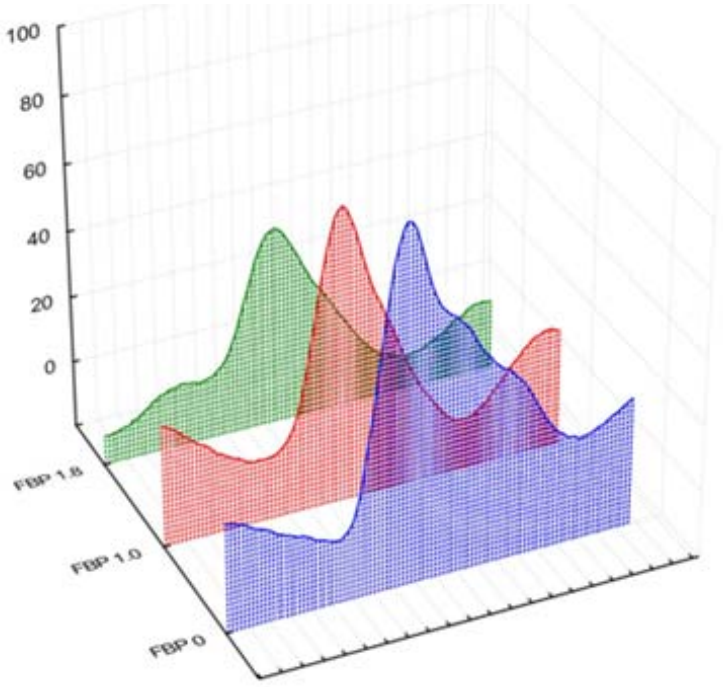

Figure 1.12: Changes in the shape of the non-invasive arterial finger pressure curve during a parabola in a representative upright subject. The green graph was taken in 1.8 G_z, the red graph was taken in 1.0 G_z, and the blue graph was taken in weightlessness. It is clearly visible that the pulse curve at 0 G_z gained a second and a third systolic maximum with respect to 1.0 and hypergravity. Thus, the determination of the systolic time interval (LVET) becomes more difficult.

The famous physiologist Otto Frank thought in 1930 about how to estimate cardiac stroke volume by analyzing of the aortic pressure curve (111). His intention was to obtain a technically simple and cheap method for cardiovascular research (112). The basic idea of stroke volume estimation through pulse curve analysis is that blood pressure and blood flow are correlated. The advantage of stroke volume determination via pulse contour analysis is that the stroke volume can be estimated online on a beat-to-beat basis. Therefore, for this thesis, the pulse curve of the arterial pressure of a finger was measured noninvasively by the volume clamp method of the Czech physiologist J Penáz (113). The Finometer MIDI® device from FMS® system was used for this purpose. However, the sticking point is that based on the pressure, information of the peripheral circulation flow of the central circulation must be back calculated. Wesseling and coworkers developed a generally accepted and widely used non-linear three-element model of the aortic input

impedance. This model calculates an aortic flow waveform from peripheral arterial pressure (114). Their method is based on the area under the systolic pressure curve and on the aortic impedance (115). For this thesis, we used the Modelflow method, which is based on the original Wesseling formula but was developed further and considers more parameters (116). However, in patients receiving cardiac surgery, the method demonstrated its reliability when the radial arterial pressure was measured invasively (117). The measurements of this thesis used non-invasive finger blood pressure measurements; thus, it is important to note that non-invasive and invasive arterial blood pressure measurements agree in healthy subjects under gravitational stress (118). In healthy subjects undergoing a bleeding simulation via a lower body negative pressure test (LBNP), the Modelflow method was therefore able to track progressive hypovolemia (119). On the other hand, a good agreement between invasive and non-invasive beat-to-beat blood pressure measurements is not the case in intensive care patients with peripheral edema or with the need for catecholamine therapy (120). Reflections of the arterial pulse wave lead to the propagation of the peripheral pulse curve and complicate deducing the central circulation. In general, pulse wave reflections increase when the total peripheral resistance decreases (121).

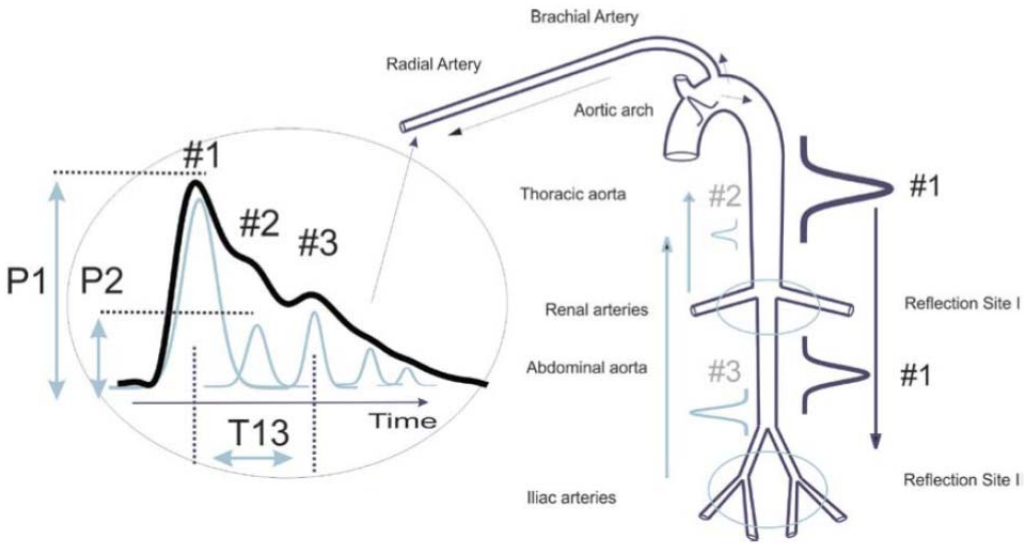

Figure 1.13: The pulse pressure curve of the radial artery includes not only the forward pulse wave of the ejection of the heart but also the backward pulse waves as reflected from the renal arterial branch and the iliac arterial bifurcation. Adapted from (122).

References

1. Rowell LB. Human cardiovascular control: Oxford University Press; 1993.
2. Gelman S, Mushlin PS. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology. 2004;100(2):434-9.
3. Yates BJ. Vestibular influences on cardiovascular control. In: Yates BJ, Miller AD, editors. Vestibular autonomic regulation. Boca Raton: CRC Press; 1996. p. 97-111.
4. Sjostrand T. The regulation of the blood distribution in man. Acta physiologica Scandinavica. 1952;26(4):312-27.
5. Hargens AR, Richardson S. Cardiovascular adaptations, fluid shifts, and countermeasures related to space flight. Respiratory physiology & neurobiology. 2009;169 Suppl 1:S30-3.
6. van Heusden K, Gisolf J, Stok WJ, Dijkstra S, Karemaker JM. Mathematical modeling of gravitational effects on the circulation: importance of the time course of venous pooling and blood volume changes in the lungs. American journal of physiology Heart and circulatory physiology. 2006;291(5):H2152-65.
7. Tarazi RC. Pulmonary blood volume. European heart journal. 1985;6 Suppl C:43.
8. West JB. Respiratory physiology : the essentials. 9th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012. viii, 200 p. p.
9. Henderson AC, Sa RC, Theilmann RJ, Buxton RB, Prisk GK, Hopkins SR. The gravitational distribution of ventilation-perfusion ratio is more uniform in prone than supine posture in the normal human lung. J Appl Physiol (1985). 2013;115(3):313-24.
10. Prisk GK, Paiva M, West JB. Gravity and the lung : lessons from microgravity. New York: M. Dekker; 2001. xii, 383 p. p.
11. Prisk GK. Microgravity and the respiratory system. The European respiratory journal. 2014;43(5):1459-71.
12. Prisk GK. Gas exchange under altered gravitational stress. Comprehensive Physiology. 2011;1(1):339-55.
13. Glenny RW, Lamm WJ, Bernard SL, An D, Chornuk M, Pool SL, et al. Selected contribution: redistribution of pulmonary perfusion during weightlessness and increased gravity. J Appl Physiol (1985). 2000;89(3):1239-48.
14. Glenny RW. Determinants of regional ventilation and blood flow in the lung. Intensive care medicine. 2009;35(11):1833-42.
15. Galvin I, Drummond GB, Nirmalan M. Distribution of blood flow and ventilation in the lung: gravity is not the only factor. British journal of anaesthesia. 2007;98(4):420-8.
16. Latham RD, Fanton JW, White CD, Vernalis MN, Crisman RP, Koenig SC. Circulatory filling pressures during transient microgravity induced by parabolic flight. The Physiologist. 1993;36(1 Suppl):S18-9.
17. Petersen LG, Damgaard M, Petersen JC, Norsk P. Mechanisms of increase in cardiac output during acute weightlessness in humans. Journal of applied physiology. 2011;111(2):407-11.
18. Crystal GJ, Salem MR. The Bainbridge and the "reverse" Bainbridge reflexes: history, physiology, and clinical relevance. Anesthesia and analgesia. 2012;114(3):520-32.
19. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. British journal of anaesthesia. 2012;108(3):384-94.
20. Iwase S, Mano T, Cui J, Kitazawa H, Kamiya A, Miyazaki S, et al. Sympathetic outflow to muscle in humans during short periods of microgravity produced by parabolic flight. The American journal of physiology. 1999;277(2 Pt 2):R419-26.
21. Liu J, Verheyden B, Beckers F, Aubert AE. Haemodynamic adaptation during sudden gravity transitions. European journal of applied physiology. 2012;112(1):79-89.
22. Sear JW. Role of cardiac reflexes in the control of heart rate: what does the anesthesiologist need to know? Anesthesia and analgesia. 2012;114(3):491-3.
23. Caiani EG, Sugeng L, Weinert L, Capderou A, Lang RM, Vaida P. Objective evaluation of changes in left ventricular and atrial volumes during parabolic flight using real-time three-dimensional echocardiography. J Appl Physiol (1985). 2006;101(2):460-8.
24. Johns JP, Vernalis MN, Karemaker JM, Latham RD. Doppler evaluation of cardiac filling and ejection properties in humans during parabolic flight. J Appl Physiol (1985). 1994;76(6):2621-6.
25. Solaro RJ. Mechanisms of the Frank-Starling law of the heart: the beat goes on. Biophysical journal. 2007;93(12):4095-6.
26. Allen DG, Kentish JC. The cellular basis of the length-tension relation in cardiac muscle. Journal of molecular and cellular cardiology. 1985;17(9):821-40.
27. Schlegel TT, Brown TE, Wood SJ, Benavides EW, Bondar RL, Stein F, et al. Orthostatic intolerance and motion sickness after parabolic flight. Journal of applied physiology. 2001;90(1):67-82.
28. Serrador JM, Shoemaker JK, Brown TE, Kassam MS, Bondar RL, Schlegel TT. Cerebral vasoconstriction precedes orthostatic intolerance after parabolic flight. Brain research bulletin. 2000;53(1):113-20.

29. Novak V, Spies JM, Novak P, McPhee BR, Rummans TA, Low PA. Hypocapnia and cerebral hypoperfusion in orthostatic intolerance. Stroke; a journal of cerebral circulation. 1998;29(9):1876-81.
30. Spiller P, Webb-Peploe MM. Blood flow. European heart journal. 1985;6 Suppl C:11-8.
31. Limper U, Gauger P, Beck LE. Upright cardiac output measurements in the transition to weightlessness during parabolic flights. Aviation, space, and environmental medicine. 2011;82(4):448-54.
32. Limper U, Beck P, Gauger P, Beck LE. Das menschliche Herz-Kreislauf-System auf Parabelflügen-Aktuelle Erkenntnisse zu gesundheitlichen Risiken. Flugmedizin· Tropenmedizin· Reisemedizin-FTR. 2013;20(04):166-71.
33. Zawadzka-Bartczak EK, Kopka LH. Cardiac arrhythmias during aerobatic flight and its simulation on a centrifuge. Aviation, space, and environmental medicine. 2011;82(6):599-603.
34. Sakowski C, Starc V, Smith SM, Schlegel TT. Sedentary long-duration head-down bed rest and ECG repolarization heterogeneity. Aviation, space, and environmental medicine. 2011;82(4):416-23.
35. Fritsch-Yelle JM, Leuenberger UA, D'Aunno DS, Rossum AC, Brown TE, Wood ML, et al. An episode of ventricular tachycardia during long-duration spaceflight. The American journal of cardiology. 1998;81(11):1391-2.
36. Clément G. Fundamentals of space medicine. 2nd ed. New York: Springer; 2011. xvii, 381 p. p.
37. Jennings RT, Stepanek JP, Scott LR, Voronkov YI. Frequent premature ventricular contractions in an orbital spaceflight participant. Aviation, space, and environmental medicine. 2010;81(6):597-601.
38. Gelman S. Venous function and central venous pressure: a physiologic story. Anesthesiology. 2008;108(4):735-48.
39. Videbaek R, Norsk P. Atrial distension in humans during microgravity induced by parabolic flights. J Appl Physiol (1985). 1997;83(6):1862-6.
40. Buckey JC. Central venous pressure. In: Prisk GK, Paiva M, West JB, editors. Gravity and the lungs. 1st. New York, NY: Marcel Dekker, Inc.; 2001.
41. Buckey JC, Gaffney FA, Lane LD, Levine BD, Watenpaugh DE, Blomqvist CG. Central venous pressure in space. The New England journal of medicine. 1993;328(25):1853-4.
42. White RJ, Blomqvist CG. Central venous pressure and cardiac function during spaceflight. J Appl Physiol (1985). 1998;85(2):738-46.
43. Guyton AC, Hall JE. Textbook of medical physiology. 11th ed. Philadelphia: Elsevier Saunders; 2006. xxxv, 1116 p. p.
44. Rex S, Brose S, Metzelder S, Huneke R, Schalte G, Autschbach R, et al. Prediction of fluid responsiveness in patients during cardiac surgery. British journal of anaesthesia. 2004;93(6):782-8.
45. Pinsky MR, Teboul JL. Assessment of indices of preload and volume responsiveness. Current opinion in critical care. 2005;11(3):235-9.
46. Perner A, De Backer D. Understanding hypovolaemia. Intensive care medicine. 2014;40(4):613-5.
47. Maas JJ, Pinsky MR, Aarts LP, Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. Anesthesia and analgesia. 2012;115(4):880-7.
48. Prisk GK, Guy HJ, Elliott AR, Deutschman RA, 3rd, West JB. Pulmonary diffusing capacity, capillary blood volume, and cardiac output during sustained microgravity. J Appl Physiol (1985). 1993;75(1):15-26.
49. Brengelmann GL. A critical analysis of the view that right atrial pressure determines venous return. J Appl Physiol (1985). 2003;94(3):849-59.
50. Beard DA, Feigl EO. Understanding Guyton's venous return curves. American journal of physiology Heart and circulatory physiology. 2011;301(3):H629-33.
51. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, et al. The Fontan circulation: who controls cardiac output? Interactive cardiovascular and thoracic surgery. 2010;10(3):428-33.
52. Nayak S, Booker P. The fontan circulation. Continuing Education in Anaesthesia, Critical Care & Pain. 2008;8(1):26-30.
53. Gottlieb EA, Andropoulos DB. Anesthesia for the patient with congenital heart disease presenting for noncardiac surgery. Current opinion in anaesthesiology. 2013;26(3):318-26.
54. Yates BJ, Bolton PS, Macefield VG. Vestibulo-sympathetic responses. Comprehensive Physiology. 2014;4(2):851-87.
55. Ray CA, Monahan KD. The vestibulosympathetic reflex in humans: neural interactions between cardiovascular reflexes. Clinical and experimental pharmacology & physiology. 2002;29(1-2):98-102.
56. Gotoh TM, Fujiki N, Matsuda T, Gao S, Morita H. Roles of baroreflex and vestibulosympathetic reflex in controlling arterial blood pressure during gravitational stress in conscious rats. American journal of physiology Regulatory, integrative and comparative physiology. 2004;286(1):R25-30.
57. Garg A, Xu D, Laurin A, Blaber AP. Physiological interdependence of the cardiovascular and postural control systems under orthostatic stress. American journal of physiology Heart and circulatory physiology. 2014.

58. Yates BJ, Kerman IA. Post-spaceflight orthostatic intolerance: possible relationship to microgravity-induced plasticity in the vestibular system. Brain research Brain research reviews. 1998;28(1-2):73-82.
59. Yates BJ, Stocker SD. Integration of somatic and visceral inputs by the brainstem: functional considerations. Experimental brain research. 1998;119(3):269-75.
60. Lehot F. Voler en apesanteur. Paris: Vuibert; 2012.
61. Gerathewohl J. [Subjective sensations during brief periods of weightlessness]. Rivista di medicina aeronautica. 1957;20(1 Suppl.):17-46.
62. Haber F, Haber H. Possible methods of producing the gravity-free state for medical research. The Journal of aviation medicine. 1950;21(5):395-400.
63. Gauer O, Haber H. Man under gravity-free conditions. German Aviation Medicine, World War II. 1950;1:641.
64. Harding R, Mills FJ. Aviation medicine. London: British Medical Association; 1983. 148 p. p.
65. Norcross J, Norsk P, Law J, Arias D, Conkin J, Perchonok M, et al. Effects of the 8 psi / 32% O2 atmosphere on the human in the spaceflight environment. NASA Technical Reports [Internet]. 2013. Available from: http://ston.jsc.nasa.gov/collections/TRS/_techrep/TM-2013-217377.pdf.
66. Campbell PD, Henninger D. Recommendations for Exploration Spacecraft Internal Atmospheres: the final report of the NASA exploration atmospheres working group. NASA JSC-63309. 2006.
67. West J, Schoene R, Milledge J. High altitude medicine and physiology. 4 ed. London, UK: Hodder Arnold; 2007.
68. Angelini C, Cogo A, Madrigale G, Pecchio O, Posani L. Increased aldosterone levels in acute mountain sickness at Capanna Regina Margherita. Wilderness & environmental medicine. 1997;8(4):247-9.
69. Jourdain B, Preunkert S, Cerri O, Castebrunet H, Udisti R, Legrand M. Year-round record of size-segregated aerosol composition in central Antarctica (Concordia station): Implications for the degree of fractionation of sea-salt particles. Journal of Geophysical Research: Atmospheres (1984–2012). 2008;113(D14).
70. McDonnell AC, Eiken O, Mekjavic PJ, Mekjavic IB. Circadian rhythm of peripheral perfusion during 10-day hypoxic confinement and bed rest. European journal of applied physiology. 2014.
71. Lumb AB, Nunn JF. Nunn's applied respiratory physiology. 6th ed. Edinburgh ; Philadelphia: Elsevier Butterworth Heinemann; 2005. xiii, 501 p. p.
72. Spinks A, Wasiak J. Scopolamine (hyoscine) for preventing and treating motion sickness. The Cochrane database of systematic reviews. 2011(6):Cd002851.
73. NOVESPACE. Parabolic flight medical document: http://www.airzerog.com/images/upload/medical_document_2013_ed4_en.pdf 2013 [updated September 2013].
74. Dill DB, Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. Journal of applied physiology. 1974;37(2):247-8.
75. Johansen LB, Videbaek R, Hammerum M, Norsk P. Underestimation of plasma volume changes in humans by hematocrit/hemoglobin method. The American journal of physiology. 1998;274(1 Pt 2):R126-30.
76. Schmidt W, Prommer N. The optimised CO-rebreathing method: a new tool to determine total haemoglobin mass routinely. European journal of applied physiology. 2005;95(5-6):486-95.
77. Andersson MF, Moller AM. Assessment of carbon monoxide values in smokers: a comparison of carbon monoxide in expired air and carboxyhaemoglobin in arterial blood. European journal of anaesthesiology. 2010;27(9):812-8.
78. Eastwood A, Hopkins WG, Bourdon PC, Withers RT, Gore CJ. Stability of hemoglobin mass over 100 days in active men. Journal of applied physiology. 2008;104(4):982-5.
79. Wachsmuth NB, Volzke C, Prommer N, Schmidt-Trucksass A, Frese F, Spahl O, et al. The effects of classic altitude training on hemoglobin mass in swimmers. European journal of applied physiology. 2013;113(5):1199-211.
80. Prommer N, Thoma S, Quecke L, Gutekunst T, Volzke C, Wachsmuth N, et al. Total hemoglobin mass and blood volume of elite Kenyan runners. Medicine and science in sports and exercise. 2010;42(4):791-7.
81. Heltne JK, Farstad M, Lund T, Koller ME, Matre K, Rynning SE, et al. Determination of plasma volume in anaesthetized piglets using the carbon monoxide (CO) method. Laboratory animals. 2002;36(3):344-50.
82. Sawano M, Mato T, Tsutsumi H. Bedside red cell volumetry by low-dose carboxyhaemoglobin dilution using expiratory gas analysis. British journal of anaesthesia. 2006;96(2):186-94.
83. Dingley J, Foex BA, Swart M, Findlay G, DeSouza PR, Wardrop C, et al. Blood volume determination by the carbon monoxide method using a new delivery system: accuracy in critically ill humans and precision in an animal model. Critical care medicine. 1999;27(11):2435-41.
84. Astin R, Puthucheary Z. Anaemia secondary to critical illness: an unexplained phenomenon. Extreme physiology & medicine. 2014;3(1):4.

85. Rice L, Alfrey CP. Modulation of red cell mass by neocytolysis in space and on Earth. Pflugers Archiv : European journal of physiology. 2000;441(2-3 Suppl):R91-4.
86. Rice L, Ruiz W, Driscoll T, Whitley CE, Tapia R, Hachey DL, et al. Neocytolysis on descent from altitude: a newly recognized mechanism for the control of red cell mass. Annals of internal medicine. 2001;134(8):652-6.
87. Rossi GP, Barisa M, Belfiore A, Desideri G, Ferri C, Letizia C, et al. The aldosterone-renin ratio based on the plasma renin activity and the direct renin assay for diagnosing aldosterone-producing adenoma. Journal of hypertension. 2010;28(9):1892-9.
88. Morgenthaler NG, Struck J, Jochberger S, Dünser MW. Copeptin: clinical use of a new biomarker. Trends in Endocrinology & Metabolism. 2008;19(2):43-9.
89. Saur J, Kraus F, Brade J, Haghi D, Behnes M, Hoffmann U, et al. Influence of Bag Volume on Reproducibility of Inert Gas Rebreathing Pulmonary Blood Flow Measurements in Patients with Pulmonary Diseases. Lung. 2013:1-7.
90. Damgaard M, Norsk P. Effects of ventilation on cardiac output determined by inert gas rebreathing. Clinical physiology and functional imaging. 2005;25(3):142-7.
91. Du Bois D, Du Bois EF. Clinical calorimetry: tenth paper a formula to estimate the approximate surface area if height and weight be known. Archives of internal medicine. 1916;17(6_2):863.
92. Leslie RA. Dr Podcast scripts for the final FRCA. Cambridge ; New York: Cambridge University Press; 2011. xvi, 498 p. p.
93. Clemensen P, Christensen P, Norsk P, Gronlund J. A modified photo- and magnetoacoustic multigas analyzer applied in gas exchange measurements. Journal of applied physiology. 1994;76(6):2832-9.
94. Sackner MA, Feisal KA, Dubois AB. Determination of Tissue Volume and Carbon Dioxide Dissociation Slope of the Lungs in Man. Journal of applied physiology. 1964;19:374-80.
95. Cander L, Forster RE. Determination of pulmonary parenchymal tissue volume and pulmonary capillary blood flow in man. Journal of applied physiology. 1959;14(4):541-51.
96. Lang CC, Karlin P, Haythe J, Tsao L, Mancini DM. Ease of noninvasive measurement of cardiac output coupled with peak VO2 determination at rest and during exercise in patients with heart failure. The American journal of cardiology. 2007;99(3):404-5.
97. Corte TJ, Wells AU, Gatzoulis MA, Cramer D, Ward S, Macdonald PS, et al. Non-invasive assessment of pulmonary blood flow using an inert gas rebreathing device in fibrotic lung disease. Thorax. 2010;65(4):341-5.
98. Agostoni P, Cattadori G, Apostolo A, Contini M, Palermo P, Marenzi G, et al. Noninvasive measurement of cardiac output during exercise by inert gas rebreathing technique: a new tool for heart failure evaluation. Journal of the American College of Cardiology. 2005;46(9):1779-81.
99. Reutershan J, Kapp T, Unertl K, Fretschner R. [Noninvasive determination of cardiac output in ventilated patients . Clinical evaluation of a simplified quick method]. Der Anaesthesist. 2003;52(9):778-86.
100. Reutershan J, Ressel M, Wagner T, Schroder T, Dietz K, Fretschner R. Non-invasive determination of effective pulmonary blood flow: evaluation of a simplified rebreathing method. Journal of medical engineering & technology. 2003;27(5):194-9.
101. Christensen P, Clemensen P, Andersen PK, Henneberg SW. Thermodilution versus inert gas rebreathing for estimation of effective pulmonary blood flow. Critical care medicine. 2000;28(1):51-6.
102. Reutershan J, Schmitt A, Dietz K, Fretschner R. Non-invasive measurement of pulmonary blood flow during prone positioning in patients with early acute respiratory distress syndrome. Clinical science (London, England : 1979). 2004;106(1):3-10.
103. Nickl W, Bugaj T, Mondritzki T, Kuhlebrock K, Dinh W, Krahn T, et al. Non-invasive assessment of cardiac output during mechanical ventilation - a novel approach using an inert gas rebreathing method. Biomedizinische Technik Biomedical engineering. 2011;56(3):147-51.
104. Kubicek WG. On the source of peak first time derivative (dZ/dt) during impedance cardiography. Annals of biomedical engineering. 1989;17(5):459-62.
105. Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. Aerospace medicine. 1966;37(12):1208-12.
106. Kramme Rd, Hoffmann K-P, Pozos RS. Springer handbook of medical technology. Berlin: Springer; 2011. xlvi, 1500 p. p.
107. Woltjer HH, Bogaard HJ, de Vries PM. The technique of impedance cardiography. European heart journal. 1997;18(9):1396-403.
108. Moertl MG, Schlembach D, Papousek I, Hinghofer-Szalkay H, Weiss EM, Lang U, et al. Hemodynamic evaluation in pregnancy: limitations of impedance cardiography. Physiological measurement. 2012;33(6):1015-26.
109. de Waal EE, Konings MK, Kalkman CJ, Buhre WF. Assessment of stroke volume index with three different bioimpedance algorithms: lack of agreement compared to thermodilution. Intensive care medicine. 2008;34(4):735-9.

110. Lewis RP. The use of systolic time intervals for evaluation of left ventricular function. Cardiovascular clinics. 1983;13(3):335-53.
111. Frank O. Schätzung des Schlagvolumens des menschlichen Herzens auf Grund der Wellen-und Windkesseltheorie. Z Biol. 1930;90:405-9.
112. Reuter DA, Goetz AE. [Measurement of cardiac output]. Der Anaesthesist. 2005;54(11):1135-51; quiz 52-3.
113. Penaz J, Voigt A, Teichmann W. [Contribution to the continuous indirect blood pressure measurement]. Zeitschrift fur die gesamte innere Medizin und ihre Grenzgebiete. 1976;31(24):1030-3.
114. Bogert LW, van Lieshout JJ. Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. Experimental physiology. 2005;90(4):437-46.
115. Jansen JR, Wesseling KH, Settels JJ, Schreuder JJ. Continuous cardiac output monitoring by pulse contour during cardiac surgery. European heart journal. 1990;11 Suppl I:26-32.
116. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol (1985). 1993;74(5):2566-73.
117. Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. British journal of anaesthesia. 2001;87(2):212-22.
118. Normand H, Lemarchand E, Arbeille P, Quarck G, Vaida P, Duretete A, et al. Beat-to-beat agreement of noninvasive tonometric and intra-radial arterial blood pressure during microgravity and hypergravity generated by parabolic flights. Blood pressure monitoring. 2007;12(6):357-62.
119. Reisner AT, Xu D, Ryan KL, Convertino VA, Rickards CA, Mukkamala R. Monitoring non-invasive cardiac output and stroke volume during experimental human hypovolaemia and resuscitation. British journal of anaesthesia. 2011;106(1):23-30.
120. Hohn A, Defosse JM, Becker S, Steffen C, Wappler F, Sakka SG. Non-invasive continuous arterial pressure monitoring with Nexfin does not sufficiently replace invasive measurements in critically ill patients. British journal of anaesthesia. 2013;111(2):178-84.
121. van den Bogaard B, Westerhof BE, Best H, Davis SC, Secher NH, van den Born BJ, et al. Arterial wave reflection decreases gradually from supine to upright. Blood pressure. 2011;20(6):370-5.
122. Baruch MC, Warburton DE, Bredin SS, Cote A, Gerdt DW, Adkins CM. Pulse Decomposition Analysis of the digital arterial pulse during hemorrhage simulation. Nonlinear biomedical physics. 2011;5(1):1.

Chapter Two

Upright Cardiac Output Measurements in the Transition to Weightlessness during Parabolic Flights (*Aviation, Space, and Environmental Medicine 2011; 82(4):448-454*)

Ulrich Limper[1], Peter Gauger[2], and Luis E. J. Beck[2]

[1] University of Witten/Herdecke, Department of Anesthesiology and Intensive Care Medicine, Merheim Medical Center, Hospitals of Cologne, Cologne, Germany

[2] DLR-Institute of Aerospace Medicine, Cologne, Germany

RESEARCH ARTICLE

Upright Cardiac Output Measurements in the Transition to Weightlessness During Parabolic Flights

Ulrich Limper, Peter Gauger, and Luis E. J. Beck

Limper U, Gauger P, Beck LEJ. *Upright cardiac output measurements in the transition to weightlessness during parabolic flights.* **Aviat Space Environ Med 2011; 82:448–54.**

Objective: Aims of this study were: 1) to determine cardiac output by inert gas rebreathing (CO_{reb}) during transition into 0 G_z in the standing position; and 2) to compare impedance cardiography (ICG) and pulse contour method (PCM) with CO_{reb} as a reference method. ***Methods:*** We measured baseline CO_{reb} and heart rate (HR) on the ground, and CO_{reb}, CO_{pcm}, CO_{icg}, and HR in standing and supine positions in the transition to weightlessness in six subjects. We conducted repeated measures ANOVA, Bland and Altman analysis, and analysis of percentage error of each data set. ***Results:*** CO_{reb} rose from 5.03 ± 0.7 upright ground control to 11.45 ± 3.6 L · min^{-1} in 0 G_z. HR and stroke volume (SV) rose from 83 ± 14 to 113 ± 19 bpm and from 61 ± 6 to 99 ± 18 ml, respectively. Mean CO_{reb}, CO_{pcm}, and CO_{icg} across all conditions were 10.45 ± 3.04, 7.42 ± 1.71, and 6.57 ± 2.46 L · min^{-1}, respectively. Overall Bland and Altman analysis showed poor agreement for CO_{pcm} and CO_{icg} compared to CO_{reb}. ***Discussion:*** Large bias for both comparisons indicated that both PCM and ICG underestimate the true CO value. Paired CO values of individual subjects showed a better correlation between methods and a broad bias range, indicating a preponderant role for large between-subjects variability. Repeated CO_{reb} determinations in 1 G_z (i.e., when the cardiovascular system is in a steady state) should be used for calibration of the PCM and of ICG data. PCM and ICG can then be used to track CO dynamics during rapid changes of acceleration profiles.

Keywords: weightlessness, cardiac output, inert gas rebreathing, pulse contour analysis, impedance cardiography.

CARDIAC OUTPUT is a fundamental variable to analyze the response of the cardiovascular system during transition into microgravity. Although hemodynamics in the transition to weightlessness has been of high interest for physiological research for decades, the rapid responses of the cardiovascular system to the very initial effects of microgravity are not yet completely understood. Parabolic flights represent a valuable means to further our understanding of this subject.

Three established methods to determine cardiac output (CO) non-invasively are inert gas rebreathing (9,20), pulse contour analysis (PCM) (10), and impedance cardiography (ICG) (8). ICG and PCM provide reliable methods to track relative stroke volume (SV) changes during rapid physiologic hemodynamic transitions. CO determination by inert gas rebreathing and by ICG has been tested under microgravity induced by parabolic flights providing coherent data sets for CO and SV. Norsk et al. (17) observed an increase of around 30% in CO determined by inert gas rebreathing in the sitting position during microgravity. Schlegel et al. (21) showed an increase in CO of about 50% in the sitting position in microgravity by ICG. Until now, inert gas rebreathing for CO determination has neither been applied during the transition into microgravity in the standing position, nor has it been compared, as a method providing absolute cardiac outputs, with the relative CO values derived from ICG and PCM during this particular condition.

Therefore, the aims of this study were twofold: 1) to get accurate CO determinations by inert gas rebreathing in the standing position in 0 G_z; and 2) to compare rebreathing cardiac outputs (CO_{reb}) with those obtained by PCM (CO_{pcm}) and ICG (CO_{icg}) to assess the reliability of these methods during parabolic flights. Also of special interest was the operational question of whether it is possible to obtain accurate CO_{reb} with a method that requires highly compliant subjects who have to keep predetermined breathing parameters in the standing position during acceleration changes in the uneasy environment of a parabolic flight.

METHODS

Subjects

Six healthy test subjects (1 woman and 5 men; 39.7 ± 11.7 yr; 178.2 ± 5.8 cm; 77.5 ± 13.6 kg) participated in a parabolic flight campaign performed by NOVESPACE in Bordeaux, France, and sponsored by the European Space Agency. All of the test subjects had experienced parabolic flights previously. The study protocol was approved in advance by the pertinent French authorities (Agence française de securité sanitaire des produits de sanité). Each subject provided written informed consent before participating. Five of six subjects received scopolamine-hydrobromide injected subcutaneously as antimotion sickness medication [175 μg (men), 125 μg (women)]. One of the male test subjects flew without any medication.

From the German Aerospace Center (DLR), Institute of Aerospace Medicine, Space Physiology, Cologne, Germany.

This manuscript was received for review in July 2010. It was accepted for publication in November 2010.

Address correspondence and reprint requests to: Mr. Luis E. J. Beck, German Aerospace Center (DLR), Institute of Aerospace Medicine, Space Physiology, Linder Höhe, 51147 Köln, Germany; Luis.Beck@dlr.de.

DOI: 10.3357/ASEM.2883.2011

None of the test subjects received any scopolamine medication during CO_{reb} measurements on the ground.

Study Design

We measured CO_{reb}, continuous beat-by-beat finger blood pressure, one-lead ECG, ICG, and respiratory movements in two subjects per day during a 3-d parabolic flight campaign. Typically, 31 parabolas are flown in each flight day. After the first parabola (numbered '0'), 2 sets of 15 parabolas each, separated by an 8–10 min break, are flown. Each set consists of three sequences of five parabolas. Short 4–5 min breaks delimit the sequences. Each subject completed an individual number of parabolas in the supine ($N = 6$) and standing ($N = 6$) positions [supine three parabolas (range one to four parabolas); standing four parabolas (range two to six parabolas)]. We adopted a rigorous rebreathing procedure that was triggered by the pilot's announcements of trajectory: 1) "Pull Up," with increased G_z load of up to 1.8 G_z; 2) "20," "30," and "40," which meant the rising angle of attack of the airplane; 3) "Injection," with rapid fall of G_z load to around ± 0.05 G_z; and 4) "Pull Out," with increased G_z load of up to 1.8 G_z. Each phase lasted approximately 20-25 s. Controlled rebreathing was initiated during the last pull-up seconds, started at the pilot's announcement "40" so that the breaths relevant for CO determination fell during the 0-g phase and the rebreathing maneuver was completed before pull out.

CO determinations on the ground were performed exclusively by inert gas rebreathing. Neither finger blood pressure nor impedance cardiography data were collected on the ground. Ground measurements were obtained at the German Aerospace Center in Cologne a week before the flights. Three to four measurements were performed in each subject both in the supine and standing body positions in the morning.

Inert Gas Rebreathing

CO_{reb} was determined with a commercial inert gas rebreathing device, INNOCOR® (Innovision A/S, Odense, Denmark). The test subjects breathe ambient air through a facemask fitted around nose and mouth. When a CO_{reb} is required, the system switches to a closed rebreathing mode. A respiration bag is automatically filled with a gas mixture composed of 29.5% O_2 in N_2, 0.5% N_2O (soluble tracer gas), and 0.1% SF_6 (non-soluble tracer gas). In our study, the volume of the respiration bag was around 40% of the vital capacity of the test subject (1.7 – 2.5 L). During rebreathing, an amount of the soluble gas disappears from the alveoli due to solution in tissue and pulmonary blood flow. The non-soluble gas distributes evenly in the whole lung-airways-tubing space and serves total system volume calculation. The gas concentrations are measured during expiration by a photoacoustic and magneto-acoustic multigas analyzer connected to the facemask as described by Clemensen et al. (4). The pulmonary blood flow, which, in the absence of significant shunts, is equal to cardiac output, is calculated on the basis of soluble tracer gas disappearance rate, the total volume of the system, and the Bunsen solubility coefficient of the tracer gas in blood. In this study, the test subjects performed the rebreathing procedure with a respiratory rate of 20 breaths per minute in around 15 s. Thus, rebreathing maneuvers lay in the limits with least effects on CO, as postulated by Damgaard and Norsk (6). Heart rate (bpm) was calculated as the inverse of the R wave to R wave interval, the peak-to-peak interval determined from the pulse oximeter plethysmogram of the inert gas rebreathing device. SV (ml) was calculated by dividing CO ($L \cdot min^{-1}$) with heart rate (bpm) multiplied by 1000 (SV = CO/HR*1000).

Beat-by-Beat Finger Blood Pressure

Continuous beat-by-beat finger blood pressure was measured with a Portapres® device [Finapres Medical Systems (FMS), Amsterdam, The Netherlands], which uses a photoplethysmographic technique based on the volume clamp method first introduced by the Czech physiologist J. Peñáz (18). The finger cuff was placed around the third finger of the left hand and the left hand was fixed by a bandage at the level of the fourth intercostal space as the assumed level of the heart. For calculation of SV_{pcm} from finger blood pressure, the nonlinear three-element model of Wesseling et al. (25) was used. CO_{pcm} was then calculated as the product of SV_{pcm} and heart rate derived from ECG tracings.

Thoracic Impedance

We used the BIOPAC impedance plethysmography device (BIOPAC Systems, Goleta, CA) to record the respiratory movements of the thorax and the ICG. Thoracic impedance changes allowed the identification of the three breaths used for calculation of CO_{reb} (**Fig. 1**). Thus, the continuous blood pressure epochs used for calculation of CO_{pcm} could be also easily delimited. The test subjects were instrumented with two pairs of electrodes on the back. The first derivative of the thoracic impedance signal (dZ/dt, also called ICG) was used to derive SV surrogates according to Kubicek et al. (13). CO_{icg} was calculated by multiplying the SV_{icg} with heart rate derived from ECG.

Data Analysis

We evaluated a total of 81 (42 ground and 39 flight) inert gas rebreathing data sets, 29 in-flight ICG and 39 in-flight PCM datasets. We compared 0 G_z CO_{reb} data of consecutive sets for reproducibility. PCM and ICG beat-by-beat SV and CO data were averaged across the three relevant breaths required for the measurement of CO_{reb}, and these averages were then handled as single data points for further analysis. We calculated the Pearson's correlation coefficient between CO_{reb} and CO_{pcm}, and between CO_{reb} and CO_{icg}. The same paired measurements were then compared according to Bland and Altman (2); i.e., we calculated the bias (mean difference between paired measurements) and its standard deviation for CO_{reb} and CO_{pcm}, and for CO_{reb} and CO_{icg}. The limits of agreement between two methods

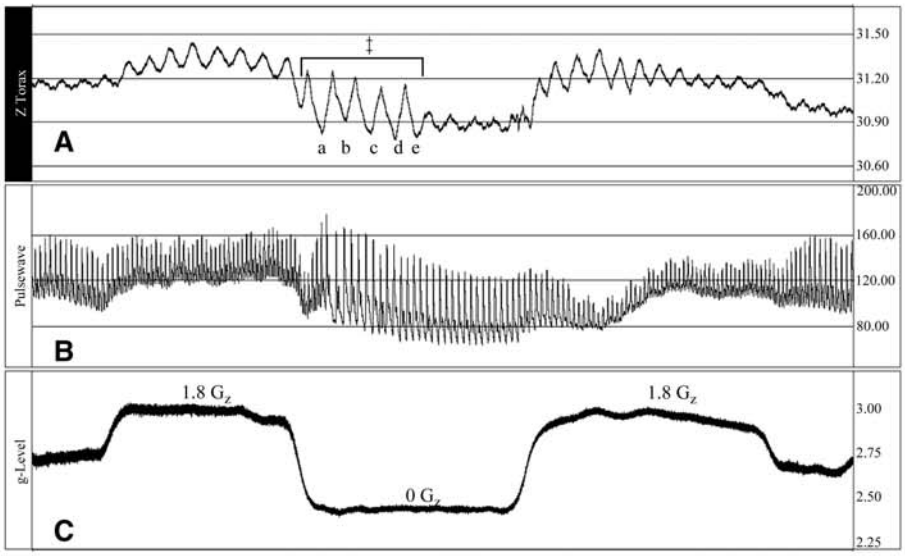

Fig. 1. Original recording of A) transthoracic impedance (Ohms); B) finger pressure wave (mmHg); and C) gravity in direction z (volts, not converted accelerometer output) collected from a representative standing test subject during a parabola. ‡ The lower case characters a to e in panel A mark the end of expiration of five distinguishable breaths of a complete CO_{reb} measurement.

were calculated as the mean difference ± 1.96 SD. We also determined percentage error (2 SD/mean CO ·100) following the Critchley and Critchley (5) recommendation. Additionally, the relative error of each data set was calculated by relating the difference between paired measurements to their average values [relative error (%) = 100 (CO_{pcm} – CO_{reb}) / 0.5 (CO_{pcm} + CO_{reb}) and correspondingly for ICG]. Repeated measures ANOVA and Tukey's Honestly Significant Difference test were done to show the level of significance of CO_{reb} in 1 G_z compared to 0 G_z. $P = 0.05$ was taken as the minimum level of significance. All statistical analyses were performed using Statistica 8 (StatSoft, Inc., Tulsa, OK).

RESULTS

Cardiac output had a good reproducibility in the standing position on the ground. Two consecutive CO_{reb} measurements did not show any significant difference ($P = 0.817$). During weightlessness, repeated CO_{reb} measurements did not reach the level of significance, either ($P = 0.073$). As depicted in **Fig. 2**, panel A, transition into weightlessness in the standing position increased CO_{reb} by 130 ± 75% to 11.45 ± 3.6 L · min^{-1} from 5.03 ± 0.7 L · min^{-1} standing ground control ($P = 0.001$) and by 63% from 7.08 ± 1.49 L · min^{-1} supine ground control ($P = 0.010$). Supine CO_{reb} (9.11 ± 2.13 L · min^{-1}) measured in the transition to weightlessness was not significantly different to supine ground control ($P = 0.227$) and it did not reach the significance level ($P = 0.082$) when compared to standing in weightlessness, either.

Fig. 2, panel B, shows that transition into weightlessness in the standing position increased SV_{reb} by 63 ± 29% to 99 ± 18 ml from 61 ± 6 ml standing ground control ($P = 0.003$) and that it was nearly identical to supine ground control (96 ± 16 ml, $P = 0.999$). Supine SV_{reb} (99 ± 18 ml) measured in the transition to weightlessness was similar to supine ground control ($P = 0.859$) and to standing in weightlessness ($P = 0.999$).

Panel C of Fig. 2 shows that HR rose by 40% from 83 ± 14 to 113 ± 19 bpm ($P = 0.012$) during transition into weightlessness in the standing position with respect to standing ground control and by 59% from 72 ± 9 to 113 ± 19 bpm ($P = 0.003$) when compared to supine ground control. HR did not reach the significance level during transition into weightlessness in the supine position with respect to supine ground control ($P = 0.057$), but it rose significantly during transition into weightlessness in the upright posture compared to supine position under zero gravity (23% from 92 ± 15 to 113 ± 18 bpm, $P = 0.046$).

The correlation between CO_{reb} and CO_{pcm} was relatively poor with a coefficient of 0.578 ($P < 0.001$) for all flight measurements taken together. Mean CO_{reb} and CO_{pcm} were 10.45 ± 3.04 L · min^{-1} (range 5.25 to 16.23 L · min^{-1}), and 7.42 ± 1.71 L · min^{-1} (range 4.15 to 11.17 L · min^{-1}), respectively. **Fig. 3** shows a Bland and Altman plot of simultaneous CO_{reb} and CO_{pcm} measurements performed in standing and supine positions in microgravity. Percentage error was 58% and 46% for CO_{reb} and CO_{pcm}, respectively. The bias was 3.03 ± 2.48 L · min^{-1}. The limits of agreement were 7.81 and −1.83 L · min^{-1}. The relative error was 31 ± 26%. The correlation between CO_{reb} and CO_{icg} yielded a coefficient of 0.778 ($P < 0.001$) for all flight measurements taken together. The distribution of the individual data sets also shows considerable between-subjects variability, especially with regard to absolute values.

Fig. 4 shows a Bland and Altman plot of simultaneous CO_{reb} and CO_{icg} measurements performed in standing and supine positions in microgravity. Mean CO_{icg} was 6.57 ± 2.46 L · min^{-1} (range 3.45 to 10.25 L · min^{-1}). Percentage error for CO_{icg} was 74%. The bias was

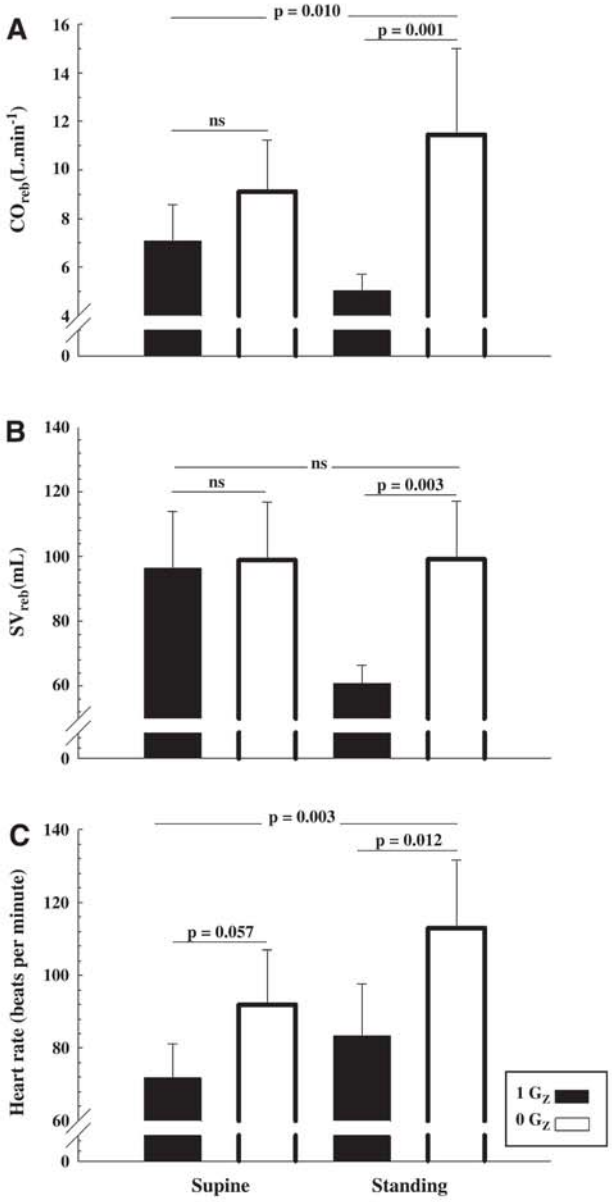

Fig. 2. A) Cardiac output (L · min^{-1}) measured by inert gas rebreathing. B) Stroke volume (ml) calculated by dividing cardiac output (L · min^{-1}) with heart rate (bpm). C) Heart rate (bpm) determined from a pulse oximeter plethysmogram. Mean values and SD, $N = 6$, in supine position on the ground and during transition into weightlessness, and standing on the ground and during transition into weightlessness; ns = non-significant.

3.76 ± 1.92 L · min^{-1}. The limits of agreement between the two methods were 7.53 and -0.01 L · min^{-1}. The relative error was 47 ± 26%.

DISCUSSION

With this study, we are the first to show that, using a stringent procedure, it is possible to measure CO by inert gas rebreathing in the standing position when entering weightlessness during parabolic flights. The variance

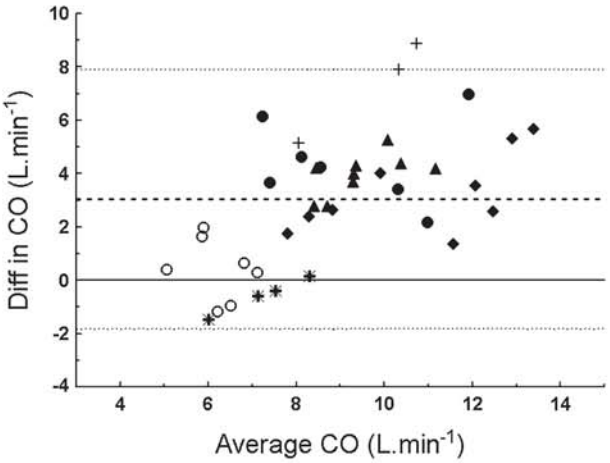

Fig. 3. Difference against mean for CO data measured with inert gas rebreathing and pulse contour method of finger blood pressure. Diff in CO = CO_{reb} − CO_{pcm}; Average CO = (CO_{reb} + CO_{pcm})/2; dashed line = mean value of the differences; dotted lines = mean value ± 1.96 SD; different symbols identify different test subjects.

of CO_{reb} in 0 G_z was, however, larger than the variance of repeated ground measurements and there seems to be a tendency for cardiac output to decrease along a flight day. A *P*-value of 0.073 might well just reflect the low power resulting from the small sample size and the larger variance of CO_{reb} determinations, which may be due to a large extent to a time-dependent component effective during the flight.

Compared with the preflight standing posture, our data show a significant rise of both CO_{reb} and SV_{reb} during transition into weightlessness. This observation is consistent with that of Mukai et al. (15), who found an increased impedance heart index in the 0 G_z standing position compared to 1 G_z. Norsk et al. (17) reported a rise in CO_{reb} of 30% when entering 0 G_z in the seated

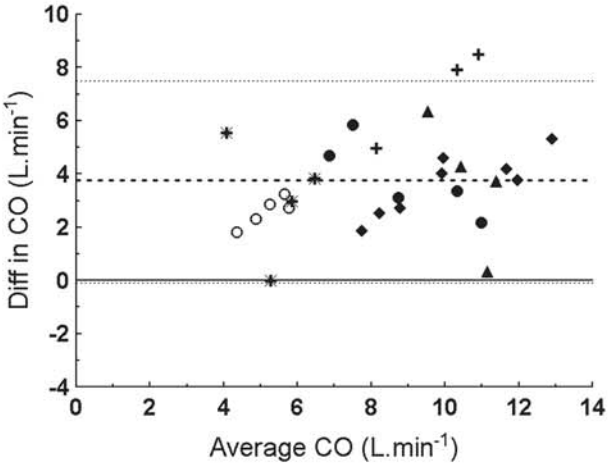

Fig. 4. Difference against mean for CO data measured with inert gas rebreathing and impedance cardiography. Diff in CO = CO_{reb} − CO_{icg}; Average CO = (CO_{reb} + CO_{icg})/2; dashed line = mean value of the differences; dotted lines = mean value ± 1.96 SD; symbols as in Fig. 3.

position. Dominique et al. (7) observed a 70% SV rise in young male subjects standing passively on a platform positioned at a 60° angle with respect to the airplane floor. Our data show an even larger rise in CO_{reb} when entering 0 G_z in the upright, standing position that amounts to 130% of standing and to 63% of supine ground measurements. In contrast to Norsk et al. (17), we found a rise in HR during transition into weightlessness with respect to the ground control, which seems to be partly responsible for the larger rise in CO_{reb} during transition into weightlessness during standing compared to a sitting position. It is unlikely that this rise in HR is caused by subcutaneous scopolamine, which was given only during the flights and not during the data collection on the ground. In accordance with this, Mayer found a decrease in HR and CO after application of 0.5 mg scopolamine subcutaneously under both resting and physical loading conditions (14). Although all of our test subjects had experienced parabolic flights before, we cannot rule out an emotional component contributing to the heart rate increase. We also found higher HR when entering weightlessness in the standing than in the supine position, which might be due to the increased physical load during standing upright compared to lying down during the 1.8-g period before injection into weightlessness.

Additionally, a larger central blood volume increase in the 0 G_z standing position compared to the 0 G_z seated position may well account for differences in SV and CO. Standing in 0 G_z facilitates venous return compared to sitting in 0 G_z due to less 'kinking' of the deep veins in the standing position. The increased central blood volume leads to larger CO through the Frank-Starling mechanism as reviewed by Truijen et al. (24). A distended right atrium as indicator for elevated central blood volume as adaption to microgravity was reported by Johns et al. (11). Notably, SV in the upright position in weightlessness were not different from supine ground SV, although the HR were significantly larger when upright in weightlessness than supine on the ground. This supports the view of an increased filling of the heart chambers leading to a more effective ejection through the Frank-Starling mechanism.

Accurate measurements of cardiac output are difficult to obtain. Critchley and Critchley (5) reviewed current methods for the measurement of CO and concluded that CO measurement lacks precision. They reported that an error of about 20% is usual for thermodilution measurements, the currently used clinical standard and reference method for CO determination. Shoemaker et al. (22) pointed out that such errors arise from cyclical changes in CO due mainly to respiration. CO by inert gas rebreathing, a method that compares well with thermodilution as reported by Tamera et al. (23), yields similar errors. According to Peyton et al. (19), the 95% confidence limits for a single CO determination by inert gas rebreathing of ±30% can be reduced to ±15% if four successive measurements are averaged. However, this recommendation for averaging multiple measurements to improve the reliability of CO_{reb} determination conflicts with the necessity of performing singular measurements to avoid a systematic error that would result by ignoring the tendency for CO to decrease along a flight day.

Another relevant aspect is that CO_{reb} determination needs a steady state of pulmonary blood flow and this is not warranted when entering weightlessness during parabolic flights. Schlegel et al. (21) reported that SV, measured by ICG in a sitting position, increases steadily for approximately 17 s from the beginning of weightlessness. Johns et al. (12) evaluated stroke volume by echocardiography in sitting subjects during parabolic flight. Their observation of significantly higher SV in late zero gravity with respect to early zero gravity is in good agreement with Schlegel et al. (21). In contrast to that, Dominique et al. (7) report a time constant of about 3 s for SV_{icg} to reach a stationary state in subjects standing passively on a platform positioned at a 60° angle with respect to the airplane floor. We believe that these results arise from two fundamental different time constants for volume shift during transition into weightlessness in the sitting position compared to the standing position. Taken together, these data would suggest a restricted applicability of CO_{reb} when going into weightlessness. The time course of SV in the standing position seems to be better compatible with theoretical requirements of the inert gas rebreathing method than the sitting position.

Overall Bland and Altman analysis shows poor agreement for CO_{pcm} and CO_{icg} compared to CO_{reb}. It yielded large bias for both comparisons in our sample, indicating that both PCM and ICG underestimate the true CO value, which is considered to be better represented by the inert gas rebreathing determinations. However, underestimation of CO by bioimpedance under conditions with very high cardiac outputs was found by Shoemaker et al. (22). Both correlation and Bland and Altman plots analysis yielded better results for the comparison of CO_{reb} with CO_{icg} than with CO_{pcm}. One possible explanation is vasoconstriction of the finger arteries because of heavy orthostatic stress. Remarkably, all CO_{icg} values are above zero in Fig. 4, indicating that ICG always delivers lower values than inert gas rebreathing in contrast to PCM. On the other hand, it should be kept in mind that errors of CO measurements show proportionality to the magnitude of the cardiac output, as demonstrated by Broomhead et al. (3) in pigs. Critchley and Critchley (5) stated that Bland and Altman plots do not compensate for the relationship between magnitude of CO and size of error. Because of the wide range of our CO_{reb} values (3.78–16.23 $L \cdot min^{-1}$), we calculated the percentage error for each data set between CO_{reb} and CO_{pcm} on the one hand and CO_{reb} and CO_{icg} on the other hand. Following the analysis of Critchley and Critchley (5) we conclude that relative errors between CO_{reb} and CO_{pcm} of 31 ± 26% are acceptable with respect to the wide range of magnitude of CO_{reb}. Relative errors between CO_{reb} and CO_{icg} of 47 ± 26% show a poor agreement of these methods.

In general, and with few exceptions, a closer look at the paired values of individual test subjects shows a

better correlation between methods and a broad range of the bias, indicating that large between-subjects variability played a preponderant role in our results. In 2007 Bland and Altman described an expansion of their method for analyzing repeated pairs of measurements on the same subject when the true value of the measured quantity may be changing (1). We also conducted this analysis, but the results were similar to (actually slightly worse than) the conventional one. An important, relevant observation for future work is that of large between-subjects variability, a condition especially accentuated by the broad range of our test subjects' demographic characteristics. This observation agrees with Newman et al. (16), who pointed out that subject choice could affect correlation between ICG and other techniques.

The present study has limitations. One of them is the small sample size ($N = 6$), which was due to the restriction imposed by the number of test subjects that can be flown on the A300 during a campaign. Furthermore, no scopolamine was given during the baseline measurements on the ground and no measurements were performed during steady flight. Thus the present data can only incompletely account for the influence of scopolamine and of independent environmental, physical, and psychological variables. Another limiting factor during parabolic flights is motion sickness. Although all our test subjects but one were anti-motion sickness medicated, motion sickness appeared in two medicated subjects and caused partial loss of data. Scopolamine itself can affect the cardiovascular system (14) and its impact on our data is not quantifiable. Peripheral vascular resistance and blood pressure values are not given. These values were outside of the scope of this paper, which was focused on technical and methodological aspects of cardiac output measurement during parabolic flights to build a foundation for future work.

In conclusion, a beat-by-beat determination of CO is important to quantify rapid CO changes during very initial microgravity. Using an adaption of the Bland and Altman plot to account for a wide range of CO values [introduced by Shoemaker et al. (22)], PCM seems to be superior to ICG. Nevertheless, both PCM and ICG can be used to track rapid CO changes if their limitations are adequately considered. Since between-subjects variability seems to be the main confounding factor, calibration of the PCM and ICG data should be done carefully on an individual basis. We recommend performing repeated measurements of CO_{reb} in different body positions, both on the ground and, if possible, in flight during 1-G_z periods, i.e., when the cardiovascular system is in a steady state, to calibrate the PCM and ICG data to absolute CO values.

ACKNOWLEDGMENTS

We are grateful to the test subjects for their participation in this study. The authors thank the European Space Agency for providing the flight opportunity during the 50th ESA Parabolic Flight Campaign. We are also thankful to W. Sies for his technical support and to the appointees of NOVESPACE for all their skilful help.

Authors and affiliations: Ulrich Limper, M.D., Department of Anaesthesiology and Intensive Care Medicine, University Witten/Herdecke, Clinics of Cologne, Cologne, Germany; and Peter Gauger, M.Sc., and Luis E. J. Beck, M.D., German Aerospace Center (DLR), Institute of Aerospace Medicine, Space Physiology, Cologne, Germany.

REFERENCES

1. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. J Biopharm Stat 2007; 17:571–82.
2. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1:307–10.
3. Broomhead CJ, Wright SJ, Kiff KM, Withigton PS. Validation of thoracic electrical bioimpedance as a porcine research tool. Br J Anaesth 1997; 78:323–5.
4. Clemensen P, Christensen P, Norsk P, Grønlund J. A modified photo- and magnetoacoustic multigas analyzer applied in gas exchange measurement. J Appl Physiol 1994; 76:2832–9.
5. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. J Clin Monit Comput 1999; 15:85–91.
6. Damgaard M, Norsk P. Effects of ventilation on cardiac output determined by inert gas rebreathing. Clin Physiol Funct Imaging 2005; 25:142–7.
7. Dominique T, Migeotte PF, Sa RC. Noninvasive beat-to-beat stroke volume computation during acute hydrostatic pressure changes in parabolic flight. J Gravit Physiol 2002; 9:P97–8.
8. Fuller HD. The validity of cardiac output measurement by thoracic impedance: a meta-analysis. Clin Invest Med 1992; 15:103–12.
9. Gabrielsen A, Videbaek R, Schou M, Damgaard M, Kastrup J, Norsk P. Non-invasive measurement of cardiac output in heart failure patients using a new foreign gas rebreathing technique. Clin Sci 2002; 102:247–52.
10. Harms MP, Wesseling KH, Pott F, Jenstrup M, Van Goudoever J, et al. Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. Clin Sci (Lond) 1999; 97:291–301.
11. Johns JP, Vernalis MN, Karemaker JM, Latham RD. Doppler evaluation of cardiac filling and ejection properties in humans during parabolic flight. J Appl Physiol 1994; 76:2621–6.
12. Johns JP, Vernalis MP, White CD, Karemaker JM, Latham RD. Echocardiographic evaluation of cardiac function during parabolic flight. Physiologist 1992; 35(1, Suppl.)S117–8.
13. Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. Aerosp Med 1966; 37:1208–12.
14. Mayer B. Phamakodynamik von Scopolamin und Ephedrin auf der Erde und in Schwerelosigkeit (Pharmacodynamics of scopolamine and ephedrine on earth and in weightlessness). Thesis, Rheinisch-Westfälische Technische Hochschule Aachen, Germany, 2001.
15. Mukai CN, Lathers CM, Bennett BS. Cardiovascular responses to repetitive exposure to hyper- and hypogravity states produced by parabolic flight. J Clin Pharmacol 1994; 34: 472–9.
16. Newman DG, Callister R. The non-invasive assessment of stroke volume and cardiac output by impedance cardiography: a review. Aviat Space Environ Med 1999; 70:780–9.
17. Norsk P, Damgaard M, Petersen L, Gybel M, Pump B, et al. Vasorelaxation in space. Hypertension 2006; 47:69–73.
18. Penáz J, Voigt A, Teichmann W. Contribution to the continuous indirect blood pressure measurement. Z Gesamte Inn Med 1976; 31:1030–3.
19. Peyton PJ, Bailey M, Thompson BR. Reproducibility of cardiac output measurement by the nitrous oxide rebreathing technique. J Clin Monit Comput 2009; 23:233–6.
20. Peyton PJ, Thompson B. Agreement of an inert gas rebreathing device with thermodilution and the direct oxygen Fick method in measurement of pulmonary blood flow. J Clin Monit Comput 2004; 18:373–8.

21. Schlegel TT, Benavides EW, Barker DC, Brown TE, Harm DL, et al. Cardiovascular and Valsalva responses during parabolic flight. J Appl Physiol 1998; 85:1957–65.
22. Shoemaker WC, Wo CCJ, Bishop MH, Appel PL, Van De Water JM, et al. Multicenter trial of a new thoracic electrical bioimpedance device for cardiac output estimation. Crit Care Med 1994; 22:1907–12.
23. Corte TJ, Wells AU, Gatzoulis MA, Cramer D, Ward S, et al. Non-invasive assessment of pulmonary blood flow using an inert gas rebreathing device in fibrotic lung disease. Thorax 2010; 65:341–5.
24. Truijen J, Bundgaard-Nielsen M, van Lieshout JJ. A definition of normovolaemia and consequences for cardiovascular control during orthostatic and environmental stress. Eur J Appl Physiol 2010; 109:141–57.
25. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 1993; 74:2566–73.

Chapter Three

Pulse contour methods to estimate cardiovascular indices in micro- and hypergravity (*Aviation, Space, and Environmental Medicine 2013; 84(11):1178-1185*)

Arai T [1,4] Limper U [2,3,4], Gauger P [2], and Beck L.E.J [2]

[1] Aerospace Biomedical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

[2] German Aerospace Center (DLR), Institute of Aerospace Medicine, Department of Space Physiology, Cologne, Germany

[3] University of Witten/Herdecke, Department of Anesthesiology and Intensive Care Medicine, Merheim Medical Center, Hospitals of Cologne, Cologne, Germany

[4] These authors contributed equally to this work

RESEARCH ARTICLE

Pulse Contour Methods to Estimate Cardiovascular Indices in Micro- And Hypergravity

Tatsuya Arai, Ulrich Limper, Peter Gauger, and Luis Beck

Arai T, Limper U, Gauger P, Beck L. *Pulse contour methods to estimate cardiovascular indices in micro- and hypergravity.* **Aviat Space Environ Med 2013; 84:1178–85.**

Background: The importance of noninvasive health monitoring in space increased as a result of the long-duration missions on the International Space Station (ISS). In order to monitor changes in cardiovascular indices such as cardiac output (CO) and total peripheral resistance (TPR), many methods have been developed using signal processing and mathematical modeling techniques. However, their performance in various gravitational conditions has not been known. ***Methods:*** The present study compared 10 methods to estimate CO and TPR by processing peripheral arterial blood pressure signals recorded from 8 subjects in multiple gravity levels (1 G, 0 G, and 1.8 G) during parabolic flights. For reference data sets, CO and TPR were simultaneously obtained by an inert gas rebreathing technique. Root normalized mean square errors and Bland-Altman plots were used to evaluate the estimation methods. ***Results:*** The corrected impedance method achieved the lowest estimation errors (20.0% CO error and 23.5% TPR error) over the three gravity levels. In microgravity, mean arterial pressure was also demonstrated to be an indicator of CO (24.5% error). ***Discussion:*** The corrected impedance method achieved low estimation errors for a wide range of the gravity levels. Gravity-dependent performance was observed in the mean arterial pressure method that achieved low errors in the short-term 0 G.

Keywords: inert gas rebreathing, parabolic flight, cardiac output, total peripheral resistance.

THE IMPACT OF SHORT and long-lasting weightlessness on the cardiovascular system, especially presyncope and fainting of astronauts after spaceflight missions (postflight orthostatic hypotension or orthostatic intolerance), has been in the focus of cardiovascular research for decades. It has been found that postflight orthostatic intolerance is caused by changes in cardiac output (CO) and vasoconstriction deficiencies before and after spaceflight (17,19). As human spaceflight entered the era of long-duration missions on the International Space Station (ISS), the importance of noninvasive health monitoring has increased in order to track changes of the cardiovascular indices and find any sign of deconditioning during and after spaceflight.

The noninvasive cardiovascular monitoring in spaceflight includes infrared finger photoplethysmography (IFP) during former Space Shuttle and Russian MIR space station missions as well as ISS missions (3,4,10). The recorded peripheral arterial blood pressure (ABP) signal can be processed to track changes in CO and total peripheral resistance (TPR). So-called pulse contour methods (PCMs) have been studied by many researchers (9,14,25) to track changes in CO and TPR, and have been introduced into clinical medicine and physiological research (3,4,21). However, just a few methods are currently used in clinical medicine on a regular basis (22). For example, the corrected aortic input impedance method introduced by Wesseling et al. is used for stroke volume (SV) estimation by pulse wave analysis (3). However, ground-based artificial gravity studies have shown that the model flow method, which was developed from the corrected impedance method, achieves different reliabilities for measurements in different body positions (6). Furthermore, the impact of microgravity on the performance of PCMs is not known. The purpose of this study was, therefore, to compare PCMs using noninvasive beat-to-beat finger blood pressure in various gravity conditions.

METHODS

Equipment

Cardiovascular data sets of noninvasive ABP, heart rate (HR) by electrocardiography, and CO were simultaneously collected during the parabolic flight campaigns of the German Aerospace Center (DLR) in 2010–2012 in Bordeaux, France, and the French Space Agency Centre National d'Etudes Spatiales during the 2011 Paris Le Bourget Air Show. All flights were performed by the NOVESPACE Company using an Airbus A300. The Finometer MIDI® system (Finapres Medical Systems, Amsterdam, The Netherlands) for blood pressure measurement, the Innocor® rebreathing system (Innovision A/S, Odense, Denmark) for obtaining cardiac output (CO_{REB}), and the Biopac® system (Biopac Systems, Goleta, CA) for data acquisition were used. The raw data of ABP and HR were stored via ACQ® software

From the Massachusetts Institute of Technology, Cambridge, MA; the DLR Institute of Aerospace Medicine, Space Physiology Branch, Cologne, Germany; and the University of Witten/Herdecke, Department of Anesthesiology and Intensive Care Medicine, Merheim Medical Center, Hospitals of Cologne, Cologne, Germany.

This manuscript was received for review in March 2013. It was accepted for publication in June 2013.

Address correspondence and reprint requests to: Tatsuya Arai, 77 Massachusetts Ave., Cambridge, MA 02139; tatsuya@alum.mit.edu.

DOI: 10.3357/ASEM.3683.2013

(Biopac Systems). The details of the in-flight experimental setup has been described previously (15).

Subjects

In short, ABP and HR data were continuously recorded throughout the flights at a 200 Hz sampling rate from eight healthy subjects in the standing position (four women, 30 ± 3 yr, 167 ± 7 cm, 61 ± 18 kg; and four men, 35 ± 9 yr, 173 ± 9 cm, 66 ± 10 kg). All the test subjects had experienced parabolic flights previously. They received scopolamine-hydrobromide injected subcutaneously as a countermeasure for motion sickness before the flights [175 μg (men); 125 μg (women)]. The study protocols had been approved in advance by the pertinent French authorities (Agence française de securité sanitaire des produits de sanité). Each subject provided written informed consent before participation.

Procedure

The following PCMs were applied to the aforementioned parabolic flight ABP data.

Mean arterial pressure: This method is one of the most simple estimators. CO is proportional to mean arterial pressure (MAP):

$$CO \propto MAP = \frac{1}{T}\int P(t)dt$$

where T is the beat duration and P(t) is ABP.

Pulse pressure (PP) (7):

$$CO \propto \sum_i \frac{PP_i}{T_i} = \sum_i \frac{SBP_i - DBP_i}{T_i}$$

where i represents the beat number, and SBP_i and DBP_i represent systolic and diastolic blood pressure values of the beat, respectively. Taking DBP into consideration, this method regards the difference of SBP and DBP as an indicator of CO. The PP method is simple and one of the most intuitive and arguably most commonly used in clinical settings (5).

Herd's pulse pressure (PP2) (9):

$$CO \propto \sum_i \frac{MAP_i - DBP_i}{T_i}$$

In the aforementioned PP method, SBP was replaced by MAP, which is known to be robust against pressure waveform distortion caused by the tapered and bifurcated arterial tree structure.

Modified Herd's method (2):

$$CO \propto \sum_i \frac{\int_{Systole} P_i(t)dt - DBP_i}{T_i}$$

This method uses only the systolic ABP signal in the Herd's method.

Liljestrand-Zander's method (14):

$$CO \propto \sum_i \frac{SBP_i - DBP_i}{SBP_i + DBP_i} \Big/ T_i$$

This method adds a scaling factor of 1/(SBP+ DBP) to the PP method.

Area under the systolic pressure curve:

$$CO \propto \sum_i \frac{\int_{systole} P_i(t)dt}{T_i}$$

Rather than taking the average of an entire single beat, this method uses only the systolic pressure signal to obtain proportional CO. This method overcomes the disadvantage of the MAP method's tendency to underestimate CO when diastolic period is abnormally extended, regardless of the systolic period.

Area under the systolic pressure curve above DBP:

$$CO \propto \sum_i \frac{\int_{systole} \left(P_i(t) - DBP_i\right)dt}{T_i}$$

Only the ABP signal above DBP is considered.

Corrected impedance (25):

$$CO \propto \sum_i \frac{\left(163 + HR_i - 0.48 \cdot MAP_i\right)\int_{t^{ED}_i}^{t^{ES}_i} \left(P_i(t) - DBP_i\right)dt}{T_i}$$

where t^{ED}_i and t^{ES}_i represent time stamps at the end diastole and end systole of the i_{th} beat, respectively.

Kouchoukos correction (13):

$$CO \propto \sum_i \frac{\left(1 + \frac{T^S_i}{T^D_i}\right)\int_{t^{ED}_i}^{t^{ES}_i} \left(P_i(t) - DBP_i\right)dt}{T_i}$$

where T^S and T^D represent systolic and diastolic durations, respectively.

AC power: Adopted by the commercial LiDCO Plus PulseCO method of pulse power analysis (20; LiDCO Ltd., London, UK), this makes use of the power of the ABP signal. The beat power factor is proportional to the nominal CO ejected into the aorta.

$$CO \propto \frac{\sqrt{\frac{1}{T}\int_T \left(P(t) - MAP\right)^2 dt}}{T}$$

Some of the CO estimation methods require identification of an end systolic time stamp. In this section, methods to identify the end systole from the ABP signal are introduced.

Exponential model: Weissler et al. (24) obtained the relationship between systolic duration and preceding RR interval, describing it as a saturating exponential curve. For the present study, the following equation was adopted to identify the systolic duration of the current beat (2):

$$Sys_i = 436\left(1 - \exp\left(-0.0057\, RR^{measured}_{i-1}\right)\right)$$

Partial pulse pressure model (1): An end diastole always comes after a systolic peak. At the end systole, the pressure value is equal to or lower than SBP. When the pressure drops from SBP to α% PP at the end systole, the end

TABLE I. CARDIOVASCULAR DATA OBTAINED DURING CO REBREATHING MEASUREMENTS IN $N = 8$.

	CO_{REB} ($L \cdot min^{-1}$)				ABP (mmHg)				HR (bpm)				TPR [mmHg/(L/min)]			
Subjects	Max	Min	Mean	SD	Max	Min	Mean	SD	Max	Min	Mean	SD	Max	Min	Mean	SD
AA	9.94	4.29	7.47	2.44	143	63	87.8	13.3	104	34	67.6	20.4	21	9	12.6	3.3
AO	5.90	2.40	4.37	1.40	136	29	71.7	16.8	105	57	85.6	11.1	39	10	18.3	7.7
AM	8.55	3.06	5.27	2.35	205	45	94.2	25.0	180	25	100.0	32.7	35	12	20.9	7.2
BX	14.90	4.20	7.95	3.94	154	41	78.3	17.7	180	47	109.6	22.2	18	6	11.4	3.9
CC	11.41	5.06	7.10	1.76	176	60	92.1	17.5	180	64	120.5	27.7	21	7	13.8	4.6
AD	14.29	4.59	7.30	4.29	182	45	81.7	19.0	160	53	108.7	26.7	18	6	12.5	3.6
AX	11.34	4.66	7.42	2.04	212	53	104.2	25.5	180	25	122.7	19.0	23	9	15.1	4.6
BR	12.29	3.64	7.18	2.62	183	46	94.7	20.8	128	62	91.2	12.7	25	7	14.9	5.7

systolic pressure can be described as $P_{ES} = P_D + \alpha (P_S - P_D)$, where P_{ES} is the time stamp of the estimated end systole. The value of α was changed from 10 to 100% PP and applied to the CO estimation methods that require end systole identifier.

Statistical Analysis

We applied the aforementioned 10 PCMs to the parabolic flight ABP data after the experiments using MATLAB® (MathWorks, Natick, MA). The ABP signal during each CO rebreathing measurement (10 s) was processed. First, peaks in the ABP signal and their preceding local minima were determined as SBP and DBP. The signal between DBPs defines a single beat. The algorithms were applied to calculate SV on a beat-by-beat basis. Then the total SV over time was calculated as a proportional CO estimate.

Note that all the PCMs provide proportional CO; i.e., the outputs are estimates within a scaling factor. Assuming arterial compliance does not change during testing, in each subject, the proportional CO estimates were scaled as

$$C_a = \frac{mean(meas)}{mean(estimated)}$$

The scaling factor was set to be consistent within each subject (1).

Using the estimated CO and measured MAP, TPR was also estimated by Ohm's Law: TPR = MAP/CO. The estimated CO and TPR values were evaluated by comparing with the corresponding reference CO (CO_{REB}) obtained by Innocor®. The reference TPR (TPR_{REB}) was also calculated by Ohm's Law: $TPR_{REB} = MAP/CO_{REB}$. As an error criterion, the root normalized mean square error (RNMSE) was adopted:

$$RNMSE = 100\sqrt{\frac{\sum_{n=1}^{N}\left(\frac{Meas - Est}{Meas}\right)^2}{N - N_f}}$$

where Meas, Est, N, and N_f represent a measured value, estimated value, number of sample, and number of freedom ($N_f = 1$, arterial compliance), respectively. The method that achieved the lowest RNMSE was compared with the other methods using the F-test. The statistical significance was defined as $P < 0.05$.

RESULTS

Table I shows an overview of the CO_{REB}, ABP, HR, and TPR characteristics of the eight subjects analyzed. Large interindividual differences are obvious, especially in the ranges of CO_{REB}, which are larger than those typically seen in hospitalized patients. We analyzed 139 CO data sets, of which 52 sets were collected within 0 G, 28 sets in 1.8 G, and 59 sets in 1 G. The overall results are summarized in **Table II**, showing that most of the methods generated their largest errors in short-term 0 G and the smallest in short-term 1.8 G.

Fig. 1A summarizes the CO errors by different methods under all tested gravity loads. For methods using

TABLE II. RNMSEs OF CO AND TPR ESTIMATION (%).

	CO RNMSEs				TPR RNMSEs			
Methods	All Gs	1 G	0 G	1.8 G	All Gs	1 G	0 G	1.8 G
Wesseling's corrected impedance (25)	20.0	19.2	27.3	16.3	23.5	17.8	30.9	17.3
Kouchoukos (13)	21.9	19.4	29.2	18.2	31.0	18.7	41.8	28.1
Area under the curve, above DBP	22.3	20.3	26.0	18.7	27.4	19.0	35.1	26.4
Modified Herd's method (2)	22.4	21.0	26.8	18.8	26.4	19.6	34.7	20.0
Area under the curve	24.7	21.5	30.3	26.1	24.3	20.8	27.7	24.4
Herd's pulse pressure (9)	25.0	24.4	29.1	24.9	31.4	22.6	41.4	25.4
AC power (20)	25.7	22.9	27.8	16.7	28.3	21.4	38.3	16.9
Pulse pressure	28.7	25.6	29.4	35.1	33.0	23.1	45.9	19.1
Liljestrand-Zander's method (14)	29.2	25.3	25.5	18.1	30.8	24.5	40.4	20.3
MAP	33.3	26.5	24.5	28.6	34.9	24.8	44.4	32.6

end systolic time stamps, the end systolic identifier that provided the lowest RNMSEs is shown. Among the methods, corrected impedance with 60% PP as end systole achieved the lowest CO RNMSE (20.0%). The 1-G loading scenario (**Fig. 1B**) yielded similar results. **Fig. 1C** shows the RNMSEs during 0 G. The MAP method achieved the lowest RNMSE of 24.5%. **Fig. 1D** shows the RNMSEs during 1.8 G. The corrected impedance method achieved the lowest RNMSE of 16.3%.

The CO estimation history of the corrected impedance method compared to CO_{REB} is shown in **Fig. 2A**, demonstrating the traceability of changes of CO by the corrected impedance method over the wide range of measured CO and gravity levels. Kouchoukos (60% PP as end systole identifier), area under the curve above DBP (60% PP as end systole identifier), and modified Herd's (using an exponential model) achieved 21.9%, 22.3%, and 22.4% RNMSEs, respectively. Other methods, especially the methods that do not use end systolic time stamps, were found to be statistically larger in RNMSEs (Fig. 1), including the Liljestrand-Zander method (29.2%, CO estimation history shown in **Fig. 2B**).

As for TPR estimation, the corrected impedance method achieved 23.5% RNMSE (**Fig. 3A**), while the Liljestrand-Zander method achieved 30.8% RNMSE (**Fig. 3B**). Bland-Altman plots of the Liljestrand-Zander and the corrected impedance methods are shown in **Fig. 4**. The corrected impedance method showed smaller correlation coefficient and 95% limits of agreement [R^2 = 0.003 and ± 2.73 mmHg/(L/min), respectively,

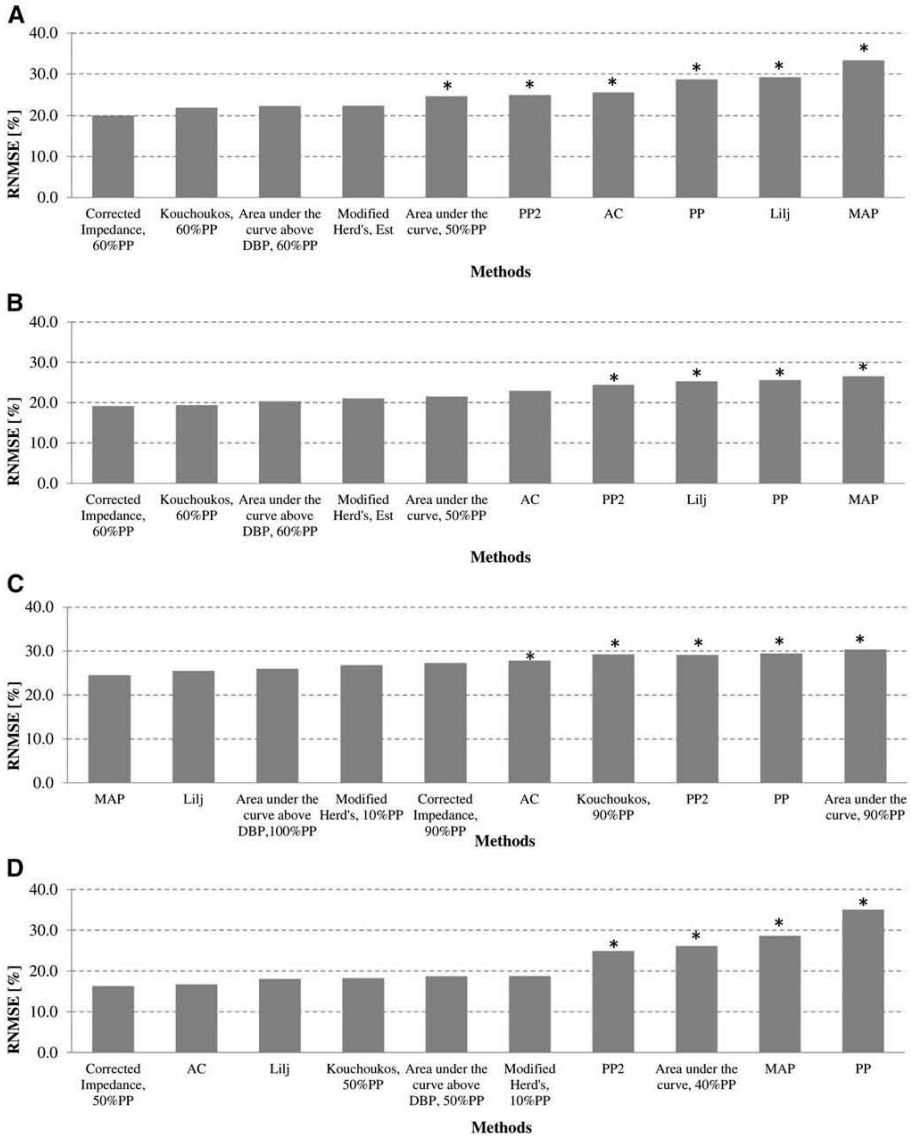

Fig. 1. A) RNMSEs of the CO estimation methods for all the gravity levels. B) RNMSEs of the CO estimation methods in 1 G. C) RNMSEs of the CO estimation methods in 0 G. D) RNMSEs of the CO estimation methods in 1.8 G. Asterisks represent significant statistical differences ($P < 0.05$) regarding the best method under the particular gravity load.

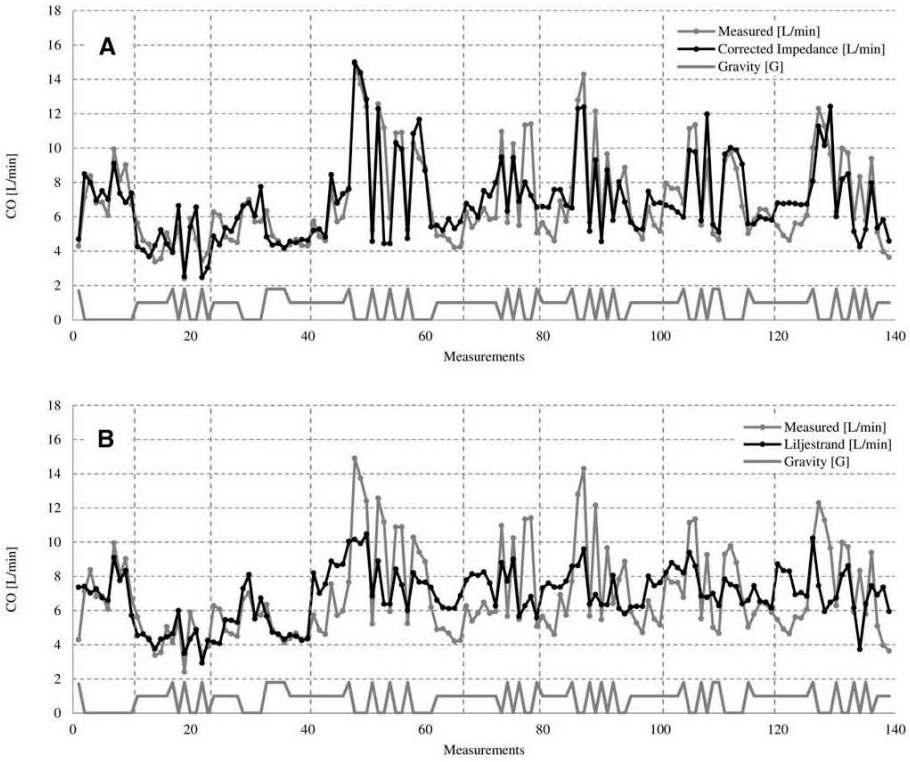

Fig. 2. A) CO estimation history by the corrected impedance method using 60% PP as end systole. B) CO estimation history by the Liljestrand-Zander method.

shown in Fig. 4B] than those of the Liljestrand-Zander method [$R^2 = 0.020$ and ± 4.12 mmHg/(L/min), respectively, shown in Fig. 4A], indicating independency from the physiological range of true CO values. Similar trends can be seen in those of TPR estimation (Figs. 4C and D).

DISCUSSION

Finger blood pressure waves obtained during parabolic flights within wide physiological ranges were processed using CO estimation methods and including different methods of end systole identification. There were 10 such estimation methods assessed against cardiac output determined by foreign gas rebreathing. The corrected impedance, Kouchoukos, area under the curve (above DBP), and the modified Herd's methods achieved the lowest RNMSEs among all 10 analyzed methods.

The high RNMSEs of the PP method could be attributed to their sensitivity to ABP waveform distortion; SBP tends to increase as the pulse wave travels through the tapered and bifurcated arterial tree. In the meantime, DBP and MAP are known to be robust against distortion. For example, the corrected impedance method and Kouchoukos correction method are based on the area under the curve method, but adopted distortion-robust scaling factors to achieve high estimation accuracy. The corrected impedance method adopted HR and MAP as scaling factors, while the Kouchoukos correction method used the ratio of systolic and diastolic durations.

The error of the MAP method stems from the assumptions of constant TPR. Interestingly, however, the MAP method achieved low error in 0 G (Fig. 1B) with respect to the other methods, which could be attributed to the baroreceptor response induced by the headwards fluid shift; likely the sympathetic system was inhibited excessively, resulting in the saturated and constant vascular response.

Herd's pulse pressure method (PP2) overcame the shortcoming of the PP method by using MAP and DBP, which are both robust against waveform distortion. However, the method is sensitive to variability in the diastolic periods. For example, if SV values are constant for several beats while diastolic periods start to decrease, MAP would decrease and SV values would be underestimated. In that light, the modified Herd's method was developed to overcome the weakness of Herd's pulse pressure method. This method takes into account only the systolic period. Since any abnormally shortened or prolonged diastolic periods (that do not contribute to SV or CO) are excluded, better estimation accuracy was expected. It was also found that the modified Herd's method is relatively insensitive to end systole identification methods (the exponential model or partial PP methods) (2).

Although the Liljestrand-Zander method had been reported by Sun et al. to work best in the data sets of patients on intensive care units (ICU) (21), the method did not achieve low RNMSEs in the present study, especially

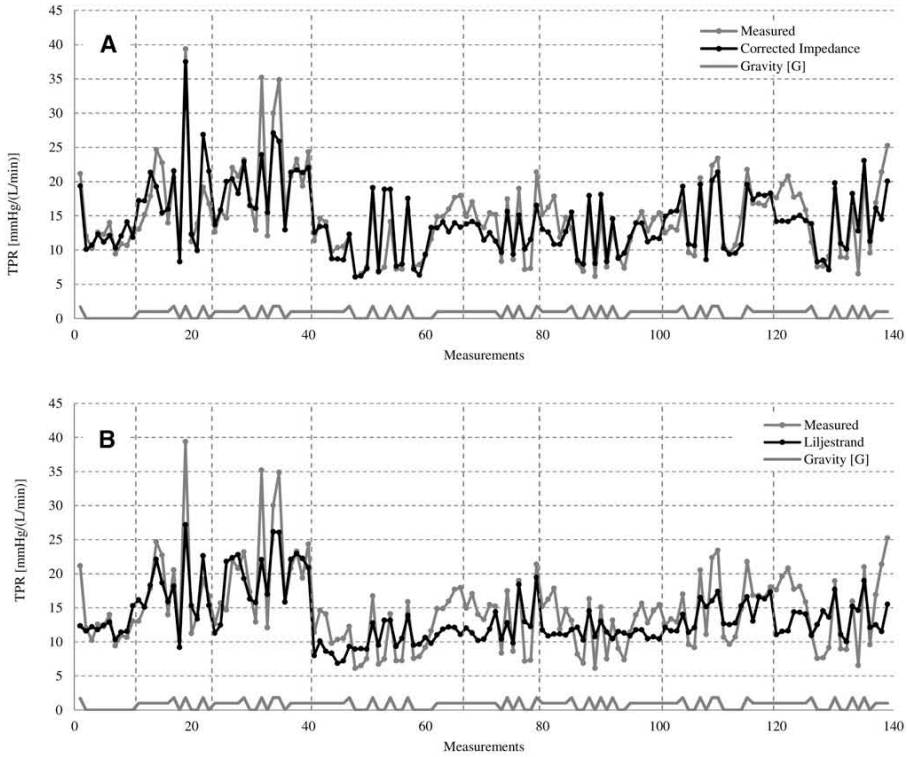

Fig. 3. A) TPR estimation history by the corrected impedance method. B) TPR estimation history by the Liljestrand-Zander method.

in 1 G and 1.8 G. The reason could be attributed to stable ICU patient data sets and the averaging effect of the method; the Liljestrand-Zander method normalizes PP by a sum of SBP and DBP. Therefore, it tends to provide relatively flat and stable CO estimates. In the ICU setting, cardiovascular indices, such as CO and ABP, of patients are carefully maintained. Thus, the averaging effect of Liljestrand-Zander favorably resulted in low RNMSEs. On the other hand, a wide range of CO and ABP, as can be seen in the present study, would challenge the method. The German physiologist Gauer pointed out that this relationship leads to good results if changes in CO are mainly the result of changes in HR (8). The Liljestrand-Zander formula was often criticized for not taking changes of elasticity and other parameters into account (8). During a parabolic flight maneuver, not only large HR changes, but also exaggerated changes in blood pressure and TPR can be observed (16).

In 0 G, higher PP values (90% or 100% PP) tended to be selected as the indicator of end systole than in other gravity scenarios. These PP values correspond to the beginning of the ABP descent immediately after SBP. This could be explained by early aortic valve closures and shortened systolic phases in the cardiac cycle in 0 G with respect to 1 G and 1.8 G. However, a shortened systolic phase in 0 G would not be well in line with the observations of Johns et al. (11), who found an increased left ventricular ejection time (LVET) in 0 G with respect to 1.8 G using ultrasound measurements. Contradictory to the findings of Johns et al. are the findings of Mukai et al. (18). They used impedance cardiography to evaluate LVET during gravity transitions in the standing position on parabolic flight. They were not able to find a significant change in LVET during the 0-G phase with respect to the initial 1.8-G phase. From our point of view it is not clear yet if higher PP values as an end systole indicator in microgravity are just a methodical adjustment or correlate with a true change in LVET.

In 1.8 G, the corrected impedance method achieved the lowest RNMSEs of 16.3% in CO and 17.3% in TPR. During the microgravity phases, however, it resulted in high RNMSEs. The higher errors could be attributed to the rapid decrease in TPR; acute changes in TPR are known to occur in weightlessness during spaceflight missions and on parabolic flights (16), and low TPR in 0 G might have resulted in the low accuracy of the corrected impedance method (6). The other PCMs also resulted in higher RNMSEs in 0 G, which could be explained by the decreased performance of PCMs in general during low TPR values (12). PCMs assume constant blood volume in the arterial system, while fluid shift between the venous and arterial systems occurs upon a rapid decrease in TPR. Estimation errors would decrease once the transient fluid exchange between the systems is stabilized in a long-duration space mission. In considering the effect of TPR changes, locations of ABP measurement could also influence the results. A lack of agreement of arm and finger ABP was reported during spaceflight (23). The larger brachial arteries could be less subject to TPR changes than the smaller

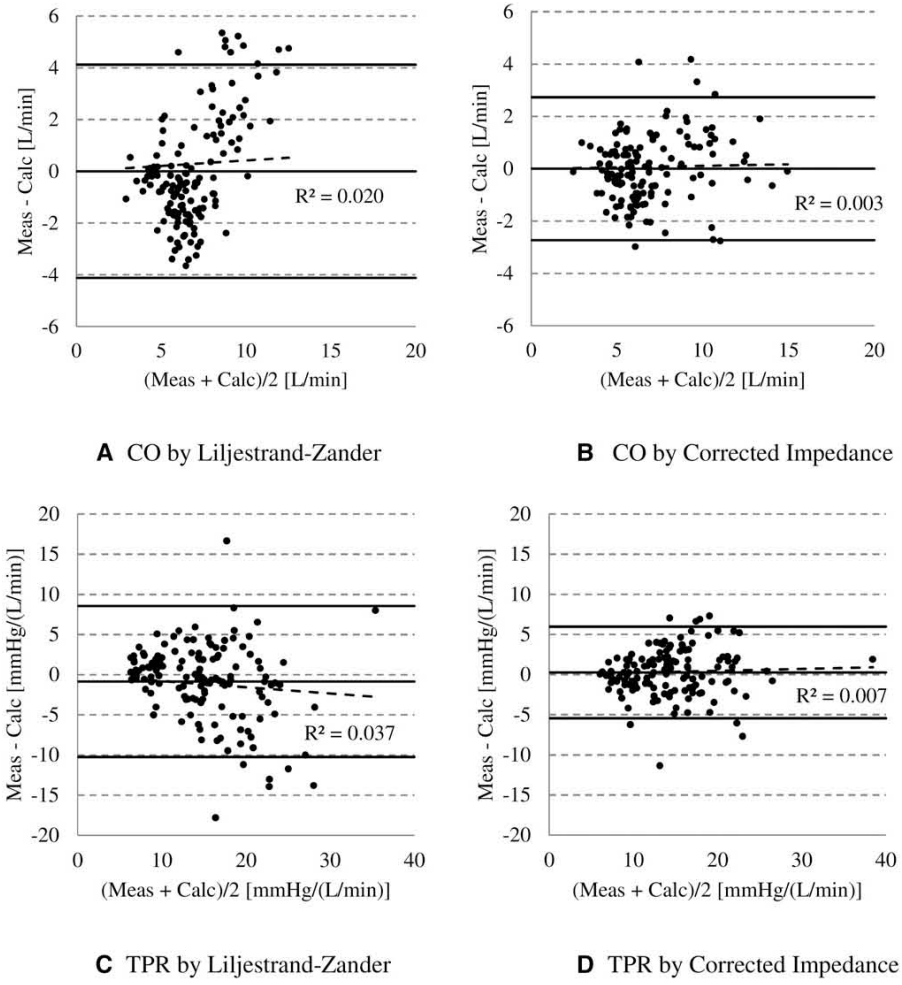

Fig. 4. Bland-Altman plots of the Liljestrand-Zander and corrected impedance methods. A) CO by Liljestrand-Zander, $R^2 = 0.020$. B) CO by corrected impedance, $R^2 = 0.003$. C) TPR by Liljestrand-Zander, $R^2 = 0.037$. D) TPR by corrected impedance, $R^2 = 0.007$.

radial arteries. Comparison of PCMs using brachial and radial arteries during parabolic flight or spaceflight would reveal the robustness of each method in response to acute changes in TPR.

To summarize, we report for the first time comparison of 10 different estimation methods of CO by processing peripheral arterial blood pressure signals under the changing gravity conditions of parabolic flights. Our main findings are: 1) changing performance of each pulse pressure estimation method was observed under changing G loads; 2) the corrected impedance method worked best on average in all tested G loads; 3) surprisingly, MAP showed the best performance of all tested methods in short-term 0 G; and 4) most of the methods showed the lowest errors in 1.8 G and the highest errors in 0 G. These preliminary results suggest that using multiple PCMs, rather than a single PCM, would be advantageous in analyzing cardiovascular systems under varying G-loads. More precisely, using the corrected impedance method for blood pressure data taken in 1 G and short-term 1.8 G, and the MAP method for the data in short-term 0 G might decrease the overall error of CO estimation.

We acknowledge the following limitations of the study: the sample size ($N = 8$) was small due to the restriction imposed by the number of parabolic flight test subjects. The phases of different G loads lasted just few seconds and further studies are necessary to compare the estimation methods during long-duration spaceflight missions. The accuracy of the CO and TPR reference method as well as the noninvasive IFP were limited (15), which might result in the large errors of all the estimation methods (> 20%) under the changing gravity conditions. Therefore, conclusions from analysis of IFP data should be drawn carefully. The most accurate cardiovascular monitoring techniques would be invasive blood flow and pressure measurement, such as an ultrasound flow probe and a catheter pressure sensor. Nevertheless, inert gas rebreathing and IFP are well-established, safe, and regularly used methods of reference CO determination and blood pressure measurement on spaceflight missions and parabolic flights. Further tuning of

the algorithm parameters in using IFP would increase the estimation accuracy. Future work should also include application of the PCM methods to ABP data sets recorded during a long-duration spaceflight on ISS. Due to the stabilized arterial blood volume in 0 G, lower estimation errors are expected.

ACKNOWLEDGMENTS

We are grateful for the test subjects' participation in the parabolic flight experiments. The authors wish to thank the German Aerospace Center (DLR) and the French National Center for Space Studies (CNES) for providing the flight opportunities during the 15th, 16th, and 19th DLR parabolic flight campaigns and the demonstration flight during the 2011 Paris Le Bourget Air Show. We are also thankful to W. Sies for his technical support and to the appointees of NOVESPACE for all their skillful help.

Authors and affiliations: Tatsuya Arai, M.S., Ph.D., Massachusetts Institute of Technology, Cambridge, MA; Ulrich Limper, M.D., Department of Anesthesiology and Operative Intensive Care Medicine, Medical Center Cologne-Merheim, University of Witten/Herdecke, Cologne, Germany; and Peter Gauger, M.Eng., and Luis Beck, M.D., German Aerospace Center (DLR), Cologne, Germany.

REFERENCES

1. Arai T. Estimation of cardiovascular indices by analysis of the arterial blood pressure signal [Doctoral Thesis]. Cambridge, MA: Massachusetts Institute of Technology; 2011.
2. Arai T, Lee K, Marini RP, Cohen RJ. Estimation of changes in instantaneous aortic blood flow by the analysis of arterial blood pressure. J Appl Physiol 2012; 112:1832-8.
3. Baisch F, Beck L, Blomqvist G, Wolfram G, Drescher J, et al. Cardiovascular response to lower body negative pressure stimulation before, during, and after space flight. Eur J Clin Invest 2000; 30:1055–65.
4. Charles J. Studies of orthostatic intolerance with the use of lower body negative pressure (LBNP). Mir 18 final science report. Houstson, TX: National Aeronautics and Space Administration, Lyndon B. Johnson Space Center; 1998.
5. Dart AM, Kingwell BA. Pulse pressure–a review of mechanisms and clinical relevance. J Am Coll Cardiol 2001; 37:975–84.
6. Dyson KS, Shoemaker JK, Arbeille P, Hughson RL. Model flow estimates of cardiac output compared with Doppler ultrasound during acute changes in vascular resistance in women. Exp Physiol 2010; 95:561–8.
7. Erlanger J, Hooker DR. An experimental study of blood-pressure and of pulse-pressure in man. Baltimore, MD: Johns Hopkins Hospital; 1904.
8. Gauer OH. Blood circulation. In: Gauer OH, Kramer K, Jung R, eds. München-Berlin-Wien, Germany: Urban & Schwarzenberg; 1972.
9. Herd JA, Leclair NR, Simon W. Arterial pressure pulse contours during hemorrhage in anesthetized dogs. J Appl Physiol 1966; 21:1864–8.
10. Hughson RL, Shoemaker JK, Blaber AP, Arbeille P, Greaves DK, et al. Cardiovascular regulation during long-duration spaceflights to the International Space Station. J Appl Physiol 2012; 112:719–27.
11. Johns JP, Vernalis MN, Karemaker JM, Latham RD. Doppler evaluation of cardiac filling and ejection properties in humans during parabolic flight. J Appl Physiol 1994; 76:2621–6.
12. Junttila EK, Koskenkari JK, Ohtonen PP, Ala-Kokko TI. Uncalibrated arterial pressure waveform analysis for cardiac output monitoring is biased by low peripheral resistance in patients with intracranial haemorrhage. Br J Anaesth 2011; 107:581–6.
13. Kouchoukos NT, Sheppard LC, McDonald DA. Estimation of stroke volume in the dog by a pulse contour method. Circ Res 1970; 26:611–23.
14. Liljestrand G, Zander E. Vergleichende Bestimmungen des Minutenvolumens des Herzens beim Menschen mittels der Stickoxydulmethode und durch Blutdruckmessung [Comparison of cardiac output determination by the nitrous oxide method and blood pressure measurement in humans]. Z Gesamte Exp Med 1928; 59:105–22 (in German).
15. Limper U, Gauger P, Beck LE. Upright cardiac output measurements in the transition to weightlessness during parabolic flights. Aviat Space Environ Med 2011; 82:448–54.
16. Liu J, Verheyden B, Beckers F, Aubert AE. Haemodynamic adaptation during sudden gravity transitions. Eur J Appl Physiol 2012; 112:79–89.
17. Meck JV, Waters WW, Ziegler MG, deBlock HF, Mills PJ, et al. Mechanisms of postspaceflight orthostatic hypotension: low alpha1-adrenergic receptor responses before flight and central autonomic dysregulation postflight. Am J Physiol Heart Circ Physiol 2004; 286:H1486–95.
18. Mukai CN, Lathers CM, Charles JB, Bennett BS. Cardiovascular responses to repetitive exposure to hyper- and hypogravity states produced by parabolic flight. J Clin Pharmacol 1994; 34:472–9.
19. Perhonen MA, Franco F, Lane LD, Buckey JC, Blomqvist CG, et al. Cardiac atrophy after bed rest and spaceflight. J Appl Physiol 2001; 91:645–53.
20. Rhodes A, Sunderland R. Arterial pulse power analysis: the LiDCO™ plus system. In: Pinsky MR, Payen D, eds. Update in intensive care and emergency medicine. Berlin: Springer-Verlag; 2005:183-92.
21. Sun JX, Reisner AT, Saeed M, Heldt T, Mark RG. The cardiac output from blood pressure algorithms trial. Crit Care Med 2009; 37:72–80.
22. Truijen J, van Lieshout JJ, Wesselink WA, Westerhof BE. Noninvasive continuous hemodynamic monitoring. J Clin Monit Comput 2012; 26:267–78.
23. Verheyden B, Liu J, Beckers F, Aubert AE. Adaptation of heart rate and blood pressure to short and long duration space missions. Respir Physiol Neurobiol 2009; 169(Suppl. 1):S13–6.
24. Weissler AM, Harris LC, White GD. Left ventricular ejection time index in man. J Appl Physiol 1963; 18:919–23.
25. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 1993; 74:2566–73.

Chapter Four

Interactions of the human cardiopulmonary, hormonal and body fluid systems in parabolic flight (*European Journal of Applied Physiology 2014; 114(6):1281-1295*)

Limper U [1, 2], Gauger P [2], Beck P [3], Krainski F [4], May F [2], Beck LEJ [2]

[1] University of Witten/Herdecke, Department of Anesthesiology and Intensive Care Medicine, Merheim Medical Center, Hospitals of Cologne, Cologne, Germany

[2] Department of Space Physiology, Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany

[3] Department of General Surgery, University Witten/Herdecke, Helios Hospital Wuppertal, Wuppertal, Germany

[4] University of Texas Southwestern Medical School, Internal Medicine, Dallas, TX, USA

Eur J Appl Physiol (2014) 114:1281–1295
DOI 10.1007/s00421-014-2856-3

ORIGINAL ARTICLE

Interactions of the human cardiopulmonary, hormonal and body fluid systems in parabolic flight

U. Limper · P. Gauger · P. Beck · F. Krainski · F. May · L. E. J. Beck

Received: 20 October 2013 / Accepted: 14 February 2014 / Published online: 13 March 2014

Abstract
Purpose Commercial parabolic flights accessible to customers with a wide range of health states will become more prevalent in the near future because of a growing private space flight sector. However, parabolic flights present the passengers' cardiovascular system with a combination of stressors, including a moderately hypobaric hypoxic ambient environment (HH) and repeated gravity transitions (GT). Thus, the aim of this study was to identify unique and combined effects of HH and GT on the human cardiovascular, pulmonary and fluid regulation systems.
Methods Cardiac index was determined by inert gas rebreathing (CI_{rb}), and continuous non-invasive finger blood pressure (FBP) was repeatedly measured in 18 healthy subjects in the standing position while they were in parabolic flight at 0 and 1.8 G_z. Plasma volume (PV) and fluid regulating blood hormones were determined five times over the flight day. Eleven out of the 18 subjects were subjected to an identical test protocol in a hypobaric chamber in ambient conditions comparable to parabolic flight.
Results CI_{rb} in 0 G_z decreased significantly during flight (early, 5.139 ± 1.326 L/min; late, 4.150 ± 1.082 L/min) because of a significant decrease in heart rate (HR) (early, 92 ± 15 min^{-1}; late, 78 ± 12 min^{-1}), even though the stroke volume (SV) remained the same. HH produced a small decrease in the PV, both in the hypobaric chamber and in parabolic flight, indicating a dominating HH effect without a significant effect of GT on PV (−52 ± 34 and −115 ± 32 ml, respectively). Pulmonary tissue volume decreased in the HH conditions because of hypoxic pulmonary vasoconstriction (0.694 ± 0.185 and 0.560 ± 0.207 ml) but increased at 0 and 1.8 G_z in parabolic flight (0.593 ± 0.181 and 0.885 ± 0.458 ml, respectively), indicating that cardiac output and arterial blood pressure rather than HH are the main factors affecting pulmonary vascular regulation in parabolic flight.
Conclusion HH and GT each lead to specific responses of the cardiovascular system in parabolic flight. Whereas HH seems to be mainly responsible for the PV decrease in flight, GT overrides the hypoxic pulmonary vasoconstriction induced by HH. This finding indicates the need for careful and individual medical examination and, if necessary, health status improvement for each individual considering a parabolic flight, given the effects of the combination of HH and GT in flight.

Keywords Inert gas rebreathing · Weightlessness · Hypobaric hypoxia · Hypobaric chamber · Gravity

Communicated by Guido Ferretti.

Electronic supplementary material The online version of this article (doi:10.1007/s00421-014-2856-3) contains supplementary material, which is available to authorized users.

U. Limper (✉)
Department of Anesthesiology and Surgical Intensive Care Medicine, Merheim Medical Center, Hospitals of Cologne, University Witten/Herdecke, Ostmerheimer Strasse 200, 51109 Cologne, Germany
e-mail: limperu@kliniken-koeln.de

U. Limper · P. Gauger · F. May · L. E. J. Beck
Department of Space Physiology, Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany

P. Beck
Department of General Surgery, Helios Hospital Wuppertal, University Witten/Herdecke, Wuppertal, Germany

F. Krainski
University of Texas Southwestern Medical School, Internal Medicine, Dallas, TX, USA

Abbreviations

ACTH	Adrenocorticotropic hormone
BMI	Body mass index
CI	Cardiac index
CI_{rb}	Cardiac index by rebreathing
CO	Cardiac output
CO_{rb}	Cardiac output by rebreathing
CORT	Optimized carbon monoxide rebreathing technique
dB	Decibel
DLR	German Aerospace Center
FBP	Finger blood pressure
FBP_{diast}	Diastolic finger blood pressure
FBP_{syst}	Systolic finger blood pressure
GT	Gravity transition
G_z	Gravity load in head to toe direction
HH	Hypobaric hypoxia
HPV	Hypoxic pulmonary vasoconstriction
HR	Heart rate
ICG	Impedance cardiography
IGR	Inert gas rebreathing
LBNP	Lower body negative pressure
m. a. s. l.	Meters above sea level
MSNA	Muscle sympathetic nerve activity
NN	Normobaric normoxia
PBF	Pulmonary blood flow
PV	Plasma volume
SI	Stroke index
SI_{rb}	Stroke index by rebreathing
SO_2	Arterial oxygen saturation
SV	Stroke volume
SV_{rb}	Stroke volume by rebreathing
VO_2	Alveolar oxygen consumption
Vt	Volume of pulmonary tissue

Introduction

Parabolic flights performed in slightly modified passenger airplanes operating in the troposphere have been used extensively in past decades for space-related human physiological research. Most of these life science experiments have been conducted on parabolic flights in a KC 135 aircraft in the USA or in an Airbus A300 aircraft in Europe. Both aircrafts achieve parabolic trajectories of different sequences. The A300 performs 31 parabolas each flight day, with a 2-min break of level flight between two consecutive parabolas and with 4-min breaks after each group of five parabolas. After the 16th parabola, a break of 8 min represents half-time of the flight. The KC 135 performed 40 parabolas per flight day and took a so-called roller coaster flight path with 10 parabolas back-to-back. Typically a KC 135 flight had 5-min breaks after the 10th and the 30th parabola and a 10-min break after the 20th parabola. Extensive previous research was aimed at investigating the cardiovascular system in the context of changing gravity in general and weightlessness in particular (Liu et al. 2012; Mukai et al. 1991; Petersen et al. 2011). Most of these experiments focused on cardiovascular responses during gravity transitions (Limper et al. 2011; Mukai et al. 1994). Fewer studies have investigated longitudinal changes in these specific cardiovascular responses over the course of a parabolic flight day. Only Mukai et al. reported longitudinal changes in cardiac index (CI), although concrete CI differences were not reported. In particular, Mukai et al. used impedance cardiography during the first 10 parabolas of a parabolic flight. Mukai et al. (1994) also demonstrated a decreased thoracic fluid index by thoracic impedance measurements, and they noted that such a decreased thoracic fluid index may indicate an increase in thoracic fluids during parabolic flight. However, to date, no research has investigated how the body fluid system is influenced by parabolic flights, although some evidence suggests that the intravascular volume may increase on the day of a parabolic flight, as stated by Schlegel et al. (2001).

Another important factor that has not been adequately addressed in prior experiments is the changing ambient atmosphere of the airplane cabin on the day of a flight. This seems astonishing because of the tremendous amount of work which has been carried out on the effects of hypoxia of commercial air travel on the human body (Gradwell 2006; Mortazavi et al. 2003). An inflight cabin atmosphere that is more hypobaric, hypoxic and dry with respect to ground control may affect the responses of the cardiovascular system, particularly to changes in gravity. The ambient pressure of the European A300 at cruising altitude is approximately 830 mbar, which is equal to the ambient pressure at 1,650 m above sea level (m. a. s. l.) (Lehot 2012). The ambient pressure of the KC 135, which is no longer in service, was 751 mbar, which is equal to an altitude of 2,438 m. a. s. l. (Lehot 2012).

Even the mild hypobaric hypoxia (HH), equivalent to 2,400 m. a. s. l., of a typical airplane cabin has been associated with a reduction of baroreflex sensitivity (Sevre et al. 2002), which is one of the most important cardiovascular control mechanisms under changing gravity. In contrast, hypoxemia with an arterial oxygen saturation of 90–95 % causes pulmonary vasoconstriction, leading to a 20 % increase in pulmonary pressure in healthy subjects during air travel (Smith et al. 2012). Hypoxic pulmonary vasoconstriction (HPV) leads to a reduction of the arterial and venous blood volume in the lungs (Sylvester et al. 2012). Consequently, we can expect opposing mechanisms to act on the pulmonary blood volume during parabolic flight: a cephalic volume shift under microgravity bouts would increase pulmonary blood volume, whereas the persistent HPV would

Table 1 Subject characteristics

No.	Subject code	Sex	Height (cm)	Weight (kg)	BMI (kg/m^2)	Age (year)	First flyer	M.S.	Hypobaric chamber
1	0AA	M	179	80	25	28	N	N	Y
2	0AC	F	172	58	20	44	N	N	Y
3	0AL	M	181	72	22	28	N	N	Y
4	0AM	F	172	67	23	27	N	N	Y
5	0AO	F	158	50	20	33	Y	N	Y
6	0AK	M	168	70	25	45	N	N	Y
7	0AD	M	182	75	23	28	N	Y	Y
8	0AP	M	191	80	22	44	Y	Y	Y
9	0AR	M	172	67	23	43	N	N	N
10	0AS	F	167	58	21	31	Y	N	Y
11	0AW	F	167	55	20	29	Y	N	Y
12	0AX	F	167	60	22	29	N	N	Y
13	0AT	F	163	52	20	34	Y	Y	N
14	0BF	M	165	58	21	36	Y	N	N
15	0BR	M	179	81	25	36	Y	N	N
16	0BX	F	172	66	22	30	Y	N	N
17	0BY	F	167	59	21	28	Y	N	N
18	0CC	M	175	80	26	30	N	N	N
Ratio		9:9					9:9	15:3	18:11
Mean			172	66	22	34			
SD			8	10	2	6			

M male, *F* female, *N* no, *Y* yes, *BMI* body mass index, *First flyer* subject had never participated in a parabolic flight before, *M.S.* motion sickness experienced by the subject, *Hypobaric chamber* subject participated in the supplemental hypobaric chamber experiment

decrease it. Furthermore, it is known today that even slight hypobaric hypoxic conditions at quite low altitudes, from 1,000 m. a. s. l., induce changes in blood volume (Bartsch and Saltin 2008). However, the effects of HH on baroreflex sensitivity, pulmonary blood volume and the body fluid system during parabolic flights have not yet been examined.

We therefore measured cardiovascular, pulmonary, hormonal and fluid volume parameters during parabolic flights and repeated these measurements in a hypobaric chamber. Our specific hypotheses were the following: (1) cardiac output in a state of weightlessness is not constant during a parabolic flight but rather increases over time because of an increase in intravascular volume; and (2) the cephalic blood volume shift in weightlessness overrules the hypoxic pulmonary vasoconstriction and leads to an increase in lung tissue volume.

When designing this study, we also considered the commercial airplane parabolic flights and upcoming suborbital commercial parabolic flights. We believe that more research must be done to clarify potential health issues that may arise from the combined effect of moderate hypobaric hypoxia and intense gravitational transitions, particularly for flight surgeons responsible for future, most likely elderly, customers of airplane and suborbital parabolic flights.

Methods

Subjects

Eighteen healthy subjects participated in the parabolic flight study, and 11 also repeated an identical test protocol in the hypobaric chamber of the German Aerospace Center (DLR) in Cologne, Germany, during the first 3 months after their flights (Table 1). The test protocols were approved by the pertinent authorities (a) for the parabolic flights: *agence française de sécurité sanitaire des produits de santé* and *comité de protection des personnes nord oeust III* and (b) for the hypobaric chamber experiments: *Ärztekammer Nordrhein*. All subjects were free of any cardiopulmonary, renal or other systemic diseases, none were taking any medications on a regular basis and each passed a special parabolic flight medical examination (requirements of the parabolic flight executing company, (NOVESPACE 2013)) based on the JAR Class III examination at the aeromedical center of the DLR, Cologne. All subjects provided written informed consent to participate in the study. Heavy exercise and alcohol were strictly prohibited beginning 24 h before any testing. Scopolamine-hydrobromide was applied subcutaneously before the flights (125 μg in women and

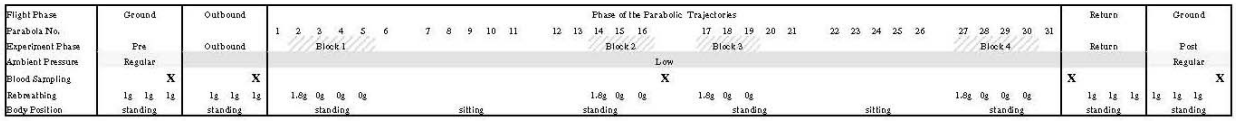

Fig. 1 Study design: measurements were performed at regular ambient pressure before and after parabolic flight and hypobaric chamber runs (pre and post, respectively); and under low ambient pressure conditions in a standing position in a parabolic flight and in the hypobaric chamber (outbound, block 1–4, return); and in a standing position combined with gravity transitions in parabolic flight and without gravity transitions in the hypobaric chamber. Measurement blocks for cardiovascular and pulmonary data acquisition and time points of blood sampling are indicated

175 μg in men) as a prophylactic against motion sickness. The same dosage was also administered before the hypobaric chamber tests to allow for comparable test conditions (Hyoscine Injection BP 400 μg/ml, UCB Pharma Ltd, Berkshire, UK). Subjects drank between 100 and 200 ml of water during an experiment day to antagonize dry mouth caused by scopolamine medication and rebreathing maneuvers.

Experiment protocols

Parabolic flights

Data were obtained during the 15th, 16th and 19th DLR parabolic flight campaigns between 2010 and 2012. The flights were performed in the Airbus A300 Zero-G of the French NOVESPACE company in Bordeaux, France. Flights took off from and returned to the Bordeaux Merignac Airport (airport altitude: 49 m. a. s. l.) where the pre- and post-flight measurements were performed. Each flight campaign consisted of three successive flight days. Thirty-one parabolas were flown on each flight day in sets of five consecutive parabolas separated by short 4–5 min phases of steady flight. The 16th and 17th parabolas were separated by a longer, 8-min break. During the flights, the cabin environmental conditions were as follows: 830 mbar pressure (equivalent to an altitude of 1,650 m. a. s. l.), approximately 15 % humidity, an ambient temperature of approximately 19 °C, an illumination level of approximately 800 lux, a light color temperature between 3,400 and 3,600 K, a noise level of 70–80 dB and a vibration level of approximately 0.008 g with a frequency spectrum of 1–400 Hz. The ambient atmospheric conditions on the ground during pre- and post-flight varied over the time period of the campaigns because of changes in weather conditions and seasons; the ambient pressure was approximately 1,005 mbar, the humidity ranged from 30 to 100 % and temperature ranged from 9 to 26 °C.

After a light breakfast, each subject was equipped with a lead-II electrocardiogram (ECG), impedance cardiogram (ICG) and finger blood pressure device (FBP). Thereafter, an indwelling short 16 G catheter for blood sampling was inserted in the antecubital vein of the right arm (Vasofix® Certo, B. Braun Melsungen AG, Melsungen, Germany). Subsequently, subjects received scopolamine at 8 a.m., and a baseline blood sampling was performed. Baseline measurements were then conducted, consisting of at least three repetitions of cardiac index measurements by rebreathing (CI_{rb}), FBP, HR and ICG in a standing position in the airplane cabin with the doors still open. The subjects were then seated for taxiing and take off for approximately 30 min. After a steady flight level was reached, three outbound data sets were collected in the standing position, and a second blood sample was obtained. During the flight phase of the parabolic trajectories, rebreathing exercises were performed in the standing position only at 0 and 1.8 G_z during parabolas 2–5 (block 1), 14–16 (block 2), 17–19 (block 3) and 27–30 (block 4). BP, HR and ICG data were collected continuously. Subjects stood in the upright body position during parabolas 1–6, 12–21 and 27–31 and were sitting during the remaining 10 parabolas (Fig. 1) to recover from the intense orthostatic challenge and thus to decrease their risk of presyncope and motion sickness. Two more blood samples were obtained after the 16th and 31st parabolas. At least three sets of rebreathing exercises and cardiovascular data points were collected during the return flight, and another three sets were collected after landing on the ground while the subjects were still in the airplane but with the doors open. The final blood sample was also collected on the ground. We adopted a rigorous rebreathing procedure that enabled us to measure two subjects at the same time (Online Resource 1). In particular, an operator indicated the breathing frequency and depth by moving his hand up and down, and both subjects triggered their breath cycles to the hand signals. During the parabolic trajectories, the rebreathing maneuvers were strictly aligned to the pilot's announcements of trajectory: (1) "10 s" (2) "pull up" with increased G_z load of up to 1.8 G_z; (3) "20", "30", and "40", signifying the rising angle of attack of the airplane; (4) "injection", with a rapid decrease of the G_z load to approximately 0.05 G_z; and (5) "pull out", with an increased G_z load of up to 1.8 G_z. Each phase lasted approximately 20–25 s. Controlled rebreathing was initiated after the pilot's announcement of "10 s" for

the hyper-g measurements or at the pilot's announcement of "40" for the 0 G_z measurements during the final pull-up seconds. Thus, the breaths relevant for CI_{rb} determination occurred during the 1.8 and 0 G_z phases, respectively, and the rebreathing maneuver was completed before injection and pull out, respectively.

Hypobaric chamber

The actual individual parabolic flight protocol for 11 of the 18 subjects was identical to that of the hypobaric chamber test. This comparison was performed to determine any potential effects of hypobaric hypoxia, restricted water intake in flight and changes in body position on the parameters of interest and to separate such effects from the effects of hyper- and microgravity. Tests were performed in the hypobaric chamber of the DLR Institute of Aerospace Medicine in Cologne, Germany, which has dimensions of 2.8 × 2 m and provides seats for six people. One subject was tested during each chamber run, supported by two operators in the chamber. The subjects received identical instructions before the chamber run and their parabolic flights. The chamber runs started at the same time as the actual parabolic flights and lasted as long as the individual flight day. The rebreathing and body position protocols were the same as those performed in flight. The subjects received an equal amount of subcutaneous scopolamine before their chamber runs, and the parabolic flight blood draw protocol was performed similarly. The chamber was depressurized to the actual inflight cabin pressure of that particular subject's flight. De- and re-pressurization of the hypobaric chamber had exactly the same duration as in the actual flight of the subject. The other environmental conditions in the chamber were approximately 60 % humidity, an ambient temperature of approximately 23 °C, an illumination level of approximately 150 lux, a light color temperature of approximately 3,000 K, a noise level of approximately 70 dB due to airflow and no significant vibrations.

Measurements

Inert gas rebreathing

Cardiac index (CI_{rb}), stroke index (SI_{rb}), oxygen consumption (VO_2) and lung tissue volume (Vt) were determined by inert gas rebreathing (IGR) using an Innocor® commercial inert gas rebreathing device (Innovision, Glamsbjerg, Denmark). Oxygen saturation (SO_2) of the arterial blood was measured during each rebreathing at a fingertip. The subjects breathed ambient air through a face mask fitted around the nose and mouth. When a CI_{rb} measurement was required, the system switched to a closed rebreathing mode. A respiration bag was automatically filled with a gas mixture composed of 29.5 % O_2 in N_2, 0.5 % N_2O (soluble tracer gas) and 0.1 % SF_6 (non-soluble tracer gas). In our study, the volume of the respiration bag was approximately 40 % of the vital capacity of the subject. The pulmonary blood flow (PBF), which, in the absence of significant shunts, is equal to cardiac output, was calculated on the basis of the soluble tracer gas disappearance rate (N_2O), the total volume of the system and the Bunsen solubility coefficient of the tracer gas in blood (Clemensen et al. 1994) (for details see Online Resource 2).

Cardiovascular parameters

Continuous beat-by-beat finger blood pressure was measured using a Finometer MIDI device [Finapres Medical Systems (FMS), Amsterdam, The Netherlands], which uses a photoplethysmographic technique based on the volume clamp method of the Czech physiologist J. Peňáz. The finger cuff was placed around the third finger of the left hand and the left hand was fixed by a bandage at the level of the fourth intercostal space at the assumed level of the heart. The mean arterial pressure was calculated from the systolic and diastolic finger blood pressures by the formula $\left[P_{\text{diast}} + \frac{P_{\text{syst}} - P_{\text{diast}}}{3}\right]$. The systemic vascular resistance was calculated by dividing the mean arterial pressure by CO_{rb} $\left[\frac{\text{MAP (mmHg)}}{\text{CO}_{\text{rb}}\left(L \times \text{min}^{-1}\right)} = \text{SVR}\left(\frac{\text{mmHg}}{\text{min} \times L}\right)\right]$. Finger blood pressure, ECG and thoracic impedance data were measured continuously during the rebreathing pre- and post-flight on the ground, during the rebreathing maneuvers in the outbound and return phases and during the entire phase of the parabolic trajectories. These data were stored at 2,000 Hz using ACQ*Knowledge*® 4.0 software (Biopac Systems Inc., Goleta, CA, USA) on a laptop (Dell Precision Workstation, Dell Inc., Round Rock, USA) for post-flight analyses. A solid-state hard drive was used for data storage to prevent automatic computer shutdown at 0 G_z, which would be triggered by the laptop built-in free-fall sensor that would mistakenly indicate that the computer was falling down during the 0 G_z phases. Rebreathing maneuvers were subsequently identified from the thoracic impedance signal. The finger blood pressure and heart rate were averaged across the three relevant breaths required for the measurement of the SI_{rb}, and these averages were then processed as single blood pressure and heart rate data points for further analysis (Limper et al. 2011).

Blood counts and intravascular volume

During parabolic flights and hypobaric chamber experiments, 10-ml serum and 6-ml EDTA blood samples were drawn. The overall amount of blood drawn during an

experiment day was 80 ml. Intravascular volume on parabolic flight days and in the hypobaric chamber was determined using the Optimized Carbon Monoxide Rebreathing Technique (CORT) (Prommer and Schmidt 2007; Schmidt and Prommer 2005). In each case, 3-ml EDTA blood samples (*S-Monovette*®, Sarstaedt AG & Co., Nümbrecht, Germany) were drawn from the antecubital vein via intravenous puncture (21 G Venofix® Safety, B. Braun Melsungen AG, Melsungen, Germany). Each subject performed the carbon monoxide rebreathing procedure only once at the German Aerospace Center in Cologne, Germany with less than 2 months between the parabolic flights and hypobaric chamber runs (Online Resource 2). During the parabolic flights and the hypobaric chamber runs, blood samples were drawn in 2.0-ml EDTA tubes via the 16 G intravenous line in the right antecubital vein. Blood draws were performed five times per experiment day: pre, outbound, post 16 (meaning after the 16th parabola), post 31 (after the 31st parabola) and post. Identical labeling was used for the blood samples of both facilities. Blood samples were immediately refrigerated at 5 °C after collection. Blood count analyses were performed following landing at a local medical laboratory via a routine clinical method (Laboratoire d'Analyses Weckerle, Martignas-sur-Jalle, France). Analyses were performed twice, and the average results of the duplicates were used for intravascular volume calculations. After the hypobaric chamber experiments, blood counts were analyzed immediately at the laboratory of the German Aerospace Center in Cologne, Germany using the ABX Pentra 60 hematology analyzer (Horiba ABX SAS, Montpellier Cedex, France).

Biochemical analyses

Following collection, all samples were refrigerated at 5 °C until centrifugation at 1,500 rpm for 15 min at 4 °C. Plasma and serum were then transferred to 1.5-ml tubes, immediately frozen on dry ice and then kept at −80 °C. Blood osmolality and albumin, cortisol, aldosterone, CT-$_{pro}$AVP, renin$_{active}$ and NT-$_{pro}$BNP concentrations were determined using standard methods by a commercial biomedical laboratory (MVZ Labor Dr. Quade und Kollegen, Cologne, Germany) within 3 months of blood sampling (for details, see Online Supplement 2).

Statistical analyses

We evaluated 631 inert gas rebreathing data sets and the same amount of simultaneously collected ECG and finger blood pressure data sets. In total, 374 data sets were collected during the parabolic flight days, whereas 257 data sets were collected during the hypobaric chamber tests; 128 and 66 inert gas rebreathing maneuvers were performed at 0 and 1.8 G_z, respectively.

Analysis of variance (ANOVA) tests using a general linear model evaluated fixed effects of facility (parabolic flight vs. hypobaric chamber) and phase ("pre"; "outbound"; "block 1, block 2, block 3 and block4"; "return" and "post", Fig. 1), and their interactions. Subject ID was used as a random factor to account for between-subject variability. Where fixed factors were significant, post hoc Tukey's Honestly Significant Difference Test was employed to identify significant differences. For Phase, identical phase names were used for both parabolic flights and the hypobaric chamber to increase clarity. $P = 0.05$ was taken as the minimum level of significance. All statistical analyses were performed using STATISTICA 10 (StatSoft, Inc., Tulsa, OK, USA).

Results

The results which are given in the following originate from a mixed-gender sample (Table 1).

Cardiovascular parameters

Figures 2, 3, 4 show the cardiovascular and pulmonary responses in parabolic flight and in the hypobaric chamber. HR decreased significantly during the hypobaric chamber run ($p < 0.001$) with respect to pre but did not differ during measurements post relative to pre ($p = 0.639$). In parabolic flight, HR was significantly decreased at 0 G_z with respect to pre ($p < 0.001$) and significantly increased at 1.8 G_z with respect to pre ($p < 0.001$). However, HR at 0 G_z decreased significantly over time (block 1 vs. block 4 $p < 0.001$). A similar attenuation in HR increase at 1.8 G_z was observed over time (block 1 vs. block 4, $p < 0.001$). HR was lower post-flight than in pre-flight measurements ($p < 0.001$).

The stroke index by rebreathing changed significantly during the hypobaric chamber run ($p < 0.001$) (Fig. 3, Online Supplements 3, 5). With respect to normobaric normoxia (NN) conditions at pre, SI_{rb} showed a significant increase during chamber outbound ($p < 0.001$) and block 2 ($p < 0.001$) and a tendency increase during block 3 and block 4 ($p = 0.0775$ and $p = 0.0798$, respectively). SI_{rb} was not significantly different between post measurements and pre measurements ($p = 0.952$). In parabolic flight, SI_{rb} was significantly enlarged at 0 G_z with respect to pre ($p < 0.001$). It was also significantly higher during outbound with respect to pre ($p = 0.026$). However, SI_{rb} did not decrease at 0 G_z over time (block 1 vs. block 4, $p = 0.682$). In the hyper-g of block 1, SI_{rb} showed no significant difference with respect to pre measurements

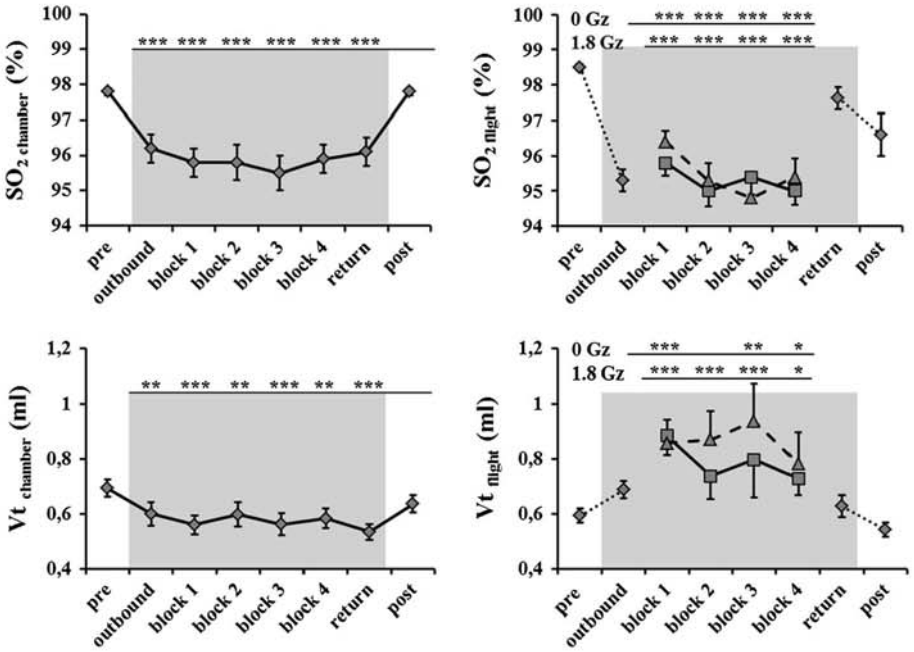

Fig. 2 Time course of main pulmonary parameters in parabolic flight in 18 subjects and in hypobaric chamber in 11 subjects is shown as the mean ± SE; *asterisks* indicate significant differences with respect to pre: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$; *gray background* indicates measurements in hypobaric hypoxia after decompression to 830 mbar

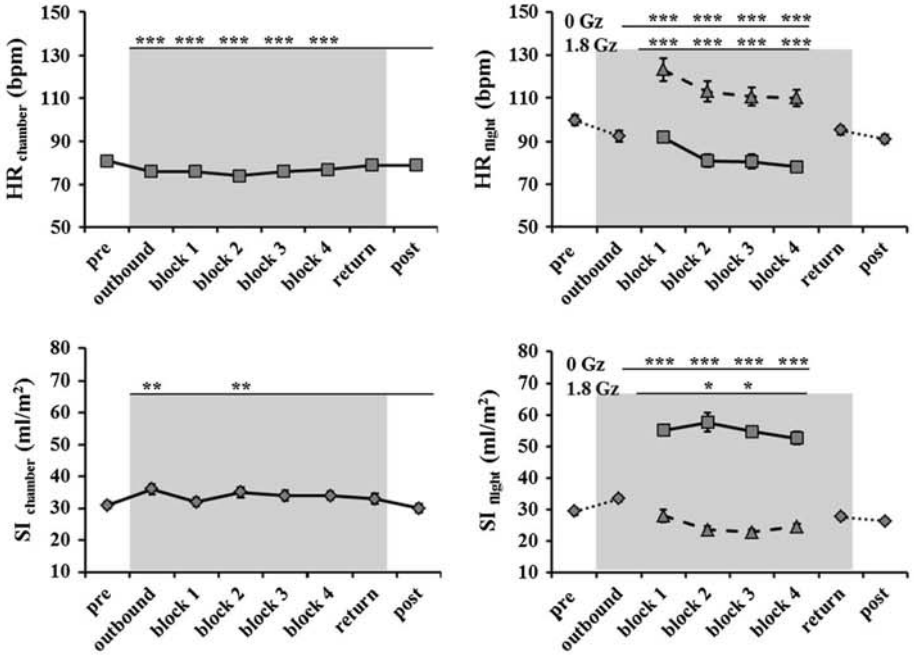

Fig. 3 Time course of heart rate and stroke index responses in the hypobaric chamber and in parabolic flight; responses in 0 G_z, *solid black graph* and at 1.8 G_z; *dashed black graph* are shown separately. *Asterisks* indicate significant changes with respect to pre separately for hyper- and microgravity values; *gray background* indicates low ambient cabin pressure

($p = 0.999$) but was subsequently smaller in block 2 and block 3 with respect to pre ($p = 0.017$ and 0.002, respectively). SI_{rb} was similar during pre- and post-flight measurements ($p = 0.323$).

With respect to pre baseline measurements, CI by rebreathing did not change significantly in any phase in the hypobaric chamber (Online Supplement 3, 5). However, in parabolic flight, CI_{rb} was significantly increased at 0 G_z with respect to pre in each block ($p < 0.001$). CI at 0 G_z decreased in a stepwise fashion (block 1 vs. block 4, $p < 0.001$). In block 1, CI_{rb} was significantly increased at 1.8 G_z with respect to pre, similar to pre in block 2 and block 4 ($p = 0.660$ and 0.817, respectively), and was significantly smaller with respect to pre measurements only

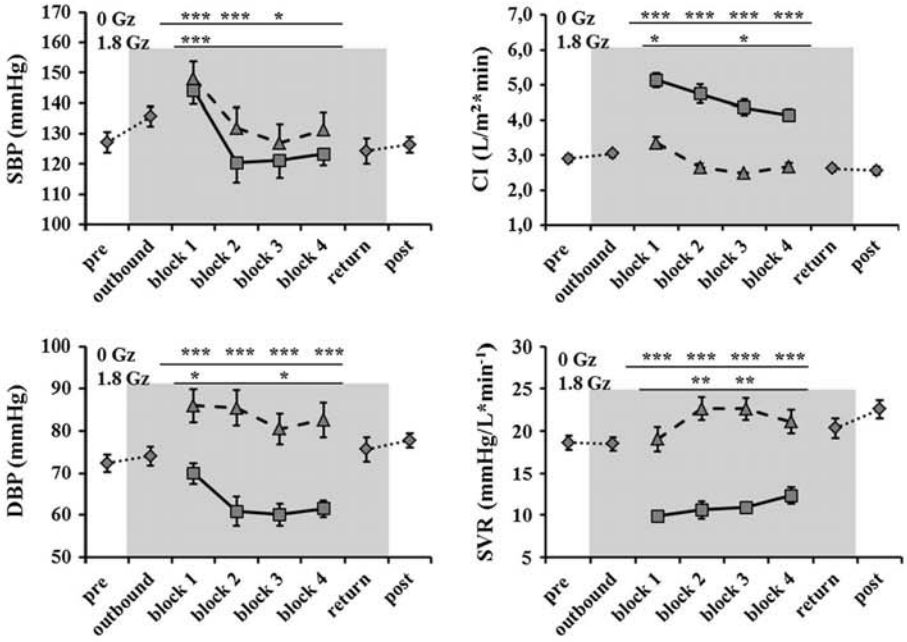

Fig. 4 Time course of arterial pressure, systemic vascular resistance and cardiac index in parabolic flight; responses at 0 G_z, *solid black graph* and at 1.8 G_z, *dashed black graph*, are shown separately. *Asterisks* indicate significant changes with respect to pre separately for hyper- and microgravity values; *gray background* indicates low ambient cabin pressure

in block 3 ($p = 0.0252$). Furthermore, CI_{rb} was significantly decreased after parabolic flight with respect to pre ($p = 0.006$).

The systolic blood pressure, shown in Fig. 4 and Online Supplements 3 and 5, did not show any significant change during the hypobaric chamber runs ($p = 0.559$). In contrast to the hypobaric chamber, FBP_{syst} changed significantly in parabolic flight, and the changes were of a similar pattern at 0 and 1.8 G_z. FBP_{syst} was significantly increased in block 1 at both 1.8 and 0 G_z with respect to pre ($p < 0.001$ and < 0.001, respectively). During block 2 and block 3, FBP_{syst} was not different at 1.8 G_z but significantly decreased at 0 G_z with respect to pre (1.8 G_z, $p = 0.195$ and 1.0, respectively; 0 G_z, $p < 0.001$ and 0.007, respectively). During block 4, FBP_{syst} did not differ significantly at 0 G_z or at 1.8 G_z with respect to pre ($p = 0.104$ and 0.537, respectively). FBP_{syst} was similar after flight with respect to pre ($p = 0.999$).

Diastolic arterial pressure (FBP_{diast}) did not show any change during the hypobaric chamber test ($p = 0.814$), as shown in the Online Supplements 3 and 5. In parabolic flight, FBP_{diast} was significantly increased at 1.8 G_z in each block with respect to pre ($p < 0.001$ each), as shown in Fig. 4. At 0 G_z during block 1, FBP_{diast} did not differ significantly from pre values ($p = 0.102$) but was significantly lower at 0 G_z in block 2 to block 4 with respect to pre ($p < 0.001$ each). After parabolic flight, FBP_{diast} remained higher than before parabolic flight ($p < 0.001$).

Systemic vascular resistance (SVR) did not change at any time in the hypobaric chamber ($p = 0.921$) (Online Supplements 3 and 5). However, in parabolic flight (Fig. 3), SVR showed a significant decrease at 0 G_z from block 1 with respect to pre ($p < 0.001$ for each block). At 1.8 G_z of block 1, SVR was statistically similar to pre ($p = 0.999$) but increased compared to pre values, in block 2 and block 3 ($p < 0.001$ each). In block 4, SVR was again not significantly different from pre values ($p = 0.198$). However, SVR was significantly increased after parabolic flight with respect to pre values ($p < 0.001$).

Pulmonary parameters

Oxygen saturation was significantly decreased in reduced ambient pressure with respect to regular ambient pressure in both parabolic flight and in the hypobaric chamber ($p < 0.001$ and $p < 0.001$, respectively) (Fig. 2 and Online Supplements 4 and 5). With respect to normobaric normoxia baseline measurements, pulmonary tissue volume was significantly decreased only in hypobaric hypoxia conditions in the hypobaric chamber ($p < 0.001$); in contrast, it was significantly increased at 0 and 1.8 G_z ($p < 0.001$ and $p < 0.001$) (Fig. 2 and Online Supplements 4 and 5). Oxygen consumption did not show any significant change in the hypobaric chamber in HH relative to regular pressure ($p = 0.330$). Oxygen consumption was not different between 1.8 G_z and baseline 1 G_z + NN but was significantly increased at 0 G_z relative to 1 G_z + NN ($p < 0.001$) (Online Supplements 4 and 5).

Plasma volume

Figure 5 shows that the response patterns of plasma volume did not differ significantly between parabolic flight and the

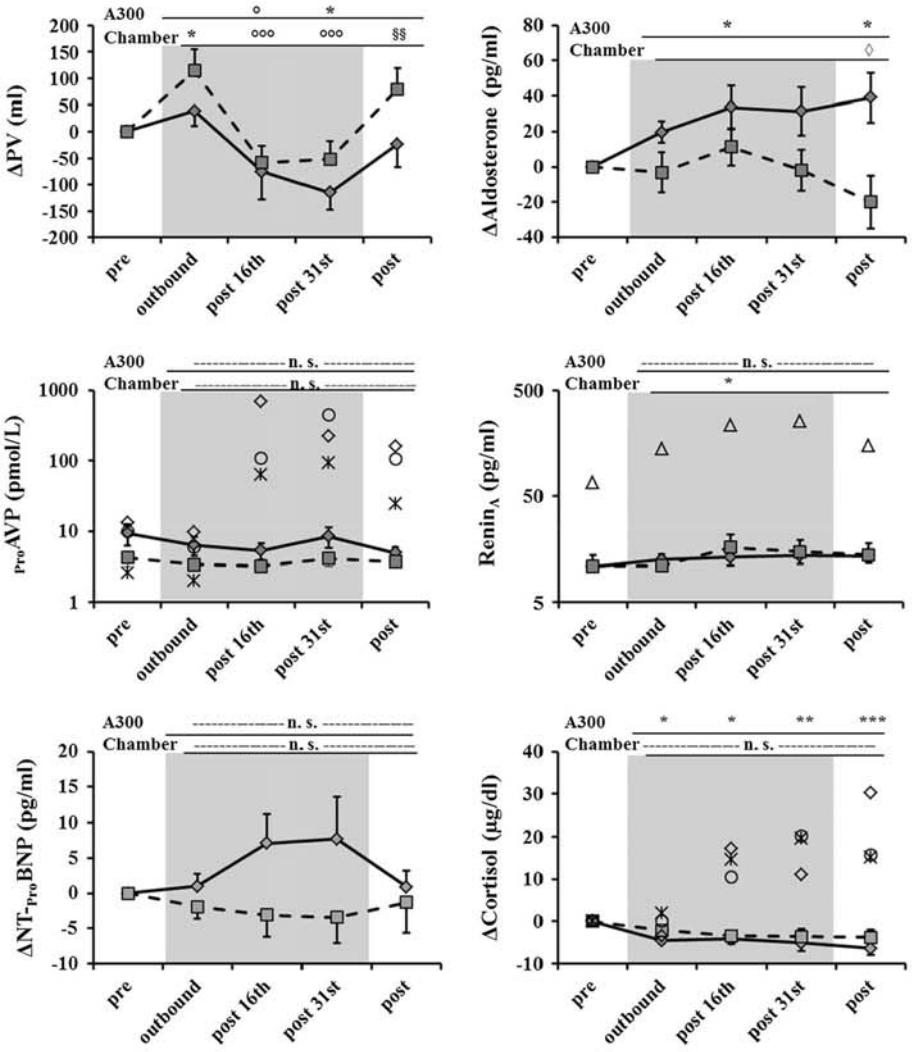

Fig. 5 Courses of plasma volume and a subset of blood hormones are shown as a continuous *black graph* for parabolic flight and as *dashed black graph* for the hypobaric chamber results; significant differences with respect to pre are indicated as *asterisk* in parabolic flight (A300) and in the hypobaric chamber (chamber); the statistical significance of plasma volume and ΔAldosterone is illustrated as *asterisk* with respect to pre; *degree symbol* with respect to outbound; *open diamond* with respect to post 16th; and *section symbol* with respect to post 31st. In the Δ_{pro}AVP and Δcortisol diagrams, the *black open circle* represents subject 0AP, the *black cross* represents subject 0AD, the *black open* diamond represents subject 0AT; in the renin$_{active}$ diagram (Renin$_A$), the *black open triangle* represents the individual responses of subject 0AL; *gray background* indicates hypobaric hypoxic conditions

hypobaric chamber ($p = 0.449$). However, responses in the hypobaric chamber seemed to be more distinct. In parabolic flight, there was a significant decrease in plasma volume after parabola 31 with respect to pre ($p = 0.034$). Pre and post values were not significantly different on the parabolic flight day ($p = 0.9728$). In the hypobaric chamber there was a significant increase in plasma volume during outbound with respect to pre (0.024) and then a significant decrease in plasma volume at post 16 and post 31 with respect to outbound ($p < 0.001$ and <0.001, respectively). Post-flight plasma volume recovered to baseline values again and was significantly higher than at post 16 and post 31 ($p = 0.004$ and 0.007, respectively) (Online Supplement 6).

Blood hormones and osmolality

Cortisol and CT-$_{pro}$AVP are strongly influenced by motion sickness (Schneider et al. 2007; Kohl 1987; Drummer et al. 1990). Thus, the three motion-sick subjects 0AD, 0AP and 0AT were excluded from the statistical analyses of cortisol and the CT-$_{pro}$AVP parabolic flight values, but their responses are shown individually in Fig. 5. Subject 0AL showed a very different renin response pattern in the hypobaric chamber; thus, the renin hypobaric chamber values of 0AL were removed from the statistical analysis but are provided individually in Fig. 5. Depending on the inter-individual variance, some parameters are shown as differences from the baseline and some as absolute values.

ΔCortisol decreased significantly after the parabolic flight relative to pre-flight measurements ($p < 0.001$). In the hypobaric chamber, a significant change in cortisol over time was also visible ($p = 0.0475$). CT-$_{pro}$AVP did not show any difference between its response to parabolic flight and its response to the hypobaric chamber ($p = 0.810$). In both facilities, CT-$_{pro}$AVP was not different after the run with respect to baseline levels ($p = 0.154$

and 0.566). Similarly, there was no significant difference in the course and absolute values of osmolality between both facilities ($p = 0.726$ and $p = 0.379$, respectively), although osmolality appeared to be slightly higher on parabolic flight days. $Renin_{active}$ did not react differently between the hypobaric chamber and parabolic flight ($p = 0.213$). However, post 16th renin showed a significant increase with respect to pre ($p = 0.013$). In parabolic flight, $renin_{active}$ did not change significantly over time ($p = 0.168$). The time course of aldosterone levels was significantly different between the hypobaric chamber and parabolic flight ($p = 0.044$). In the hypobaric chamber, aldosterone levels tended to decrease over time with respect to pre without reaching statistical significance ($p = 0.0926$), but the decrease was significant after the chamber run with respect to post 16th ($p = 0.0458$). In parabolic flight, aldosterone levels increased over time. At post 16th and post-flight, aldosterone levels were significantly elevated with respect to pre ($p = 0.041$ and 0.011, respectively). The time course of $NT\text{-}_{pro}BNP$ was statistically not different between the hypobaric chamber and parabolic flight ($p = 0.136$). However, it showed a strong tendency to increase in the parabolic flight ($p = 0.075$) and to decrease in the hypobaric chamber ($p = 0.056$) (Online Supplement 6).

Discussion

The major findings of the study are fourfold. *First*, confirmation of the observations of the studies of Iwase et al. (1999a) and Beckers et al. (2003) who found that cardiovascular responses to the transition into weightlessness in a standing position are different between the early parabolas of a parabolic flight and the later parabolic phases. Our results give new insights into the mechanisms of those differences by showing that, in the early phase of the flight, there is no distinct blood pressure decrease after the injection of 0 G_z, which would have been expected. However, SVR is decreased at 0 G_z from the early phase of the flight on. Thus, blood pressure is kept elevated by a lack of heart rate decrease after injection together with an already increased stroke volume. Over the course of a parabolic flight day, the heart rate at 0 G_z decreases and through decreased cardiac output leads to a pronounced blood pressure drop at 0 G_z in the later phases. *Second*, the plasma volume response pattern in the hypobaric chamber and during parabolic flight is comparable. With respect to the baseline, an increase in PV during outbound was observed in both facilities, followed by a decrease after the 16th and 31st parabola and an increase after recompression. This pattern suggests that changes in plasma volume depend mainly on changes in body position and changes in ambient and oxygen partial pressure and depend to a lesser degree on gravity changes produced by parabolic trajectories. *Third*, differences in hormonal responses occur between the two facilities. Whereas the combination of hypobaric hypoxia and gravity changes in parabolic flight induces an increase in aldosterone, the opposite is the case after the hypobaric chamber run. $NT\text{-}_{pro}BNP$ shows a strong tendency to increase during parabolic flight maneuvers but not in hypobaric hypoxia in a hypobaric chamber alone. $Renin_{active}$ is increased in the hypobaric chamber but is not affected by parabolic flight. *Fourth*, the lungs and the cardiovascular system interact differently in the two facilities. Whereas in the hypobaric chamber, lung tissue volume is decreased by hypoxic pulmonary vasoconstriction, lung tissue volume is increased at 0 and in 1.8 G_z in parabolic flight.

Our results show that the cardiovascular response to microgravity transitions in the standing position differs between the early and later parabolas. This finding is of importance for the design and the interpretation of cardiovascular experiments on parabolic flights. Our results suggest that data collected during the initial five parabolas of a parabolic flight should be discarded to increase the homogeneity of the cardiovascular results. The observed variability may be partly derived from the administration of scopolamine, which has a serum elimination half-life of approximately 2 h (Stetina et al. 2005). This point may suggest that half-elimination of scopolamine from the circulation has already occurred after an early parabolic flight phase. However, the increased level of psychomotor excitement is also certainly of importance. In contrast, changing interactions of the baroreflex and a "Bainbridge-like Reflex" may explain changes in cardiovascular responses over the parabolic flight. Whereas the Bainbridge-like reflex induces tachycardia triggered by a central volume increase by a volume shift at 0 G_z (Petersen et al. 2011), the baroreflex would induce bradycardia. It is possible that the Bainbridge-like reflex predominates in early parabolic flight because the vagotropic blocking capability of Scopolamine suppresses the vagal efferent outflow of the baroreflex. The sympathetic withdrawal effect of the baroreflex at 0 G_z seems to be unaffected, as indicated by a decreased SVR at 0 G_z from the very first parabola (Fig. 3) and as found by Iwase et al. (1999b). However, whether factors other than scopolamine, e. g., hypobaric hypoxia, influence arterial and cardiac regulation remains unclear. Systolic and diastolic blood pressure was unaffected in the hypobaric chamber, whereas heart rate decreased, which could indicate a resetting of the baroreflex. However, the neutral, rather tedious environment of the confined hypobaric chamber experiment could well have contributed a further decrease in heart rate. How the baroreflex behaves in hypoxia and hypobaric pressure has been inconsistently defined in the literature. Halliwill and Minson (2002) present data supporting that hypoxia resets the baroreflex and

muscle sympathetic nerve activity (MSNA) to higher levels without changing the baroreflex sensitivity, whereas Sevre et al. (2002) found evidence for reduced baroreflex sensitivity in a hypobaric chamber experiment simulating an airplane cabin atmosphere with a pressure equivalent to an altitude of 2,400 m (Sevre et al. 2002; Halliwill and Minson 2002). Finally, heart rate increases typically in hypoxia caused by decreased oxygen partial pressure in the blood (West et al. 2007), which was contrary to the findings of our hypobaric chamber runs.

We found a slight intermittent decrease in plasma volume over both parabolic flight and hypobaric chamber courses. This finding was contrary to our expectations. Schlegel reported that the 16 subjects of the parabolic flight experiment had on average a larger stroke volume in the supine position when compared between and after the flight, suggesting an increase in blood volume (Schlegel et al. 2001). During the parabolas, the subjects had been in an upright sitting position, which allowed a certain value of volume shift through gravity transitions. Schlegel did not measure intravascular volume and hormone concentrations directly but actually focused on the question of whether changing levels of arginine vasopressin (AVP) and renin–angiotensin–aldosterone could lead to an increase in intravascular volume during parabolic flights. Schlegel suggested, based on previous work, that the predominance of hyper G_z during the flight with respect to μG_z may have led to the expansion of intravascular volume. Indeed, the overall durations of the μG_z and hyper G_z phases during a parabolic flight were approximately 1,000 and 2,000 s, respectively, on the KC 135 and approximately 700 and 1,400 s, respectively, on the A300 Zero-G, and therefore twice as long under hyper than under μG_z. Those longer micro- and hypergravity phases and the different flight profile on KC 135 parabolic flights may be an explanation for the different findings between Schlegel's and our work. Nevertheless, we found, in accordance with the concept of a modification of the Starling–Landis pressure under changing gravity as noted by Hargens and Richardson (2009), a plasma volume loss during parabolic flight and a recovery to baseline values after re-pressurization. Again, we would have expected that such a contraction of intravascular volume through the effects of hyper G_z and μG_z on the Starling–Landis equation during the parabolic flight day would have been aggravated by hemoconcentration because of the hypobaric hypoxia of the airplane cabin inflight. It is well known that hypoxia induces a reduction in plasma volume that increases the hematocrit and thereby improves tissue oxygenation (Bartsch and Saltin 2008). This finding is already accounted for from just slight hypobaric hypoxia, i.e., in an ambient pressure equivalent to an airplane cabin inflight. However, in contrast to our expectation, Yamashita et al. were not able to find a significant effect of 130 min of quiet sitting in a hypobaric chamber in an ambient pressure equivalent to the pressure at 2,000 m and a low relative humidity of 20 % on hematocrit levels with respect to the regular ambient pressure of sea level (Yamashita et al. 2005). However, they did find a significant decrease of body weight (100–200 g) after the chamber test with respect to baseline values. This finding may indicate a loss of extracellular water with a concomitant preservation of intravascular volume. Yamashita et al. concluded that low humidity conditions may have a higher effect on fluid loss than the hypobaric hypoxia itself. However, we found more pronounced changes in plasma volume over the course of the hypobaric chamber testing than during the parabolic flight, whereas the response pattern for the plasma volume in both facilities seemed to be similar. An explanation for the greater plasma volume changes in the hypobaric chamber, in addition to the smaller subject collective, may involve a different volume status of the subjects during the chamber runs as indicated by a slightly lower average osmolality during the chamber runs. The high average osmolality of approximately 310 mosmol/kg in the subjects during the parabolic flights is a strong indicator for a dehydrated state on the flight days. AVP is known to be increased in volume-contracted subjects, and CT-$_{pro}$AVP shows a similar pattern for changes in blood volume (Szinnai et al. 2007). The reduced fluid volume in parabolic flight may be explained by the participants' overnight fasting and then only having a slight breakfast without much morning fluid intake. The lower humidity in the airplane cabin inflight with respect to the chamber may have been an additional factor in the differences in osmolality, but the difference was already apparent during the baseline measurements. However, it should be taken into account that high osmolality has an impact on cardiovascular reflexes. Charkoudian et al. reported that hyperosmolality of even 290 mosmol/kg increases the baroreflex sensitivity in young subjects and has a sympathoexcitatory influence in general (Charkoudian et al. 2005).

In the present study, hormones related to volume regulation and their precursor peptides responded differently to scopolamine, standing position, gravity changes and HH in the airplane cabin on the one hand and to scopolamine, standing position and HH in the hypobaric chamber on the other hand.

Whereas aldosterone values increased in HH in combination with changing g-loads during the parabolic flight, they decreased in HH in the hypobaric chamber. Aldosterone levels are expected to decrease after a move to higher altitude and in hypoxia (Slater et al. 1969; Shigeoka et al. 1985). However, an aldosterone increase at altitude was reported by Humperler et al. (1980) and attributed by Richalet (2001) to the physical exercise in the study. Under orthostatic stress, aldosterone levels are known to increase

(Laszlo et al. 2001). Taken together, these studies underpin the following interpretation of our own results: in the hypobaric chamber, the serum aldosterone concentration decreased in response to HH. In contrast in parabolic flight, increased orthostatic stress and muscular load of standing upright during hyper-g phases, and increased postural muscular work due to turbulent flight phases, and potentially increased muscular work, induced by the airplane's whole-body vibrations, increased aldosterone release. This finding could be interpreted as supporting the effects of orthostatic and exercise stress on the effect of the stress of HH during parabolic flight on aldosterone release.

Indeed, $renin_{active}$ did not show a parallel response with aldosterone. The $renin_{active}$ post 16th measurement during hypobaric chamber testing showed a slightly significant increase with respect to pre. However, $renin_{active}$ did not show any further significant response, neither in parabolic flight nor in hypobaric chamber. This implies a dissociation of the aldosterone level and renin response under the particular conditions of parabolic flight. Interestingly, dissociation of plasma aldosterone levels and plasma renin activity has previously been reported in subjects experiencing presyncope and in subjects undergoing repeated orthostatic challenges by tilt table testing and lower body negative pressure (LBNP) tests (Roessler et al. 2011; Hinghofer-Szalkay et al. 2011). The works of Roessler et al. and Hinghofer-Szalkay et al. indicate furthermore that during orthostatic challenge aldosterone is rather controlled by adrenocorticotropic hormone (ACTH) than by renin, which may serve as an explanation of the dissociated aldosterone–renin response in parabolic flight.

NT-$_{pro}$BNP shows a strong tendency toward a different response in the chamber with respect to parabolic flight ($p = 0.0524$). Parabolic flight induces an increase, whereas only hypobaric hypoxia and a standing position do not affect NT-$_{pro}$BNP. This finding is in agreement with the literature, which reports that NT-$_{pro}$BNP does not increase with an acute ascent to altitude (Toshner et al. 2008) and during tilt table orthostatic tests, but does increase after an increase in thoracic blood volume-by-volume loading in healthy volunteers (Heringlake et al. 2004). This finding may indicate that the trend toward increased NT-$_{pro}$BNP during parabolic flight is triggered by reiterative increasing in the thoracic blood volume at 0 G_z. With subjects 0AT, 0AP and 0AD excluded from the analysis of the parabolic flight data for cortisol because of possible stress responses arising from motion sickness, cortisol showed a significant decrease over the day in both facilities. This finding underpins the observation of a decreased heart rate during the flights and shows that the stress level decreases. However, this response results not only from decreasing excitement during the experiments but also from the distinct circadian rhythm of cortisol. The blood cortisol concentration shows a physiological peak between 8 and 9 a.m. and a continuous decrease thereafter. Peak values in healthy subjects are approximately 16 μg/dl and decrease to approximately 12 μg/dl at noon (Debono et al. 2009). The baseline measurements before the flights and the chamber runs were obtained between 8 and 9 a.m., i.e., during the physiological cortisol peak, and post-intervention measurements were obtained between noon and 1 p.m. The measured cortisol values at these time points were similar to the circadian values of these day phases given in the literature by Debono et al. (2009)

Opposing alterations of pulmonary tissue volume in hypergravity and microgravity compared with hypoxia have been shown in different experiments. Snyder et al. (2006) showed a decrease in lung water and lung tissue volume under moderate hypoxia of 12.5 % inspired oxygen in resting healthy subjects. Rohdin and Linnarson found increased lung tissue volume in healthy subjects during 2 and 3 G_z centrifugation in a sitting position. Furthermore, they reanalyzed the parabolic flight data of Vaida et al. and noted an increase in lung tissue volume in weightlessness (Vaida et al. 1997; Rohdin and Linnarsson 2002). Vaida had performed the experiment during parabolic flights in the former European Caravel parabolic flight airplane under a hypobaric ambient pressure of 793 mbar. Thus, the results of Snyder, Rohdin and Vaida are in line with our observations of decreased Vt in the hypobaric chamber and increased Vt during weightlessness and hypergravity in parabolic flight. However, we are the first to show in the same subjects that the reduction in blood volume in hypobaric hypoxia of the airplane cabin is reversed by a central volume shift in weightlessness and by sequestration, as suggested by Rohdin and Linnarsson, of blood in the dependent parts of the lung circulation in the hypergravity phases. This finding could be of benefit for potential parabolic flight candidates suffering from pulmonary hypertension, which would be aggravated by the hypobaric hypoxia of the airplane cabin and which may be attenuated by the pulmonary response to hyper- and microgravity.

Limitations

The study design included some limitations that we tried to consider in our interpretation of the results. *First*, temperature, humidity, noise level, vibrations and light conditions in the hypobaric chamber were not fully comparable to parabolic flight because of a lack of air-conditioning in the hypobaric chamber, and because of a fixed installed non-changeable illumination system in the hypobaric chamber. It seems unlikely that the slightly higher temperature in the hypobaric chamber of approximately 23 °C, with respect to approximately 19 °C in the cabin of the A300 inflight, led

to changes in the orthostatic or volume-regulating behavior of the cardiovascular system for instance by skin vasodilation or even by increase of the core body temperature (Allan and Crossley 1972). There was a 10 dB difference in the noise level during parabolic flight with respect to hypobaric chamber runs. Thus, in both facilities the noise level was comparable and below 90 dB which is known to increase the degree of physiological arousal (Harding and Mills 1983) and therefore we do not assume a significant effect of differences in the noise levels of the two facilities on our data. On the other hand, vibrations which appeared only inflight and not in hypobaric chamber might have had a certain minor impact on our results. Although exposure to moderate levels of whole-body vibrations does not lead to consistent changes in basic measures of the cardiovascular system, there may be an increase in muscle activity to maintain body posture which may again lead to peripheral vasoconstriction (Rollin Stott 2006). Furthermore, whole-body vibration induces a slight increase in metabolic rate which is comparable with that seen in light exercise and to hyperventilation with a reduction in CO_2 (Rollin Stott 2006). However, forced hyperventilation due to vibrations inflight, with respect to the hypobaric chamber, would have led to an increase in SO_2 of the arterial blood inflight with respect to SO_2 in the hypobaric chamber, which indeed cannot be found in our data. The differences in illumination between the hypobaric chamber and the cabin of the A300 were approximately 650 lux in brightness and 600 K in light color temperature. Noguchi investigated the influence of 50 and 150 lux of light brightness and 3,000 and 5,000 K of light color temperature on the activity of the autonomic nervous system. They could not find any difference in the activity of the autonomous nervous system under these conditions what makes us doubting a significant effect of the differences in light characteristics in our study on our data (Noguchi and Sakaguchi 1999). *Second*, it is known that vestibular–autonomic interactions (Yates 1996) and cardio-postural interactions (Goswami et al. 2012; Blaber et al. 2009) affect cardiovascular responses during orthostatic stress. Therefore, subjects were instructed to avoid head movements during the hypergravity phases to minimize potential vestibular–autonomic interactions. However, minor differences in cardio-postural interactions in parabolic flight with respect to hypobaric chamber can be considered possible because in parabolic flight subjects were standing on a floor covered with soft padding and trying to adjust their upright body posture for turbulences using their postural muscles. Furthermore, large muscle groups may have been activated by airplane whole-body vibrations during flight. These advanced postural adjustments, which almost did not occur in hypobaric chamber, may have led to increased muscle pumping and increased venous return inflight with respect to the hypobaric chamber. *Third*, only 11 of the 18 subjects of the parabolic flights were available to participate thereafter in the hypobaric chamber tests. *Fourth*, three of the 18 subjects developed motion sickness in parabolic flight, which affects cardiovascular and hormonal regulation and removes the homogeneity of the subject population. It is well known that levels of AVP and cortisol are extensively increased in motion sickness; therefore, the CT-$_{pro}$AVP and cortisol values of the motion-sick subjects were excluded from the statistical analysis of the blood hormones, and individual data are shown instead. Furthermore, we did not analyze blood levels of ACTH what might had allowed us to identify a close relationship between ACTH and aldosterone in parabolic flight as it is known for orthostatic stress during tilting and LBNP (Roessler et al. 2011; Hinghofer-Szalkay et al. 2011). *Fifth*, rebreathings at 0 G_z fell into the early 0 G_z phases, which are characterized by a sympathetic withdrawal and acute activation of the vagal nervous system. Later in the 0 G_z phase, there would be an increasing dominance of the sympathetic nervous system. We did not perform most of the rebreathings in this phase, and thus our results mainly represent the cardiovascular responses in the early 0 G_z phases. *Sixth*, forced breathing, as performed for the rebreathing maneuvers for CI_{rb} determination, modulates cardiovascular regulation during gravity transitions (Schlegel et al. 1998; Iwase et al. 1999b). However, using a breathing frequency of 20 breaths per minute and a rebreathing volume between 1.5 and 2.5 L, we were in the range of the low effect of breathing parameters on CO_{rb} influencing noted by Damgaard and Norsk (2005).

Conclusion

In conclusion, the cardiovascular, pulmonary and body fluid system are influenced not only by micro- and hypergravity but also by the hypobaric hypoxic cabin environment of the parabolic flight airplane. This finding leads, in some cases, to antagonistic reflex patterns in which reflexes triggered by GT abolish those triggered by HH. The compensation of the hypoxic pulmonary vasoconstriction by volume shift and the increases in cardiac output during parabolic flight maneuvers could have a positive effect on some potential parabolic flight participants with restricted health status, e.g., patients with mild chronic obstructive pulmonary disease or right ventricular strain; these effects should be investigated in future studies.

Acknowledgments We are grateful to all of our subjects for their participation in the parabolic flights and the hypobaric chamber runs and for the amount of dedicated work they provided to support this study. We are also thankful to Dr. Petra Frings-Meuthen and Dr. Judith Bühlmeier for laboratory work and blood specimen handling during the parabolic flight campaigns. We would like to thank Wolfram Sies

for constructing the parabolic flight experiment rack and for his technical support during each phase of the study. We are grateful to Hartmuth Friedrich for operating the DLR hypobaric chamber and to Gernot Plath for his helpful technical mentoring. Furthermore, we thank the staff of the NOVESPACE Company for their help before and during the parabolic flights and the DLR/German Aerospace Agency for providing the flight opportunities in the 15th, 16th and 19th DLR parabolic flight campaigns.

Conflict of interest The authors declare that they have no conflicts of interest.

References

Allan JR, Crossley RJ (1972) Effect of controlled elevation of body temperature on human tolerance to +G z acceleration. J Appl Physiol 33(4):418–420

Bartsch P, Saltin B (2008) General introduction to altitude adaptation and mountain sickness. Scand J Med Sci Sports 18(Suppl 1):1–10. doi:10.1111/j.1600-0838.2008.00827.x

Beckers F, Seps B, Ramaekers D, Verheyden B, Aubert AE (2003) Parasympathetic heart rate modulation during parabolic flights. Eur J Appl Physiol 90(1–2):83–91. doi:10.1007/s00421-003-0854-y

Blaber AP, Landrock CK, Souvestre PA (2009) Cardio-postural deconditioning: a model for post-flight orthostatic intolerance. Respir Physiol Neurobiol 169(Suppl 1):S21–S25. doi:10.1016/j.resp.2009.04.007

Charkoudian N, Eisenach JH, Joyner MJ, Roberts SK, Wick DE (2005) Interactions of plasma osmolality with arterial and central venous pressures in control of sympathetic activity and heart rate in humans. Am J Physiol Heart Circ Physiol 289(6):H2456–H2460. doi:10.1152/ajpheart.00601.2005

Clemensen P, Christensen P, Norsk P, Gronlund J (1994) A modified photo- and magnetoacoustic multigas analyzer applied in gas exchange measurements. J Appl Physiol 76(6):2832–2839

Damgaard M, Norsk P (2005) Effects of ventilation on cardiac output determined by inert gas rebreathing. Clin Physiol Funct Imaging 25(3):142–147. doi:10.1111/j.1475-097X.2005.00602.x

Debono M, Ghobadi C, Rostami-Hodjegan A, Huatan H, Campbell MJ, Newell-Price J, Darzy K, Merke DP, Arlt W, Ross RJ (2009) Modified-release hydrocortisone to provide circadian cortisol profiles. J Clin Endocrinol Metab 94(5):1548–1554. doi:10.1210/jc.2008-2380

Drummer C, Stromeyer H, Riepl RL, Konig A, Strollo F, Lang RE, Maass H, Rocker L, Gerzer R (1990) Hormonal changes after parabolic flight: implications on the development of motion sickness. Aviat Space Environ Med 61(9):821–828

Goswami N, Roma PG, De Boever P, Clément G, Hargens AR, Loeppky JA, Evans JM, Peter Stein T, Blaber AP, Van Loon JJWA, Mano T, Iwase S, Reitz G, Hinghofer-Szalkay HG (2012) Using the moon as a high-fidelity analogue environment to study biological and behavioural effects of long-duration space exploration. Planet Space Sci 74:111–120

Gradwell DP (2006) Hypoxia and hyperventilation. In: Rainford D, Gradwell DP, Ernsting J (eds) Ernsting's aviation medicine, 4th edn. Hodder Arnold; Distributed in the United States of America by Oxford University Press, London, pp 41–56

Halliwill JR, Minson CT (2002) Effect of hypoxia on arterial baroreflex control of heart rate and muscle sympathetic nerve activity in humans. J Appl Physiol 93(3):857–864. doi:10.1152/japplphysiol.01103.2001

Harding R, Mills FJ (1983) Aviation medicine. British Medical Association, London

Hargens AR, Richardson S (2009) Cardiovascular adaptations, fluid shifts, and countermeasures related to space flight. Respir Physiol Neurobiol 169(Suppl 1):S30–S33. doi:10.1016/j.resp.2009.07.005

Heringlake M, Heide C, Bahlmann L, Eichler W, Pagel H, Schmucker P, Wergeland R, Armbruster FP, Klaus S (2004) Effects of tilting and volume loading on plasma levels and urinary excretion of relaxin, NT-pro-ANP, and NT-pro-BNP in male volunteers. J Appl Physiol 97(1):173–179. doi:10.1152/japplphysiol.01196.2003

Hinghofer-Szalkay H, Lackner HK, Rossler A, Narath B, Jantscher A, Goswami N (2011) Hormonal and plasma volume changes after presyncope. Eur J Clin Invest 41(11):1180–1185. doi:10.1111/j.1365-2362.2011.02523.x

Humpeler E, Skrabal F, Bartsch G (1980) Influence of exposure to moderate altitude on the plasma concentration of cortisol, aldosterone, renin, testosterone, and gonadotropins. Eur J Appl Physiol 45(2–3):167–176

Iwase S, Jian C, Kitazawa H, Kamiya A, Miyazaki S, Sugiyama Y, Mukai C, Kohno M, Mano T, Nagaoka S (1999a) Changes in muscle sympathetic nerve activity and effects of breathing maneuvers in humans during microgravity induced by parabolic flight. J Gravitat Physiol: J Int Soc Gravit Physiol 6(1):P71–P72

Iwase S, Mano T, Cui J, Kitazawa H, Kamiya A, Miyazaki S, Sugiyama Y, Mukai C, Nagaoka S (1999b) Sympathetic outflow to muscle in humans during short periods of microgravity produced by parabolic flight. Am J Physiol 277(2 Pt 2):R419–R426

Kohl RL (1987) Hormonal responses of metoclopramide-treated subjects experiencing nausea or emesis during parabolic flight. Aviat Space Environ Med 58(9 Pt 2):A266–A269

Laszlo Z, Rossler A, Hinghofer-Szalkay HG (2001) Cardiovascular and hormonal changes with different angles of head-up tilt in men. Physiol Res/Academia Scientiarum Bohemoslovaca 50(1):71–82

Lehot F (2012) Voler en apesanteur. Vuibert, Paris

Limper U, Gauger P, Beck LE (2011) Upright cardiac output measurements in the transition to weightlessness during parabolic flights. Aviat Space Environ Med 82(4):448–454

Liu J, Verheyden B, Beckers F, Aubert AE (2012) Haemodynamic adaptation during sudden gravity transitions. Eur J Appl Physiol 112(1):79–89. doi:10.1007/s00421-011-1956-6

Mortazavi A, Eisenberg MJ, Langleben D, Ernst P, Schiff RL (2003) Altitude-related hypoxia: risk assessment and management for passengers on commerical aircraft. Aviat Space Environ Med 74(9):922–927

Mukai CN, Lathers CM, Charles JB, Bennett BS, Igarashi M, Patel S (1991) Acute hemodynamic responses to weightlessness during parabolic flight. J Clin Pharmacol 31(10):993–1000

Mukai CN, Lathers CM, Charles JB, Bennett BS (1994) Cardiovascular responses to repetitive exposure to hyper- and hypogravity states produced by parabolic flight. J Clin Pharmacol 34(5):472–479

Noguchi H, Sakaguchi T (1999) Effect of illuminance and color temperature on lowering of physiological activity. Appl Hum Sci: J Physiol Anthropol 18(4):117–123

NOVESPACE (2013) Parabolic flight medical document. http://www.airzerog.com/images/upload/medical_document_2013_ed4_en.pdf

Petersen LG, Damgaard M, Petersen JC, Norsk P (2011) Mechanisms of increase in cardiac output during acute weightlessness

in humans. J Appl Physiol 111(2):407–411. doi:10.1152/japplphysiol.01188.2010
Prommer N, Schmidt W (2007) Loss of CO from the intravascular bed and its impact on the optimised CO-rebreathing method. Eur J Appl Physiol 100(4):383–391. doi:10.1007/s00421-007-0439-2
Richalet J (2001) The endocrine system. In: Hornbein T, Schoene R (eds) High altitude. An exploration of human adaptation, 1st edn. Marcel Dekker Inc., New York, pp 601–644
Roessler A, Goswami N, Haditsch B, Loeppky JA, Luft FC, Hinghofer-Szalkay H (2011) Volume regulating hormone responses to repeated head-up tilt and lower body negative pressure. Eur J Clin Invest 41(8):863–869. doi:10.1111/j.1365-2362.2011.02476.x
Rohdin M, Linnarsson D (2002) Differential changes of lung diffusing capacity and tissue volume in hypergravity. J Appl Physiol 93(3):931–935. doi:10.1152/japplphysiol.01271.2001
Rollin Stott J (2006) Vibration. In: Rainford D, Gradwell DP, Ernsting J (eds) Ernsting's aviation medicine, 4th edn. Hodder Arnold; Distributed in the United States of America by Oxford University Press, London, pp 231–246
Schlegel TT, Benavides EW, Barker DC, Brown TE, Harm DL, DeSilva SJ, Low PA (1998) Cardiovascular and Valsalva responses during parabolic flight. J Appl Physiol 85(5):1957–1965
Schlegel TT, Brown TE, Wood SJ, Benavides EW, Bondar RL, Stein F, Moradshahi P, Harm DL, Fritsch-Yelle JM, Low PA (2001) Orthostatic intolerance and motion sickness after parabolic flight. J Appl Physiol 90(1):67–82
Schmidt W, Prommer N (2005) The optimised CO-rebreathing method: a new tool to determine total haemoglobin mass routinely. Eur J Appl Physiol 95(5–6):486–495. doi:10.1007/s00421-005-0050-3
Schneider S, Brummer V, Carnahan H, Dubrowski A, Askew CD, Struder HK (2007) Stress hormone stability: processing of blood samples collected during parabolic flight. A pre-flight comparison of different protocols. Clin Biochem 40(16–17):1332–1335. doi:10.1016/j.clinbiochem.2007.07.022
Sevre K, Bendz B, Rostrup M (2002) Reduced baroreceptor reflex sensitivity and increased blood pressure variability at 2400 m simulated cabin altitude. Aviat Space Environ Med 73(7):632–634
Shigeoka JW, Colice GL, Ramirez G (1985) Effect of normoxemic and hypoxemic exercise on renin and aldosterone. J Appl Physiol 59(1):142–148
Slater JD, Tuffley RE, Williams ES, Beresford CH, Sonksen PH, Edwards RH, Ekins RP, McLaughlin M (1969) Control of aldosterone secretion during acclimatization to hypoxia in man. Clin Sci 37(2):327–341
Smith TG, Talbot NP, Chang RW, Wilkinson E, Nickol AH, Newman DG, Robbins PA, Dorrington KL (2012) Pulmonary artery pressure increases during commercial air travel in healthy passengers. Aviat Space Environ Med 83(7):673–676
Snyder EM, Beck KC, Hulsebus ML, Breen JF, Hoffman EA, Johnson BD (2006) Short-term hypoxic exposure at rest and during exercise reduces lung water in healthy humans. J Appl Physiol 101(6):1623–1632. doi:10.1152/japplphysiol.00481.2006
Stetina PM, Madai B, Kulemann V, Kirch W, Joukhadar C (2005) Pharmacokinetics of scopolamine in serum and subcutaneous adipose tissue in healthy volunteers. Int J Clin Pharmacol Ther 43(3):134–139
Sylvester JT, Shimoda LA, Aaronson PI, Ward JP (2012) Hypoxic pulmonary vasoconstriction. Physiol Rev 92(1):367–520. doi:10.1152/physrev.00041.2010
Szinnai G, Morgenthaler NG, Berneis K, Struck J, Muller B, Keller U, Christ-Crain M (2007) Changes in plasma copeptin, the c-terminal portion of arginine vasopressin during water deprivation and excess in healthy subjects. J Clin Endocrinol Metab 92(10):3973–3978. doi:10.1210/jc.2007-0232
Toshner MR, Thompson AA, Irving JB, Baillie JK, Morton JJ, Peacock AJ (2008) NT-proBNP does not rise on acute ascent to high altitude. High Alt Med Biol 9(4):307–310. doi:10.1089/ham2008.1054
Vaida P, Kays C, Riviere D, Techoueyres P, Lachaud JL (1997) Pulmonary diffusing capacity and pulmonary capillary blood volume during parabolic flights. J Appl Physiol 82(4):1091–1097
West J, Schoene R, Milledge J (2007) High altitude medicine and physiology, 4th edn. Hodder Arnold, London
Yamashita K, Yamaguchi K, Yamamoto T, Shirabe S, Hashiguchi N, Kaji M, Tochihara Y (2005) Hematological change in venous blood of the lower leg during prolonged sitting in a low humidity and hypobaric environment. J Physiol Anthropol Appl Hum Sci 24(6):611–615
Yates BJ (1996) Vestibular influences on cardiovascular control. In: Yates BJ, Miller AD (eds) Vestibular autonomic regulation. CRC Press, Boca Raton, pp 97–111

Appendix

The original publication presented in this chapter contains supplementary material in the form of online references that can be found on the homepage of the *European Journal of Applied Physiology*: http://link.springer.com/article/10.1007%2Fs00421-014-2856-3.

Online reference 1 contains a video showing an inflight measurement sequence. The supplementary texts of online reference 2 regarding the CORB and the inert gas rebreathing method as well as the biochemical blood analyses have been included in the methods section of chapter one of this thesis. The supplementary numerical results of online references 3 to 6 are shown below.

Parameter	$Ground_{Pre}$	Outbound	Gz	Block I	Block II	Block III	Block IV	Return	$Ground_{Post}$
HR	100 ± 15	93 ± 18	0	92 ±15	81 ± 14	81 ± 15	78 ± 12	95 ± 11	91 ± 12
(bpm)			1.8	123 ± 21	113 ± 19	111 ± 17	110 ± 15		
FBP_{syst}	127 ± 22	136 ± 21	0	144 ± 26	120 ± 30	121 ± 26	123 ± 22	124 ± 23	126 ± 14
(mmHg)			1.8	148 ± 21	132 ± 27	127 ± 24	131 ± 20		
FBP_{diast}	72 ± 14	74 ± 14	0	70 ± 14	61 ± 17	60 ± 12	62 ± 12	76 ± 15	78 ± 10
(mmHg)			1.8	86 ± 14	85 ± 16	80 ± 14	83 ± 15		
FBP_{mean}	90 ± 15	93 ± 15	0	94 ± 16	81 ± 17	80 ± 15	81 ± 14	91 ± 18	92 ± 10
(mmHg)			1.8	105 ± 14	101 ± 17	96 ± 15	96 ± 19		
SI_{rb}	29 ± 8	33 ± 7	0	55 ± 11	58 ± 13	55 ± 8	53 ± 12	28 ± 6	26 ± 5
$\left(\frac{ml}{m^2}\right)$			1.8	28 ± 8	24 ± 4	± 23 ± 4	24 ± 4		
CI_{rb}	2.905 ± 0.678	3.052 ± 0.746	0	5.139 ± 1.326	4.742 ± 1.260	4.364 ± 1.038	4.150 ± 1.082	2.622 ± 0.542	2.564 ± 0.757
$\left(\frac{L}{min\times m^2}\right)$			1.8	2.986 ± 0.743	2.653 ± 0.418	2.486 ± 0.411	2.677 ± 0.446		
SVR	19 ± 5	18 ± 5	0	11 ± 3	11 ± 4	11 ± 3	12 ± 6	20 ± 6	23 ± 6
$\left(\frac{mmHg}{L\times min}\right)$			1.8	19 ± 5	23 ± 5	23 ± 5	21 ± 5		

Online reference #3

Parameter	$Ground_{Pre}$	Outbound	G_z	Block I	Block II	Block III	Block IV	Return	$Ground_{Post}$
SpO_2	98 ± 0.6	95 ± 2	0	96 ± 2	95 ± 2	95 ± 2	95 ± 2	97 ± 2	97 ± 4
(%)			1.8	96 ± 1	95 ± 2	95 ± 2	95 ± 2		
Vt	0.593 ± 0.181	0.688 ± 0.230	0	0.885 ± 0.458	0.737 ± 0.384	0.797 ± 0.642	0.729 ± 0.391	0.627 ± 0.230	0.542 ± 0.177
(L)			1.8	0.858 ± 0.357	0.870 ± 0.417	0.938 ± 0.562	0.783 ± 0.445		
VO_2	3.9 ± 1.1	4.0 ± 1.2	0	9.6 ± 2.4	9.4 ± 2.8	8.8 ± 2.4	8.1 ± 2.6	3.2 ± 0.8	3.1 ± 1.0
(ml/kg*min)			1.8	4.0 ± 1.2	3.3 ± 0.9	3.2 ± 1.0	3.3 ± 1.2		

Online reference #4

Parameter	$Ground_{Pre}$	Outbound	Block I $_{1G}$	Block II $_{1G}$	Block III $_{1G}$	Block IV $_{1G}$	Return	$Ground_{Post}$
Cardiovascular								
HR (bpm)	81 ± 11	76 ± 9	76 ± 10	74 ± 9	76 ± 10	77 ± 8	79 ± 10	79 ± 10
FBP_{syst} (mmHg)	117 ± 16	123 ± 12	122 ± 14	124 ± 18	117 ± 14	118 ± 20	116 ± 18	124 ± 20
FBP_{diast} (mmHg)	68 ± 12	68 ± 10	71 ± 14	73 ± 18	70 ± 15	70 ± 19	68 ± 18	75 ± 18
FBP_{mean} (mmHg)	85 ± 12	86 ± 10	87 ± 14	89 ± 18	85 ± 15	85 ± 20	84 ± 18	90 ± 18
SI_{rb} $\left(\frac{ml}{m^2}\right)$	31 ± 7	36 ± 10	32 ± 8	35 ± 8	34 ± 8	34± 9	33± 8	30± 8
CI_{rb} $\left(\frac{L}{min \times m^2}\right)$	2.509 ± 0.618	2.673 ± 0.714	2.423 ± 0.632	2.600 ± 0.679	2.561 ± 0.568	2.591 ± 0.695	2.538 ± 0.592	2.345 ± 0.561
SVR $\left(\frac{mmHg}{L \times min}\right)$	84.5 ± 12.2	86.0 ± 9.9	87.2 ± 14.2	89.4 ± 18.3	84.8 ± 14.7	84.7 ± 19.6	83.7 ± 18.0	90.3 ± 18.0
Respiratory								
SpO_2 (%)	98 ± 0.6	96 ± 2	96 ± 2	96 ± 2	96 ± 3	96 ± 2	96 ± 2	98 ± 1
Vt (L)	0.694 ± 0.185	0.600 ± 0.243	0.560 ± 0.207	0.598 ± 0.226	0.562 ± 0.209	0.584 ± 0.214	0.535 ± 0.151	0.636 ± 0.171
VO_2/kg (ml)	3.0± 0.9	3.2 ± 0.9	3.0 ± 1.0	3.1 ± 1.1	3.1 ± 0.8	2.9 ± 1.0	3.1 ± 1.0	2.7 ± 0.9

Online reference #5

Parameter	Facility	$Ground_{Pre}$	Outbound	Post 16th	Post 31st	$Ground_{Post}$
Plasma Volume (ml)	**Airplane**	3375 ± 602	3414 ±592	3299 ±527	3330 ±571	3352 ±659
	Chamber	3126 ±732	3241 ±726	3067 ±662	3074 ±692	3206 ±704
Albumin $\left(\frac{g}{L}\right)$	**Airplane**	46.3 ±2.9	46.0 ±3.1	47.3 ±2.7	46.9 ±4.2	47.9 ±2.8
	Chamber	45.7 ±3.0	44.4 ±2.2	47.0 ±9.4	46.5 ±2.4	45.1 ±2.5
#Cortisol $\left(\frac{\mu g}{dl}\right)$	**Airplane**	17.4 ±3.7	12.9 ±4.0	13.2 ±4.5	12.3 ±6.2	11.0 ±4.8
	Chamber	14.0 ±6.7	11.9 ±4.1	10.6 ±3.1	10.4 ±4.0	10.2 ±3.3
Aldosterone $\left(\frac{pg}{ml}\right)$	**Airplane**	126.5 ±51.7	146.2 ±58.0	160.2 ±74.1	157.9 ±70.5	165.5 ±64.9
	Chamber	157.0 ±78.9	154.0 ±78.9	168.5 ±80.8	155.2 ±78.0	137.1 ±77.9
‡$Renin_{active}$ $\left(\frac{pg}{ml}\right)$	**Airplane**	10.8 ±4.8	12.5 ±8.0	13.2 ±9.0	13.6 ±8.6	13.5 ±7.3
	Chamber	10.9 ±9.5	11.0 ±9.8	16.3 ±16.6	14.8 ±13.8	13.9 ±12.7
Osmolality $\left(\frac{mosmol}{kg}\right)$	**Airplane**	312.1 ±15.1	310.8 ±10.8	310.7 ±14.0	312.1 ±16.2	308.8 ±13.3
	Chamber	300.5 ±4.9	301.2 ±5.3	300.5 ±4.0	299.8 ±4.2	298.7 ±4.4
#CT-$_{pro}$Vasopressin $\left(\frac{pmol}{L}\right)$	**Airplane**	9.4 ±11.7	6.3 ±7.2	5.3 ±5.1	8.5 ±10.0	4.9 ±3.8
	Chamber	4.2 ±3.4	3.4 ±1.6	3.2 ±1.9	4.1 ±2.8	3.7 ±2.2
NT-$_{pro}$BNP $\left(\frac{pg}{ml}\right)$	**Airplane**	65.9 ±52.5	66.9 ±50.5	72.9 ±57.1	73.6 ±51.6	66.8 ±45.9
	Chamber	60.6 ±43.9	58.7 ±39.3	57.5 ± 36.2	57.2 ±35.3	59.3 ±33.6

Online reference #6

Chapter Five

5 Final considerations and clinical implications

What can we learn from this work for clinical physiology and medicine? This thesis addresses many aspects; however, the four main points of its content are as follows: first, how do non-invasive methods of cardiac output determination perform in non-steady state cardiovascular conditions; second, how does cardiac output, as the key variable of the circulation, behave during intense orthostatic and anti-orthostatic stress; third, how does pulmonary circulation react to orthostatic and anti-orthostatic stress in a hypoxic environment; and fourth, how do the human endocrine system and plasma volume respond to a combination of hypobaric hypoxia and gravity changes.

5.1 Cardiac output determination in non-steady state cardiovascular conditions

In general, methods of cardiac output determination can be categorized into ‘invasive’ and ‘non-invasive’, ‘calibrated’ and ‘uncalibrated’, ‘absolute’ and ‘relative’, ‘continuous’ and ‘intermittent’ and into the categories of the principles of how they work. The four main function principles are the Doppler method, the applied Fick’s principle, bioimpedance and pulse wave analysis (1). Each of these methods has particular advantages and disadvantages. Usually, the more invasive the method is, the more exactly it works. However, the more invasive a method is, the more complications its application generates. Calibrated and absolute methods provide true cardiovascular indices, and continuous methods provide trends. Only non-invasive methods of cardiac index estimation are applied in space flight-related research due to the already complex and hostile environmental conditions. The procedural risks of cardiac output determination as related to space flight must not increase the overall risk of the mission. The results of these measurements may be therefore only relative or intermittent. However, the approach of non-invasive cardiovascular index estimation is also gaining importance in clinical and intensive care medicine. This trend began with the abandoning of cardiovascular monitoring based on the highly invasive pulmonary artery *Swan-Ganz* catheter after less-invasive methods were developed (2), and it continues in the effort of establishing uncalibrated or non-invasive cardiovascular monitoring methods in intensive care medicine (3, 4). Two still promising methods of minimal or non-invasive cardiovascular monitoring in intensive care medicine are the bioimpedance method and the pulse curve analysis (5-8). Although these methods have so far shown a lack of precision in cardiac output determination in critically ill patients compared to thermodilution techniques, they still have the ability to become an established part of clinical cardiovascular monitoring. This ability is especially the case under the perspective of an integrative approach of cardiac output monitoring (9). Both of these methods are also well established in space flight-related research and in operational space medicine because of the need of this field for riskless monitoring methods. The

question is therefore 'can we learn something new about these methods by testing them in space flight-related environments'? The answer is 'yes' because test environments, similar to parabolic flights, create a unique cardiovascular stress with great bidirectional volume shift. By undergoing the parabolic flight maneuver in a standing body position, the thorax of the test subjects gets volume depleted and volume re-substituted within seconds, leading to significant changes in the cardiac output and systemic vascular resistance. Testing bioimpedance and non-invasive pulse curve analysis in this setting are therefore very different from the tests of these methods in an intensive care setting where the cardiovascular system of the patient is carefully maintained in a steady state. This interesting point can be illustrated by comparing the results of this thesis with the results of the work of Sun et al. (10). Sun and colleagues compared different methods of cardiac output estimation based on arterial pressure measurement to thermodilution in intensive care patients. These authors found that the old method of Liljestrand and Zander from 1928 performed very well in this population, which was surprising because the algorithm is based on only pulse pressure divided by the sum of systolic and diastolic pressure multiplied by a calibration factor $\left(CO = \frac{P_{syst}-P_{diast}}{P_{syst}+P_{diast}} \times k\right)$ (11). Compared to the patients in an intensive care unit (as reported by Sun et al.), who had a mean cardiac output of 5 L/min and a mean range of 2 L/min per patient, the subjects of this thesis were measured during cardiovascular transitions that were induced by rapid gravity changes. This difference resulted in great changes in the cardiac output between 3 and 16 L/min and in the total systemic resistance. The consequence was that none of the arterial pulse methods performed best under all gravity conditions. Although Wesseling's corrected aortic impedance method (12) showed the lowest error in 1 and 1.8 G_z, the mean arterial pressure (MAP) and the Liljestrand and Zander method had the lowest errors in 0 G_z (13). In 0 G_z, a decreased total peripheral resistance can be observed with a great impact on the performance of the arterial pressure-based cardiac output estimation methods. The issue of a less-adequate performance of those methods in patients showing a decreased systemic vascular resistance is also problematic in intensive care patients (14). Furthermore, low and high systemic vascular resistance leads to the under- or overestimation of cardiac output as estimated by impedance cardiography, respectively (15). The impedance cardiography data that were tracked in parabolic flight and presented in chapter two agree with this statement as they underestimate cardiac output in microgravity when total peripheral resistance is low with respect to inert gas rebreathing.

In conclusion, the evaluation of cardiac output estimation methods based on impedance cardiography and arterial pulse pressure in healthy parabolic flight subjects shows similar limitations of the methods with respect to their application in critically ill patients. Therefore, it seems useful to supplement the mandatory feasibility studies of these techniques in critically ill patients with studies in parabolic flight to test these methods over the maximal range of cardiac performance and without the ethical issues of performing research in patients lacking consent capacity. Furthermore, because of the very rapid cardiovascular changes in parabolic flight, this setup is predestinated to test the trending capability of those methods.

5.2 Behavior of cardiac output as the key variable of the circulation during intense orthostatic and anti-orthostatic stress in parabolic flight

Cardiac output is one of the key variables of circulation and serves therefore as a global indicator of the level of operation of the circulation. Cardiac output describes the total blood flow that is generated by the heart, which, in normal adults at rest, is 5 L/min on average and ranges from 4.0 to 6.5 L/min (16). At this point, it is noticeable that the mean cardiac output of the patients of the study of Sun et al. as cited above was approximately 5 L/min, which indicates circulation not being under maximal stress. Without nerve excitation, a normal heart can increase its pumping capability up to 13 L/min if it receives the appropriate amount of venous return (17). Under the influence of sympathetic stimulation and vagal inhibition, which leads to increased contractility and tachycardia, the normal heart can pump up to 25 L/min (17). However, the heart itself does not control the amount of blood that it pumps but the venous return. The heart simply pumps the blood that returns to it. The Frank Starling mechanism guarantees that the heart can adapt to increased amounts of blood flowing into its chambers. The venous return on the other hand is the sum of all of the local blood that flows through all of the particular tissue compartments of the peripheral circulation (17). Indeed, this pattern is not the case in parabolic flight. The results of chapters two and four show that cardiac output increases up to 16 L/min in microgravity in healthy subjects undergoing a parabolic flight maneuver in a standing position, which is approximately the cardiac output observed in healthy subjects performing dynamic exercise (18). However, this pattern is not the case because peripheral tissues demand this cardiac output in parabolic flight, because this maneuver requires only moderate static exercise from the subject, and because the disappearance of the hydrostatic column lasting on the venous system leads to a prompt increase in venous return coupled with a still sympathetically activated heart. The sympathetic activation of the heart arises from the increased orthostatic stress in the preceding hypergravity phase. Thus, the short microgravity phase of a parabolic flight maneuver provokes a hyperperfusion of the circulation, which is fortunately immediately limited by the regulatory reflex responses of circulation.

During hypergravity, cardiac output decreases with respect to 1 G_z but not with the same magnitude as it increases during microgravity. This result is understandable because most of the blood volume, approximately 500 ml, shifts from the central to the dependent compartments after standing up in 1 G_z. Increasing G_z causes only an additional 12-50 ml/G_z of blood pooling in the legs, which takes only 25 sec (19). This result means that for the parabolic flight maneuver, in the brief 1.8 G_z hypergravity phase, less than 100 ml of additional blood is shifted to the legs with respect to 1 G_z.

In clinical medicine, circulatory hyperperfusion syndromes due to low total peripheral resistance are observed in patients with liver cirrhosis (20) and in patients suffering from an insufficient quantity of thiamine in the diet (*Beriberi disease*) (17). Furthermore, a hyperdynamic circulatory state can be triggered by cytokines, such as Il-2 and TNF-alpha, which lead to a *systemic*

inflammatory response syndrome (21). However, cardiac outputs of greater than 12 L/min are seldom observed in anesthesiology and intensive care medicine.

5.3 Response of the pulmonary circulation to orthostatic and anti-orthostatic stress in a moderately hypobaric hypoxic environment

The cabin of a commercial airplane, such as the A300 Zero-G, exposes subjects and passengers to a moderately hypobaric hypoxic atmosphere during flight. The impact of this particular atmosphere on the pulmonary gas exchange of individuals has been of great interest even for the anesthesiologist. In 2005, Humphreys and colleagues published an article on the effect of high-altitude commercial air travel on oxygen saturation in *Anaesthesia* (22). These authors found a significant reduction in oxygen saturation in their 84 subjects during flight with respect to ground control. Smith et al. investigated pulmonary arterial pressure during commercial air travel in healthy passengers with respect to their ground controls and found a significant increase in systolic pulmonary arterial pressure in flight, even though the average arterial oxygen saturation only decreased from 98 to 95%. This result agrees with the decreased oxygen saturation that is observed in the subjects of this thesis both in flight and in the hypobaric chamber and is reproducible by the simple physiological model that is shown in fig. 5.1. By applying the model of fig. 5.1, one obtains an arterial partial oxygen pressure of approximately 67 mmHg for a subject during his sojourn in the A300 Zero-G cabin. Furthermore, the rebreathings in the hypobaric chamber at A300 Zero-G cabin atmosphere equivalent indicate a reduced pulmonary tissue volume, confirming that hypoxic pulmonary vasoconstriction already exists at this relatively high predicted arterial partial oxygen pressure. This result could be surprising regarding Cutaia's and Rounds's report of 60-mmHg partial oxygen pressure as threshold for the hypoxic pulmonary vasoconstriction (26). However, the data of Humphreys and Smith and the results of this thesis suggest that the oxygen pressure threshold above which no hypoxic pulmonary vasoconstriction appears must be higher than 60 mmHg, which fully agrees with the review of Sylvester and colleagues, who found 83 mmHg of partial oxygen pressure as the threshold for hypoxic pulmonary vasoconstriction (27).

The value of 83 mmHg partial oxygen pressure as threshold for hypoxic pulmonary vasoconstriction might be interesting for the anesthesiologist when considering the best inspiratory oxygen fraction during thoracic anesthesia. Furthermore, it might be interesting in the rare cases of providing anesthesia in patients with Fontan circulation undergoing non-cardiac surgery. In these patients, keeping pulmonary resistance down is of eminent importance for the filing of their single ventricle (28).

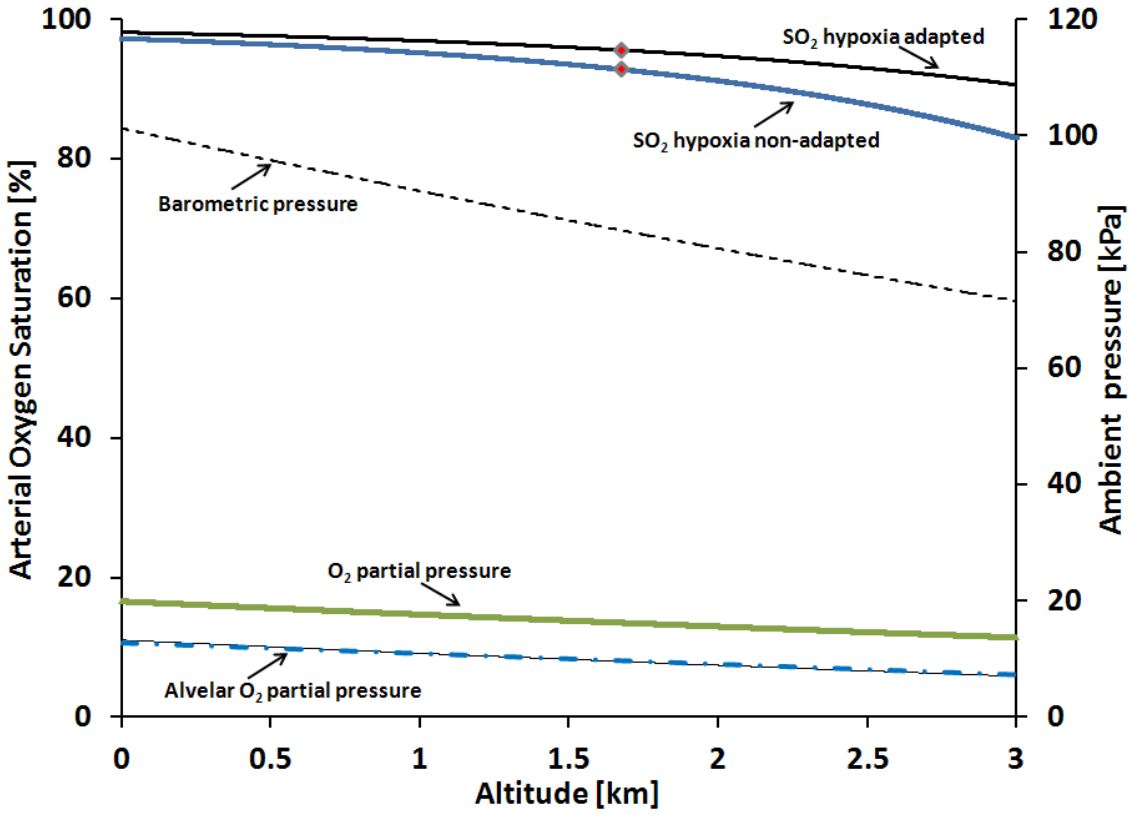

Figure 5.1: Red rhombs show the predicted arterial oxygen saturation (SO_2) inflight inside the cabin of the A300 Zero-G based on the model atmosphere of J. West (23). The x-axis shows the altitude that is equivalent to the cabin pressure. The blue graph shows SO_2 in a subject who does not hyperventilate due to the hypobaric hypoxic environment, whereas the black graph shows SO_2 in a hypoxia-adapted subject with hyperventilation. The dashed black graph provides the barometric pressure with respect to altitude. The green graph represents the ambient partial oxygen pressure, and the blue dashed graph provides the alveolar oxygen partial pressure that was calculated via the classical alveolar gas formula (24). An oxygen partial pressure difference of 5 mmHg is assumed between the alveolar space and the pulmonary capillaries due to a small physiological ventilation/perfusion inequality (25).

A further important aspect of this thesis regarding pulmonary circulation is the fact that the pulmonary tissue volume decreased in hypobaric hypoxia but increased in hypobaric hypoxia coupled with microgravity or hypergravity. Assuming the absence of any interstitial edema formation during the measurements, let changes in lung tissue volume solely depend on changes in pulmonary capillary blood volume. Although Snyder et al. showed a reduced lung tissue volume in moderate hypoxia (29) and Rohdin and Linnarsson showed an increased lung tissue volume in hypergravity (30) and estimated an increased lung tissue volume in microgravity based on the parabolic flight data of Vaida et al. (31), this thesis shows for the first time in the same subject that the reduction in pulmonary blood volume in hypobaric hypoxia is reversed by a central blood volume shift in weightlessness and by the sequestration of blood in the dependent parts of the lung circulation in the hypergravity phases. From a clinical standpoint, these observations lead to the conclusion that hypoxic pulmonary vasoconstriction is affected by the cardiac output and the

thoracic blood volume. Thus, an anesthesiologist should consider these two variables when trying to influence the hypoxic pulmonary vasoconstriction during anesthesia.

5.4 How the human body fluid and endocrine systems respond to a combination of moderate hypobaric hypoxia and gravity changes

The human body fluid regulation system is simultaneously exposed to three stresses in parabolic flight: first, the aridity of the airplane cabin atmosphere; second, hypobaric hypoxia; and third, changing orthostatic loads. All of these stresses are expected to decrease the plasma volume, but their simultaneous impacts on the human body have not been well investigated prior to this thesis. However, the plasma volume showed only similar and moderate changes in parabolic flight and in the hypobaric chamber in the range of ±100 ml. This result is not surprising because an adequate plasma volume is crucial for an adequate filling of the heart and thus for an adequate cardiac performance. It is therefore natural that the human body does everything in its power to preserve intravascular volume. Body fluid changes in the magnitude of only 100 ml have also previously been reported from tests in hypobaric chambers operating at an altitude equivalent of 2000 a. m. s. l. (32) and in zero-humidity environments (33). Thus the work of this thesis shows again the stability of the human plasma volume despite significant environmental stress. From a hormonal standpoint, this thesis confirms the well-known fact that hypoxia induces a negative fluid status, whereas orthostatic stress triggers the storage of fluids as observed from increased aldosterone values in the hypobaric chamber and decreased aldosterone values in parabolic flight. However, it is remarkable that renin did not show a parallel response with aldosterone in parabolic flight, suggesting a dissociation of the aldosterone level and renin response under the conditions of parabolic flight. Interestingly, dissociation of plasma aldosterone levels and plasma renin activity has previously been reported in subjects experiencing presyncope and in subjects undergoing repeated orthostatic challenges (34, 35).

NT-proBNP, which is involved in the fluid homeostasis of the human body and is therefore of interest for the anesthesiologist, showed two remarkable behavior patterns with importance for clinical medicine within the framework of this thesis. First, the baseline value of NT-proBNP was significantly higher in female than in male subjects. Higher basic values in women have been previously reported (36) and should be considered for the interpretation of borderline values of NT-proBNP. Second, NT-proBNP increased in parabolic flight, most likely due to the central blood volume shift in microgravity; this did not occur during head-down tilt but during volume loading in the study of Heringlake and others (37).

5.5 Outlook

The subject population of this thesis contained an equal number of both genders, and thus a gender analysis regarding differences in hormonal and cardiovascular responses to parabolic orthostatic stress coupled with moderate hypobaric hypoxia would be reasonable and should be the scope of a future analysis of the datasets.

The behavior of hypoxic pulmonary vasoconstriction under orthostatic stress should be further examined by increasing hypoxia by the rebreathing of hypoxic gas mixtures via a face mask during parabolic flights.

The method of non-invasive cardiovascular index estimation via pulse curve analysis should be improved, especially in circulatory states with low total peripheral resistance in microgravity.

References

1. Hofer CK, Rex S, Ganter MT. Update on minimally invasive hemodynamic monitoring in thoracic anesthesia. Current opinion in anaesthesiology. 2014;27(1):28-35.
2. Rajaram SS, Desai NK, Kalra A, Gajera M, Cavanaugh SK, Brampton W, et al. Pulmonary artery catheters for adult patients in intensive care. The Cochrane database of systematic reviews. 2013;2:Cd003408.
3. Broch O, Renner J, Gruenewald M, Meybohm P, Schöttler J, Caliebe A, et al. A comparison of the Nexfin® and transcardiopulmonary thermodilution to estimate cardiac output during coronary artery surgery. Anaesthesia. 2012;67(4):377-83.
4. Slagt C, Malagon I, Groeneveld AB. Systematic review of uncalibrated arterial pressure waveform analysis to determine cardiac output and stroke volume variation. British journal of anaesthesia. 2014;112(4):626-37.
5. Cybulski G, Strasz A, Niewiadomski W, Gasiorowska A. Impedance cardiography: recent advancements. Cardiology journal. 2012;19(5):550-6.
6. Hirschl MM, Binder M, Gwechenberger M, Herkner H, Bur A, Kittler H, et al. Noninvasive assessment of cardiac output in critically ill patients by analysis of the finger blood pressure waveform. Critical care medicine. 1997;25(11):1909-14.
7. Popovich MJ, Hoffman WD. Noninvasive cardiac output monitoring. Critical care medicine. 1997;25(11):1783-4.
8. Fellahi J-L, Fischer M-O. Electrical Bioimpedance Cardiography: An Old Technology With New Hopes for the Future. Journal of cardiothoracic and vascular anesthesia. 2014;28(3):755-60.
9. Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: an integrative perspective. Critical care. 2011;15(2):214.
10. Sun JX, Reisner AT, Saeed M, Heldt T, Mark RG. The cardiac output from blood pressure algorithms trial. Critical care medicine. 2009;37(1):72-80.
11. Liljestrand G, Zander E. Vergleichende bestimmungen des minutenvolumens des herzens beim menschen mittels der stickoxydulmethode und durch blutdruckmessung. Zeitschrift für die gesamte experimentelle Medizin. 1928;59(1):105-22.
12. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol (1985). 1993;74(5):2566-73.
13. Arai T, Limper U, Gauger P, Beck L. Pulse contour methods to estimate cardiovascular indices in micro- and hypergravity. Aviation, space, and environmental medicine. 2013.
14. Junttila EK, Koskenkari JK, Ohtonen PP, Ala-Kokko TI. Uncalibrated arterial pressure waveform analysis for cardiac output monitoring is biased by low peripheral resistance in patients with intracranial haemorrhage. British journal of anaesthesia. 2011;107(4):581-6.
15. Critchley LA, Peng ZY, Fok BS, James AE. The effect of peripheral resistance on impedance cardiography measurements in the anesthetized dog. Anesthesia and analgesia. 2005;100(6):1708-12.
16. Miller RD, Eriksson L, Fleisher L, Wiener Kronish J, Young W. Miller's Anesthesia. Philadelphia: Churchill Livingstone. Elsevier; 2010.
17. Guyton A, Hall J. Cardiac output, venous return, and their regulation. In: Guyton A, Hall J, editors. Textbook of medical physiology. 11th ed. Philadelphia: Elsevier Saunders; 2006. p. 238-41.
18. Spiller P, Webb-Peploe MM. Blood flow. European heart journal. 1985;6 Suppl C:11-8.
19. Scharf SM, Cassidy SS. Heart-lung interactions in health and disease. New York: Dekker; 1989. xxv, 1135 p. p.
20. Bolognesi M, Di Pascoli M, Verardo A, Gatta A. Splanchnic vasodilation and hyperdynamic circulatory syndrome in cirrhosis. World journal of gastroenterology : WJG. 2014;20(10):2555-63.
21. Finck-Seelen R, Lampert R, Brandt L. Hyperdyname Hämodynamik während hochdosierter Interleukin-2/Interferon-α-Therapie bei Patienten mit metastasierendem Nierenzellkarzinom Immuntherapie als klinisches Sepsismodell? Der Anaesthesist. 1996;45(12):1171-8.
22. Humphreys S, Deyermond R, Bali I, Stevenson M, Fee JP. The effect of high altitude commercial air travel on oxygen saturation. Anaesthesia. 2005;60(5):458-60.
23. West JB. Prediction of barometric pressures at high altitude with the use of model atmospheres. J Appl Physiol (1985). 1996;81(4):1850-4.
24. West J, Schoene R, Milledge J. High altitude medicine and physiology. 4 ed. London, UK: Hodder Arnold; 2007.
25. Wagner P. Gas exchange. In: Hornbein T, RB S, editors. High altitude: an exploration of human adaptation. 1. New York: Marcel Dekker, Inc.; 2001. p. 199-234.
26. Cutaia M, Rounds S. Hypoxic pulmonary vasoconstriction. Physiologic significance, mechanism, and clinical relevance. Chest. 1990;97(3):706-18.
27. Sylvester JT, Shimoda LA, Aaronson PI, Ward JP. Hypoxic pulmonary vasoconstriction. Physiological reviews. 2012;92(1):367-520.

28. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, et al. The Fontan circulation: who controls cardiac output? Interactive cardiovascular and thoracic surgery. 2010;10(3):428-33.
29. Snyder EM, Beck KC, Hulsebus ML, Breen JF, Hoffman EA, Johnson BD. Short-term hypoxic exposure at rest and during exercise reduces lung water in healthy humans. Journal of applied physiology. 2006;101(6):1623-32.
30. Rohdin M, Linnarsson D. Differential changes of lung diffusing capacity and tissue volume in hypergravity. Journal of applied physiology. 2002;93(3):931-5.
31. Vaida P, Kays C, Riviere D, Techoueyres P, Lachaud JL. Pulmonary diffusing capacity and pulmonary capillary blood volume during parabolic flights. Journal of applied physiology. 1997;82(4):1091-7.
32. Yamashita K, Yamaguchi K, Yamamoto T, Shirabe S, Hashiguchi N, Kaji M, et al. Hematological change in venous blood of the lower leg during prolonged sitting in a low humidity and hypobaric environment. Journal of physiological anthropology and applied human science. 2005;24(6):611-5.
33. Macnamara WD, Nicholson AN. Study of the effect of cabin environment on insensible water loss. Aerospace medicine. 1969;40(6):657-9.
34. Roessler A, Goswami N, Haditsch B, Loeppky JA, Luft FC, Hinghofer-Szalkay H. Volume regulating hormone responses to repeated head-up tilt and lower body negative pressure. European journal of clinical investigation. 2011;41(8):863-9.
35. Hinghofer-Szalkay H, Lackner HK, Rossler A, Narath B, Jantscher A, Goswami N. Hormonal and plasma volume changes after presyncope. European journal of clinical investigation. 2011;41(11):1180-5.
36. Raymond I, Groenning BA, Hildebrandt PR, Nilsson JC, Baumann M, Trawinski J, et al. The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. Heart (British Cardiac Society). 2003;89(7):745-51.
37. Heringlake M, Heide C, Bahlmann L, Eichler W, Pagel H, Schmucker P, et al. Effects of tilting and volume loading on plasma levels and urinary excretion of relaxin, NT-pro-ANP, and NT-pro-BNP in male volunteers. Journal of applied physiology. 2004;97(1):173-9.

Summary

In this thesis, the estimation of circulatory indices was performed non-invasively from several bio-signals in healthy subjects whose cardiovascular system was in a non-steady state due to rapid gravity transitions that were created by parabolic flight maneuvers. Furthermore, the interactions of the cardiopulmonary, the hormonal and the body fluid systems in parabolic flight were investigated.

Chapter one provides a detailed introduction to gravitational physiology in general and to cardiovascular physiology in parabolic flight in particular. Great scientific overlap of the fields of extreme environmental physiology and anesthesiology is demonstrated based on the relevant clinical and physiological literature. Furthermore, the scientific methods and facilities that were used in this thesis are discussed in detail.

Chapter two describes the primary study of this thesis in which beat-to-beat cardiac output estimation in parabolic flight by thoracic impedance and finger blood pressure analysis were compared to the non-invasive gold standard of absolute cardiac output determination, namely the test gas re-breathing method. The compatibility of the methods was determined by the Bland and Altman analysis. The absolute cardiac output was determined for the first time by re-breathing during transition from hypergravity to microgravity in standing subjects.

Chapter three describes a more advanced comparative analysis of cardiac index estimation by ten pulse curve methods that were applied during gravity transitions. The results of the pulse curve analyses were compared to the results of the cardiac output data that were simultaneously collected by inert gas re-breathing.

Chapter four describes the final physiological experiment that was based on the two former studies and that investigated the physiology of the human cardiovascular system during gravity transitions in parabolic flight in great detail. Emphasis was placed on the body fluid regulation system, the hormonal system and the pulmonary circulation. The effects of the hypobaric hypoxic atmosphere of the airplane cabin were emphasized in particular.

Chapter five presents the results of the thesis within a physiological and clinical context. It is demonstrated that the methods of cardiovascular index estimation based on pulse curve analysis and impedance cardiography have similar methodical limitations in the intensive care setting and in parabolic flight. It is furthermore illustrated that cardiac output after transition in microgravity in parabolic flight is higher than that required by the peripheral tissues and that the pulmonary vasculature and the human body fluid system underlie a nested physiological regulation as influenced by multiple environmental factors.

Zusammenfassung

Im Rahmen dieser Doktorarbeit wurden Parameter des Herzkreislaufsystems gesunder Probanden aus verschiedenen Biosignalen berechnet. Die Messungen wurden in den Schwerkraftsübergängen von Parabelflügen durchgeführt, während sich das Herzkreislaufsystem in keinem Gleichgewichtszustand befand. Außerdem wurden Interaktionen von kardiopulmonalem und hormonellem System und der Flüssigkeitshomöostase im Parabelflug untersucht.

Kapitel eins gibt eine detaillierte Einleitung in die Gravitationsphysiologie und in die Herzkreislaufphysiologie auf Parabelflügen. Wissenschaftliche Überschneidungen von Physiologie unter extremen Umweltbedingungen und Anästhesiologie werden anhand klinischer und physiologischer Literatur aufgezeigt. Die wissenschaftlichen Methoden und Versuchseinrichtungen, die dieser Doktorarbeit zugrunde liegen, werden im Detail beschrieben.

Kapitel zwei beschreibt das erste Experiment dieser Doktorarbeit im Rahmen dessen das Herzzeitvolumen kontinuierlich mittels Thoraximpedanzmethode und Fingerblutdruckanalyse auf Parabelflügen untersucht und mit dem nichtinvasiven Goldstandard der absoluten Herzzeitvolumenbestimmung, der Testgasrückatmung, verglichen wurde. Die Vergleichbarkeit der Methoden wurde mittels Bland und Altman Analyse bestimmt. Das absolute Herzzeitvolumen der stehenden Probanden wurde zum ersten Mal mittels der Rückatemmethode während des Übergangs von Hypergravitation in Mikrogravitation bestimmt.

Kapitel drei beschreibt den Vergleich der Berechnung des Herzzeitvolumens auf der Grundlage von zehn verschiedenen Pulskontourmethoden während Schwerkraftsübergängen. Das Herzzeitvolumen der verschiedenen Pulskontourmethoden wurde mit dem gleichzeitig mittels Testgasrückatmung bestimmten Herzzeitvolumen verglichen.

Kapitel vier stellt das abschließende physiologische Experiment der Arbeit dar, welches auf den Resultaten der Kapitel zwei und drei basiert. Dieses hatte die detaillierte Untersuchung des menschlichen Herzkreislaufsystems während Schwerkraftsübergängen im Parabelflug zum Ziel. Besonderes Gewicht wurde dabei auf die hormonelle Regulation des Wasserhaushalts und auf die Lungenzirkulation gelegt. Die Auswirkungen des verminderten Luftdrucks und des verminderten Sauerstoffpartialdrucks der Flugzeugkabine wurden berücksichtigt.

Im fünften Kapitel werden die Ergebnisse dieser Arbeit in den klinischen und physiologischen Kontext eingeordnet. Dabei wird klar, dass die Pulskontourmethoden und die impedanzkardiographischen Methoden der kardiovaskulären Indexberechnung ähnliche methodische Limitationen in der Weltraummedizin wie auf einer Intensivstation haben. Außerdem wird klar, dass das Herzzeitvolumen in der Mikrogravitation eines Parabelflugs höher ist, als in dieser Situation vom Körper benötigt und dass die Lungenzirkulation und die Flüssigkeitshomöostase verschachtelten Regulationsmechanismen unterliegen, die von einer Vielzahl der Umweltfaktoren eines Parabelflugs beeinflusst werden.

Abbreviations

a. m. s. l.	above mean sea level
ATP	ambient temperature and pressure
AVP	arginine vasopressin
BCG	bromocresol green
BTPS	body temperature and pressure, saturated
CI	cardiac index
CI_{rb}	cardiac index by rebreathing
CNES	Centre national d'études spatiales
CO	cardiac output
COHB	carboxyhemoglobin
CORB	optimized carbon monoxide rebreathing method
CO_{rb}	cardiac output by rebreathing
CVP	central venous pressure
DLR	Deutsches Zentrum für Luft- und Raumfahrt (German Aerospace Center)
DRA	direct renin activity
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FBP	finger blood pressure
FBP_{diast}	diastolic finger blood pressure
FBP_{syst}	systolic finger blood pressure
F_iO_2	inspiratory oxygen fraction
G_x	acceleration along the sagittal axis
G_y	acceleration along the frontal axis
G_z	acceleration along the head to toe axis
HR	heart rate
ICG	impedance cardiography
ISS	International Space Station
JAR	Joint Aviation Requirements
LVET	left ventricular ejection time
MAP	mean arterial pressure
PBF	pulmonary blood flow
p_ACO_2	alveolar partial pressure of carbon dioxide
p_AO_2	alveolar partial pressure of oxygen
pH_2O	partial pressure of water vapor
POI	postflight orthostatic intolerance
pO_2	partial pressure of oxygen
PV	plasma volume
RQ	respiratory quotient
SI	stroke index
SO_2	arterial oxygen saturation
SI_{rb}	stroke index by rebreathing
SV	stroke volume
SV_{rb}	stroke volume by rebreathing
tHb	total hemoglobin mass
VO_2	alveolar oxygen consumption
Vt	volume of pulmonary tissue

Declaration of funding and conflict of interests

The experiment that led to the results of chapter two was performed on the 50th ESA Parabolic Flight Campaign in Bordeaux, France. The flight opportunity was funded by the European Space Agency (ESA). Expenses for technical equipment and travel of the subjects and parts of the science team were met by internal funding of the Institute of Aerospace Medicine of the DLR. The work of U. Limper was mainly covered by internal funding of the Department of Anaesthesiology and Intensive Care Medicine of the University Witten/Herdecke at the Merheim Medical Center, Cologne.

The work of chapter three is based on cardiovascular data that were collected during the 15th, 16th and 19th DLR parabolic flight campaigns and on the CNES demonstration flight during the 2011 Paris Le Bourget Air Show. The flight opportunities on these flights were funded by the DLR Space Administration and the French CNES. Expenses for technical equipment and travel were met by a grant of the German Federal Ministry of Economics and Technology (50WB1155), by internal funding of the Institute of Aerospace Medicine of the DLR and by internal funding of the Department of Anaesthesiology and Intensive Care Medicine of the University Witten/Herdecke at the Merheim Medical Center, Cologne.

The experiments that are reported in chapter four were performed during the 15th, 16th and 19th DLR parabolic flight campaigns. These flight opportunities were provided by the DLR Space Administration. An additional ground study in a hypobaric chamber, travel expenses, technical equipment and biochemical analyses were covered by internal funding of the Institute of Aerospace Medicine of the DLR. The work of U. Limper was mainly covered by internal funding of the Department of Anaesthesiology and Intensive Care Medicine of the University Witten/Herdecke at the Merheim Medical Center, Cologne.

Between 2011 and 2014, U. Limper was supported by the grants 50WB1155 and 50WB1255 of the German Federal Ministry of Economics and Technology.

In 2013, work of U. Limper that was not part of this thesis was supported by a grant from the European Space Agency (ESA).

U. Limper declares no conflicts of interest.

Curriculum Vitae

26.05.1982	geboren in Bergisch Gladbach
Juni 2001	Abitur am Dietrich-Bonhoeffer-Gymnasium, 51674 Wiehl
Juli 2001 – April 2002	Zivildienst im Rettungsdienst des Oberbergischen Kreises und Ausbildung zum Rettungssanitäter
Sommersemester 2002	Beginn des Studiums der Humanmedizin in Würzburg
März 2004	Physikum (Note 1,66)
Juli 2005 – März 2006	Wissenschaftlicher Mitarbeiter im Rahmen der SL7-Studie am Deutschen Zentrum für Luft- und Raumfahrt in Köln
Februar 07 – Januar 08	Praktisches Jahr im Leopoldina-Krankenhaus Schweinfurt.
Juni 2008	Staatsexamen in Humanmedizin (Note: 1,0) an der Universität Würzburg
2008	Approbation
September 08 – Dezember 08	Arzt am Institut für Luft- und Raumfahrtmedizin in Köln-Porz Wissenschaftliche Arbeit an der Kurzarmzentrifuge der ESA
Januar 2009 bis Mai 2014	Facharztweiterbildung im Fach Anästhesiologie an der Klinik für Anästhesie und operative Intensivmedizin der Universität Witten/ Herdecke, Krankenhaus Köln Merheim.
Oktober 2011 – April 2014	Wissenschaftlicher Mitarbeiter der Universität Witten/Herdecke
Juni 2012	Fachkunde Rettungsdienst
Juli – Dezember 2012	Hauptamtlicher Notarzt bei der Berufsfeuerwehr Köln
Mai 2014	Facharztanerkennung für Anästhesie

List of publications

1. **Limper U**, Gauger P, Beck LE. Upright cardiac output measurements in the transition to weightlessness during parabolic flights. Aviat Space Environ Med. 2011 Apr;82(4):448-54. PubMed PMID: 21485403.

2. **Limper U**, Lynch J. Removal of epidural catheter under dual antiplatelet therapy following acute coronary syndrome : scenario without special consideration to the current guidelines on epidural regional anesthesia. Anaesthesist. 2012 Aug;61(8):686-90. doi: 10.1007/s00101-012-2067-4. German. PubMed PMID: 22847559.

3. Ganse B, **Limper U**, Bühlmeier J, Rittweger J. Petechiae: reproducible pattern of distribution and increased appearance after bed rest. Aviat Space Environ Med. 2013 Aug;84(8):864-6. PubMed PMID: 23926665.

4. **Limper U**, Beck P, Gauger P, Beck LE. Das menschliche Herz-Kreislauf-System auf Parabelflügen – Aktuelle Erkenntnisse zu gesundheitlichen Risiken. Flugmedizin·Tropenmedizin·Reisemedizin-FTR, 20(04), 166-171.

5. Luchitskaya E, Deliere Q, Diedrich A, Pattyn N, Almorad A, Beck L, Gauger P, **Limper U**, Funtova I, Baevsky RM, Migeotte PF, Tank J. Timing and source of the maximum of the transthoracic impedance cardiogram (dZ/dt) in relation to the H-I-J complex of the longitudinal ballistocardiogram under gravity and microgravity conditions. Conf Proc IEEE Eng Med Biol Soc. 2013;2013:7294-7. doi: 10.1109/EMBC.2013.6611242. PubMed PMID: 24111429.

6. Arai T, **Limper U**, Gauger P, Beck L. Pulse contour methods to estimate cardiovascular indices in micro- and hypergravity. Aviat Space Environ Med. 2013 Nov;84(11):1178-85. PubMed PMID: 24279232.

7. **Limper U**, Gauger P, Beck P, Krainski F, May F, Beck LE. Interactions of the human cardiopulmonary, hormonal and body fluid systems in parabolic flight. Eur J Appl Physiol. 2014 Jun;114(6):1281-95. doi: 10.1007/s00421-014-2856-3. PubMed PMID: 24623065.

8. Leguy CAD, Beck P, Gauger P, Beck LEJ, **Limper U**. Carotid arterial wall dynamics during gravity changes on partial-g parabolic flights. Microgravity Sci Technol 2014, Published online ahead of print. doi: 10.1007/s12217-014-9381-1.

Danksagung

Ich danke meinem wissenschaftlichen Lehrer **Herrn Dr. Luis Beck** dafür, dass er mich für die Physiologie begeistert hat und dass er sein großes Wissen und Verständnis für das Herzkreislaufsystem mit mir geteilt hat. Außerdem bin ich ihm sehr dankbar, dass er diese Dissertation aktiv von Anfang an betreut und unterstützt hat. Alles was ich über das menschliche Herzkreislaufsystem weiß, habe ich von ihm gelernt. Dieses Wissen ist mir im Übrigen auch bei meiner täglichen Arbeit als Anästhesist von unschätzbarem Wert und verleiht mir Sicherheit in meinem klinischen Handeln und ein tieferes Verständnis für die Pathophysiologie meiner Patienten.

Herrn **Prof Dr. med. Frank Wappler** danke ich für Übernahme der Betreuung dieser Doktorarbeit. Außerdem bin ich ihm zu großem Dank verpflichtet, dass er mich die Jahre über in der Durchführung dieser Projekte unterstütz und er es mir ermöglicht hat, diese Arbeiten trotz meiner klinischen Tätigkeit in seiner Klinik durchzuführen. In der Zeit der Anfertigung dieser Doktorarbeit habe ich bei Herrn Prof. Wappler meine Ausbildung zum Facharzt für Anästhesie durchlaufen, wofür ich ihm ganz unabhängig von dieser Arbeit, sehr dankbar bin.

Herrn **Prof. Dr. med. Rupert Gerzer** danke ich dafür, dass ich diese Doktorarbeit in seinem Institut durchführen konnte und dass er mir in persönlichen Gesprächen den richtigen Weg aufgezeigt und mein wissenschaftliches Denken geschärft hat. Dass man hypothesenbasierte Wissenschaft durchführen sollte, habe ich von ihm gelernt und mir zu Herzen genommen.

Herrn **Dipl. Ing. Peter Gauger** danke ich für die viele gemeinsame Zeit, die wir mit der Durchführung wissenschaftlicher Projekte verbracht haben und die nur gemeinsam zum Erfolg gebracht werden konnten. Außerdem danke ich ihm für die Freundschaft, die sich in dieser Zeit aus der gemeinsamen Arbeit entwickelt hat.

Ich danke meinem Vater, **Herrn Dipl. Ing. Klaus Limper**, für viele wissenschaftliche Diskussionen und für hilfreiche Hinweise besonders zu technischen und ingenieurswissenschaftlichen Aspekten dieser Arbeit. Zum Verständnis des menschlichen Herzkreislaufsystems waren die Sichtweisen eines Ingenieurs häufig außerordentlich hilfreich.

Allen **Probanden** danke ich für ihre Teilnahme an den Parabelflügen und den Bodenexperimenten. Sie haben viele unangenehme Prozeduren bereitwillig über sich ergehen lassen. Außerdem haben sie die Projekte durch ihre Mitarbeit im Labor und durch technische Hilfeleistungen unterstützt.

Herrn Hartmut Friedrich danke ich für die Bedienung der Höhenkammer und der Langarmzentrifuge während der Bodenstudien. **Herrn Guido Petrat** danke ich für die technische Unterstützung während der Parabelflüge und für viele nützliche technische Diskussionen und Hinweise.

Klaus Ulrich Limper

Königsforststrasse 58b

51109 Köln

Eidesstattliche Erklärung

Ich versichere (an Eides statt), dass ich die zur Erlangung des Doktorgrades der Medizin vorgelegten Dissertationsschrift mit dem Thema „**Cardiopulmonary and Circulatory Interactions During Gravity Transitions in Parabolic Flight - Joint Approach of Gravitational Physiology and Anaesthesiology -**“ selbstständig und ohne fremde Hilfe angefertigt und die in der Arbeit verwendete Literatur vollständig zitiert habe.
Ich habe diese Dissertation weder in dieser noch in einer ähnlichen Form an einer anderen Hochschule eingereicht.

Köln, 26.09.2014

Klaus Ulrich Limper