Diplomarbeit

Anatomical and Physiological Changes to the Heart in Microgravity and Simulated Microgravity: A Literature Review

eingereicht von

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unter der Anleitung von

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Graz, am 10. Juli 2018

1. Eidesstattliche Erklärung

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Graz, am 10. Juli 2018 Julian Brottrager eh.

2. Acknowledgements

There is a number of people tho need to receive thanks and gratitude for supporting me in creating this work. To my supervisors Assoz. Prof. Priv.-Doz. Dr.med. Nandu Goswami MMedSci PhD and Ao. Univ.-Prof. Mag Dr.rer.nat. Andreas Rössler for their support and academic and creative input and guidance throughout the creation of this thesis.

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You are all part of this thesis.

3. Abstract

Introduction: Spaceflight has long been known to effect the human body. Long term missions into orbit and the space stations have led to skeletal muscle and bone density loss. Knowledge about other, less well researched physiological systems, is less profound and needs further research. The cardiovascular system being one of them.

Objective: This thesis investigated how microgravity and simulated microgravity effect the human heart's physiology and anatomy and how these changes could pose a risk for future long term space flight missions.

Methods: The literature was searched for studies looking at studies researching cardiac health in (simulated) microgravity. Keywords such as "Heart", "Spaceflight", "Weightlessness" or "Simulated Microgravity" were used. Primary and secondary sources were searched as well as standard textbooks in anatomy and physiology. Cardiac parameters and vital signs as well as possible countermeasures to these effects where identified and analyzed.

Results: There is little textbook knowledge so far about the effects of microgravity. Because only about her 600 people have been to space ground based simulation is required to research long term effect. Head Down Bed Rest has proven the most applicable simulation technique. The literature search turned out about 90 papers on adaptations and changes to the heart due to (simulated) microgravity exposure. Like all other physiological systems the heart is effected by spaceflight. Cardiac performance and blood pressure are maintained throughout spaceflight missions and upon returning to earth. The main risk from spaceflight is post-flight orthostatic intolerance. This could be a result of plasma volume changes and cardiac remodeling. Little data supports the notion that cardiac compliance and contractility are effected by spaceflight.

Conclusions: While deleterious effects of microgravity exposure to the human heart cannot be entirely excluded, the studies indicate no severe damage to structure and function of the heart. A deeper understanding of cardiac adaptation mechanisms in space is desirable, however deterioration of other physiological systems, especially the musculoskeletal system, poses a greater threat to spaceflight missions.

4. Zusammenfassung

Einleitung: Verschiedene Veränderungen des menschlichen Organismus sind seit längerem als Folge von Raumfahrt bekannt. Längere Raumfahrtmissionen haben zu Abbau der Skelettmuskulatur und der Knochendichte geführt. Das Wissen über andere Organsysteme ist teilweise noch wesentlich weniger ausgeprägt, darunter das kardiovaskuläre System.

Forschungsfrage: Diese Diplomarbeit untersucht wie Mikrogravitation und simulierte Mikrogravitation Anatomie und Physiologie des menschlichen Herzens beeinflusst und wie solche Veränderungen ein Risiko für zukünftige Raumfahrtmissionen bergen können.

Methoden: Die Literatur wurde nach Studien durchsucht die das Herz in (simulierter) Schwerelosigkeit untersuchen. Suchbegriffe waren unter Anderem “Heart”, “Spaceflight”, “Weightlessness” oder “Simulated Microgravity”. Primär-, Sekundärliteratur sowie Lehrbücher der Anatomie und Physiology wurden einbezogen. Vitalparameter und Parameter der kardinalen Leistungsfähigkeit wurden ebenso wie mögliche Gegenmaßnahmen zu Veränderungen am Herzen identifiziert und analysiert.

Ergebnisse: Bisher gibt es kaum Lehrbuchwissen über die Auswirkungen von Schwerelosigkeit. Erst ca. 600 Menschen erreichten bisher den Weltraum, daher sind bodengebundene Simulationsprogramme notwendig. Head Down Bed Rest hat sich als sie tauglichste Methode bewährt. In der Literatur fanden sich ca 90 Studien zu kardinalen Veränderungen durch (simulierte) Schwerelosigkeit. Wie alle anderen Organsysteme ist das Herz-Kreislauf-System auch durch Schwerelosigkeit beeinflusst. Kardinale Leistungsfähigkeit und Blutdruck können während Raumfahrtmissionen und nach Rückkehr auf die Erde weitestgehend erhalten werden. Als größtes Risiko wird orthostatische Dysregulation und Hypotension angesehen. Diese kann Konsequenz von Blut-Plasma Verlusten oder kardinalen Remodellierungsprozessen sein. Veränderungen in Herz-Kontraktilität und -Compliance konnten in einigen Studien gezeigt werden.

Schlussfolgerungen: Bisher gibt es wenige Hinweise auf Schäden am Herzen als Folge von längeren Aufenthalten in Mikrogravitation. Ein besseres Verständnis wie das Herz-Kreislauf-System an Mikrogravitation angepasst wird sollte auch in Zukunft Forschungsziel sein. Allerdings lässt die heutige Datenlage darauf schließen, dass Veränderungen an anderen Organsystemen, insbesondere Abbau des Bewegungsapparates, größere Risiken für Raumfahrtmissionen darstellen.

5. Table of Contents

6. Glossary and Abbreviations

AV	Atrioventricular (node)
BP	Blood Pressure [mmHg]
cf.	compare
CO	Cardiac Output
CT	Computer Tomography
DBP, Dia	Diastolic Blood Pressure [mmHg]
ECG	Electrocardiogram
EDV	End-diastolic-volume [ml]
EF	Ejection fraction
EDA	End Diastolic Area [cm^2]
ESA	End Systolic Area [cm^2]
ESV	End-systolic-volume [ml]
e.g.	lat. *exempli gratia*
FL	Fluid Loading
HDBR	Head Down Bed Rest
HR	Heart Rate
ISS	International Space Station
kcal	kilo calories
LBNP	Lower Body Negative Pressure
LVDdia	Left Ventricular (End) Diastolic Diameter [cm]
LVDV	Left Ventricular (End) Diastolic Volume [ml]
LVDVI	Left Ventricular (End) Diastolic Volume Index [ml/m^2]
LVSdia	Left Ventricular (End) Systolic Diameter [cm]
LVSV	Left Ventricular (End) Systolic Volume [ml]
MAP	Mean Arterial Pressure [mmHg]
MBP, Mean	Mean Blood Pressure [mmHg]
MHC	Myosin Heavy Chain
MRI	Magnetic resonance imaging
NASA	National Aeronautics and Space Administration
RAAS	Renin–Angiotensin–Aldosterone System
SA	Sinoatrial (node)
SBP, Sys	Systolic Blood Pressure [mmHg]
SF	Space flight
SMS	Space Motion Sickness
SV	Stroke Volume
TPR	Total Peripheral Resistance [$dyn \cdot s/cm^5$]
ULLS	Unilateral Lower Limb Suspension
vs.	versus
zero-G	zero gravity, weightlessness

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9. Introduction

9.1. Anatomy of the Heart

The heart is a muscular organ that lies centrally within the thoracic cavity, right behind the sternum and the thymus enclosed in a sac made of connective tissue, the pericardium (Standring, 2016). It is one organ with its distinct borders, composed of two functionally in part separated subunits, the left and right heart. The heart lies in front of the oesophagus and vertebral column and between the left and right lung. Its downward facing surface lies on top of the diaphragm. Accordingly, the hearts position within the thorax is influenced by degree of inspiration.

Its weight varies averages around 250 g for females and 300 g for males, with approximate dimensions of 12 cm x 8 cm x 9 cm and can be described as an upside down cone with the tip - the apex of the left heart - pointing down, left and anteriorly (Standring, 2016).

Each subunit has an atrium and a ventricle. Blood from the body's veins enters the atria and is ejected from the ventricles into the arterial blood stream. Between atria and ventricles as well as the ventricles and the pulmonary artery and aorta respectively valves are located to direct blood flow.

The left and right heart produce the same output in volume, their distinct dimensions are governed by the amount of pressure required to sustain blood flow against subsequent resistance within the vascular system. Within physiological limits the heart is able to adapt to changes to those pressure levels.

The right atrium receives blood from the big central veins, the superior and inferior vena cava as well as the majority of the hearts own venal drainage through the coronary sinus. The minority of cardiac blood is drained through smaller veins - named thebesian veins - into atria or ventricles, with a high degrees of variations (Schünke et al., 2009, Standring, 2016).

The right atrium opens into the right ventricle through the atrioventricular opening, guarded by the tricuspid atrioventricular valve. From the right ventricle the blood is pumped into the pulmonary trunk and consequently into the left and right pulmonary arteries. The pulmonary valve, a semilunar valve, guards the outlet of the right ventricle into the pulmonary trunc.

Correspondingly, on the left the pulmonary veins drain oxygen enriched blood into the left atrium. In the opening into the left ventricle sits the mitral - bicuspid atrioventricular - valve and the barrier between the left ventricle and the ascending aorta is another semilunar valve, the aortic valve.

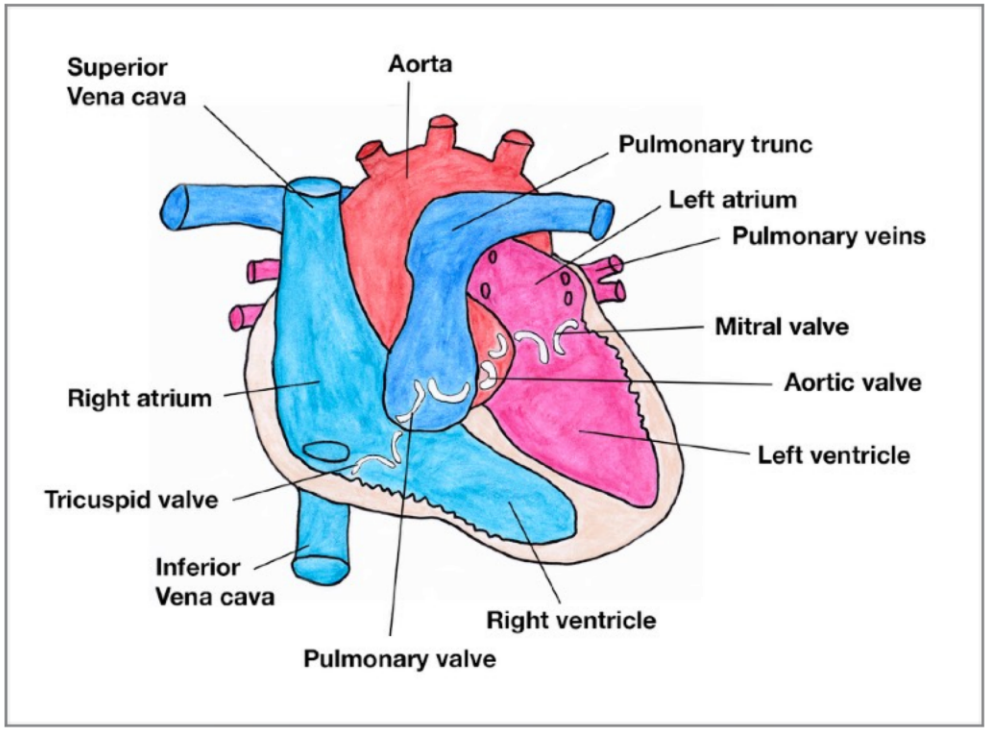

Figure 1: Anatomy of the heart

Blue vessels carry deoxygenated blood, red vessels carry oxygenated blood. © Brottrager

The muscular walls of the left and right heart, particularly the ventricles, reflect the physiological requirements they need to meet. The muscle walls of the left ventricle, including the interventricular septum are thicker by a ratio of about 1:3 with the left ventricle averaging 4 mm and the right 11 mm (Waldeyer and Fanghänel, 2003, Standring, 2016). This reflects the high pressure system it supports with normal pressures of around 120 mmHg compared to about 20 mmHg within the pulmonary artery (Klinke and Baumann, 2010).

The heart valves, two atrioventricular and two semilunar valves govern and direct blood flow from atria, to the ventricles and into the big vessels of the body. All four valves sit at almost the same level within the heart, at the so called base of the heart.

The two types of valves are structurally distinct. While the pulmonary and aortic, the semilunar, valves are supported by a rigid fibrous ring that enables them to withstand the

high pressures, the atrioventricular valves are embedded more flexibly. This allows adaptations to variations in filling volumes of the heart. Tendinous cords support the more flexible atrioventricular valves when pressure increases in systole. These are fibrous collagenous structures attached to the valves and papillary muscles inside the ventricles. The papillary muscles contract synchronized with the ventricular muscle, pulling on the tendinous cords to prevent regurgitation of blood or excessive bulging of the valve back into the atria (Jenkins and Tortora, 2013, Standring, 2016).

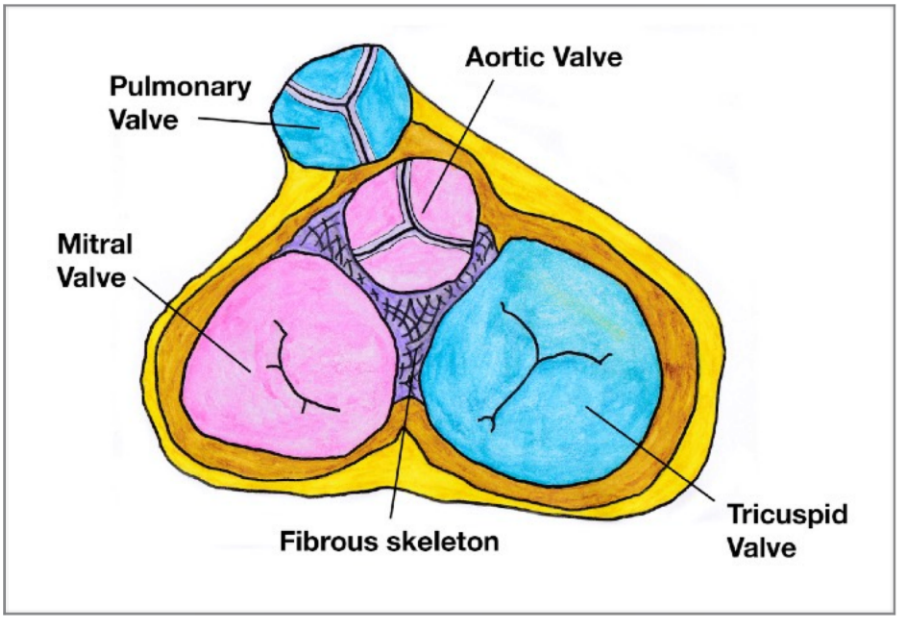

Figure 2: Base of the heart, view from above
In early systole, during isovolumetric contraction, all valves are shut. © Brottrager

As the heart beats rhythmically it needs specialized tissue to conduct the signals through the muscle. Contrary to other parts of the body not nerve cells but specialized muscle cells are responsible for signal transduction. These cells contain fewer myofibrils than normal muscle tissue but are closely connected by highly permeable gap junctions for rapid, directed conduction of electric signals (Hall, 2010). Rhythmical excitation signals the heart muscle to contract and relax in a coordinated manner, on average once every second, sixty times a minute and three billion times in an 80-year lifespan. Signal conduction starts in the sinoatrial (SA) node within the right lateral wall of the right atrium next to the opening of the superior vena cava. From the SA node the impulse spreads to both atria and to the

atrioventricular (AV) node.[1] The AV node sits in the right and posterior part of the interatrial septum close to the opening of the coronary sinus into the right atrium (Schünke et al., 2009, Hall, 2010).

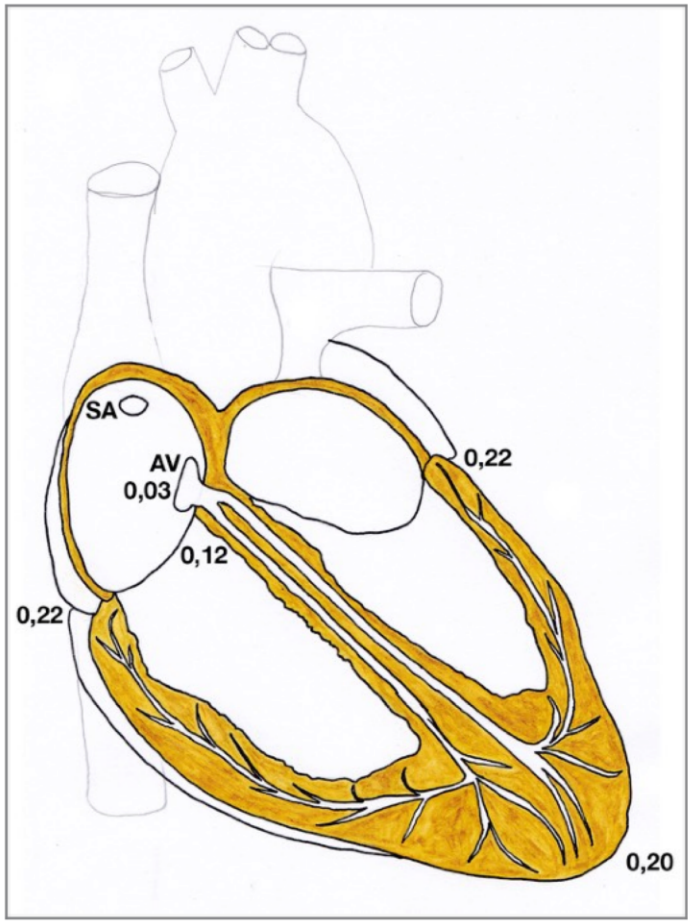

Figure 3: Conduction of depolarization within the heart
Number show delay of signal (sec) after SA node. SA: Sinoatrial node, AV: Atrioventricular node. © Brottrager

In the normal healthy heart the ventricles are isolated from the atria by the fibrous skeleton of the heart. This skeleton does not conduct electrical signals, serving as an insulator between atria and ventricles. Only the AV bundle (of His), subsequent to the AV node, penetrates this isolating layer, making it the only location where excitations are transported into the ventricles of the heart (Standring, 2016).

[1] In the literature no unanimous opinion can be found whether special conductive tissue exists between the SA and AV node. Historically some have said (Hall, 2010, Waldeyer and Fanghänel, 2003) this is the case, others (Standring, 2016) claim differently.

The AV bundle penetrates the interventricular septum, consecutively separating into the left and right bundles. These bundles travel down to the apex of the heart first and the following conductive fibers retrogradely back towards the base of the heart, reaching all muscle.

9.2. Physiology of the Heart

Functionally, the heart is composed of two pumps that operate synchronous as one organ to pump blood through both the small and large vascular system of the body. The atria serve as weak primer pumps for the ventricles, though about 80 % of the filling is done passively following pressure gradients assisted by the valves of the heart. The structure of the cardiac muscle and its close interconnections between cells, as well as conducting and contracting cells, is described as a syncytium. Due to the fibrous disk between atria and ventricles it is possible to speak of two distinct systems, an atrial and a ventricular syncytium, connected only at the AV bundle (Hall, 2010).

The cells of the heart have unique patterns of depolarization perfectly adapted to their physiological requirements. There are two main types of depolarization pattern: one found in the contracting muscle cells and one for the specialized conduction tissue.

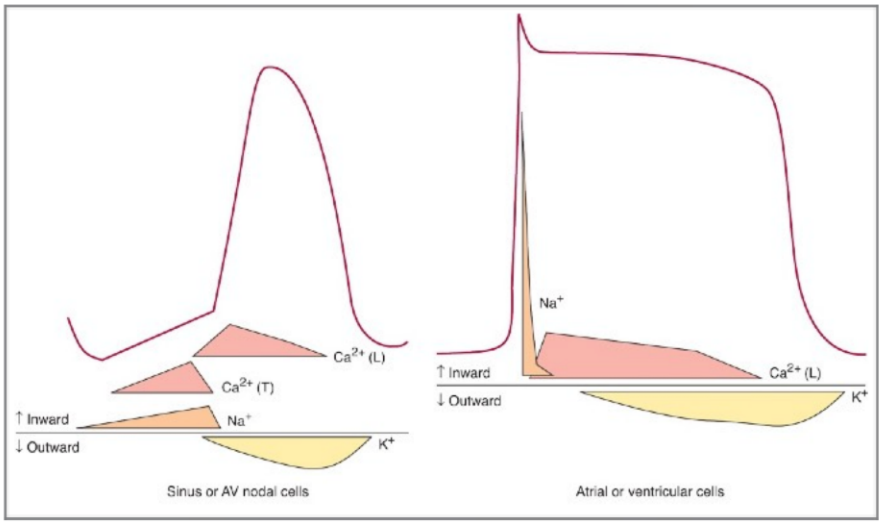

Figure 4: Depolarization patterns of cardiac cells

Left: Cardiac pacemaker cells, right: working muscle cells. Obtained from Hammer and McPhee, 2018

These patterns result from the specific types of ion channels that are expressed by cardiac cells and their distribution. Same as in normal muscle in cardiac cells fast sodium channels

are responsible for the initial influx of Na+ ions and rapid depolarization of the cell. In contracting muscle cells the subsequent interaction of low calcium influx and blockage of fast potassium outflow channels are responsible for the characteristic plateau phase of depolarization. Then channels are reset, allowing potassium to exit, and rapid repolarization to about -90 mVolts resulting in the resting phase of the cardiac cell (Hall, 2010). In the pacemaker cells of the heart these ion channels are expressed different from the working muscle cells. These cells have a less negative resting state of only -55 mVolts to begin with. Due to a higher sodium permeability the positive ions diffuse into the cell slowly raising the membrane potential until it reaches the threshold to open the Ca++ channels, that in turn causes the depolarization of the cell. After about 100 to 150 ms these channels close again and the diffusion of K+ ions out of the cell repolarizes the cell (Hall, 2010).

In the healthy heart the SA node depolarizes at a higher frequency than the following structures that are able for spontaneous self excitation, the AV node - which has a self-depolarizing rate of about 40/min - and to some extend the Purkinje fibers of the ventricles - about 20/min. Each of this SA excitations cause the rest of the cardiac muscle to depolarize and contract coordinately thus overwriting their own intrinsic rhythm of depolarization (Hall, 2010, Klinke and Baumann, 2010).

In case the SA node as primary pacemaker fails, the lower structures are able to step in and take over the roll ensuring the coordinated contraction and output of the heart, however at a lower frequency. Sometimes other cardiac tissues spontaneously depolarize causing a less coordinated spread of contraction through the cardiac muscle, making the initial point of depolarization a so-called ectopic pacemaker (Klinke and Baumann, 2010).

The cardiac cycle repeats periodically with every heartbeat. It is the composition of electrical activity of the heart, muscle contraction, valve action and pressure curves. ECG events and heart sounds are sometimes considered part of the cardiac cycle as they can be documented corresponding to it.

The cardiac cycle has different phases. They can be distinguished in systole and diastole.

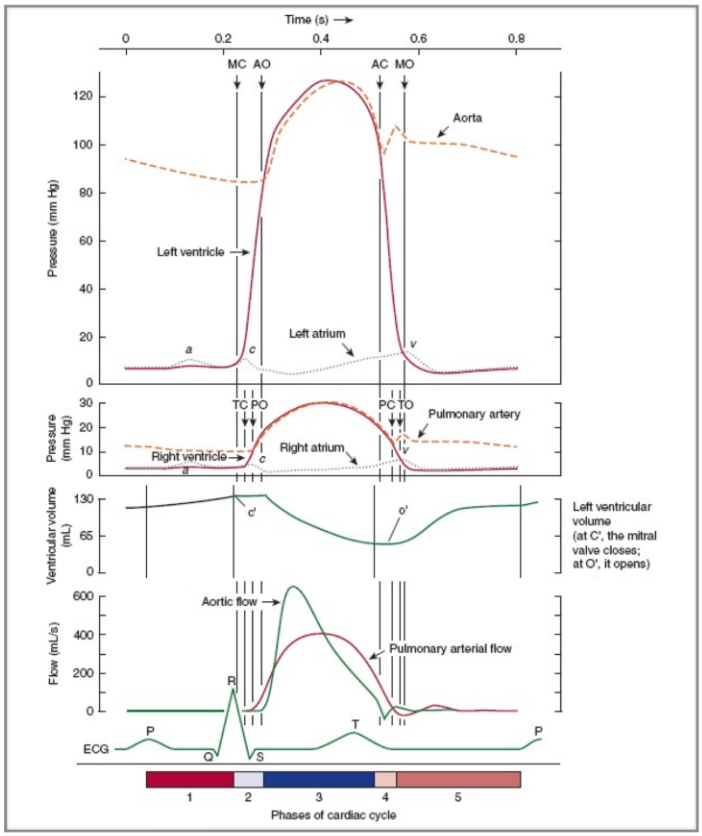

Figure 5: Cardiac cycle

Pressure, volume and flow speed of one cardiac cycle (one heart beat). M: Mitral valve, A: Aortic valve, T: Tricuspid valve, P: Pulmonary valve, O: opening, C: closing, a-c-v: pressure spikes in the left atrium. Below, readings on a normal ECG. Obtained from Hammer and McPhee, 2018

In systole the heart contracts and ejects blood, in diastole it relaxes and fills up with blood again.[2]

During diastole the ventricles relax with both the atrioventricular and the semilunar valves shut, the so called isovolumic relaxation, until pressure in the ventricles falls below atrial pressure, opens the atrioventricular valves and blood fills the ventricles. Most of the blood flows passively only the last 20 percent being pumped in by atrial contraction.[3]

Once ventricular pressure exceeds atrial pressure again due to filling the AV valves snap shut - 1st heart sound - and the ventricles start to contract. As both AV and semilunar

[2] The general terms systole and diastole describe the activity in the ventricles. The atria have both phases within their own timeframe.

[3] Atrial fibrillation often goes unnoticed for long periods due of this.

valves are closed at this point it is a phase of isovolumic contraction. Once pressure levels exceed around 80 mmHg in the left and 8 mmHg in the right ventricles the semilunar valves open, pumping blood into the aorta and pulmonary artery respectively. At the end of systole pressure falls again, forcing closure of the semilunar valves - 2nd heart sound - restarting diastole (Hall, 2010).

Filling volume at the end of diastole is around 120 ml at rest and residual volume after systole is around 40 ml. This results in a stroke volume of 80 ml and an ejection-fraction of about 0,66. Both end-diastolic filling and and systolic volume can be changed to accommodate higher physiological demand, e.g.: exercise (Klinke and Baumann, 2010).

To support the normal cardiac output of 5.000 ml of blood every minute at this stroke volume a heart rate of 63/min is required. To average both men and women over different age groups 70/min x 70 ml is often cited. Depending on training level stroke volume increases of up to 100 ml are observed. Consequently, the resting heart rate in these individuals drops to around 50 beats per minute (McArdle et al., 2014). While little differences are observed in maximum heart rate in trained and untrained individuals maximum stroke volume can be dramatically increased. This results an up to seven-fold increase in cardiac output at maximum exercise level in professional endurance athletes compared to the four-fold increase in the untrained average adult (Hall, 2010).

Two terms describe variables that fundamentally influence cardiac function and behavior: cardiac *preload* and *afterload.*

Preload is the end-diastolic filling volume of the heart and the resulting pressure within the chambers. It is highly dependent on factors such as body position, muscle pump, blood volume or blood volume distribution.

Afterload is the pressure within the great vessels - aorta and pulmonary artery - against which the heart has to pump the blood. Afterload is dependent of factors like vascular compliance, peripheral resistance or blood volume within the vessels (Speckmann et al., 2008, McArdle et al., 2014).

The **Frank-Starling-mechanism** describes a most basic characteristic of the heart and its intrinsic capability to self-regulate cardiac output depending on venous return, independent of vegetative nervous system influences.

„Within physiological limits the heart pumps all the blood that returns to it by way of veins.“ (Hall, 2010)

Like all striated muscle the heart has the property to increase contractility depending on the strain that is put on it. When preload increases all muscle fibers are stretched, thus creating a more forceful ejection stroke. This is attributed to changed Ca++ affinity within the fibers as a result of the stretching and to a lesser degree a more optimal arrangement of the muscle filaments (Speckmann et al., 2008, McArdle et al., 2014). The higher pressure upon increased preload also stretches the walls of the left atrium where the SA node is located. The stretching of the tissue causes the SA node to increase heart rate. Further the so-called *Bainbridge*-reflex signals the stretching to the central nervous centers. Through sympathetic and parasympathetic efferent nerves both heart rate and contractility are consequently increased (Hall, 2010). These effects combined are necessary to fully utilize the heart's cardiac output reserves.

Aside its intrinsic ability to regulate beating rate the heart is also under the influence of the sympathetic and parasympathetic nervous system. The parasympathetic system, via the vagus nerve, innervates mostly the SA and AV node exerting a decelerating stimulus. The effects on the atria are reduced heart rate as well as contractility. Little effects on the ventricles have been described. Acetylcholine is the key transmitter of the vagus nerve. The sympathetic nerves, originating from various cervical and thoracic segments, insert in both ventricles and atria. The effects are positively chronotropic on the conduction system and positively inotropic on the muscle cells of the heart. Various catecholamines are the neurotransmitter in the sympathetic system.

The sympathetic effects raise cardiac output while parasympathetic stimuli decrease cardiac output (McArdle et al., 2014, Stanfield, 2017).

9.3. The Circulatory System

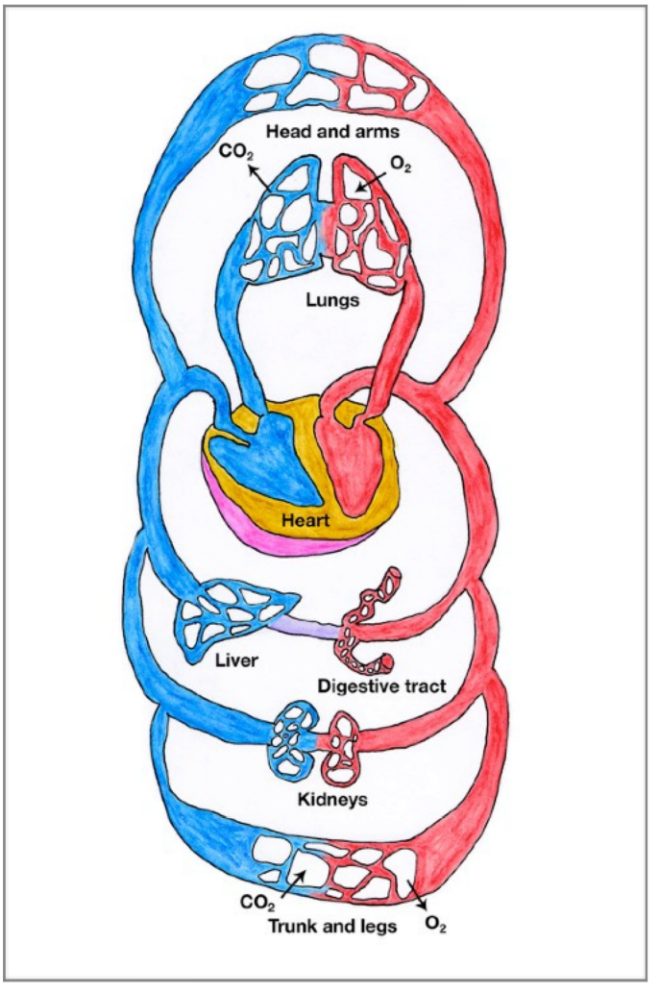

Figure 6: Overview of the circulatory system
Showing the small and the large circulation of the body.
© Brottrager

The circulatory system is comprised of two circuits. In the small, pulmonary circulation the right ventricle pumps the oxygen deprived blood through the pulmonary artery into the lungs. It returns, oxygenated, to the left atrium via the pulmonary vein. The left ventricle supports the entire large, systemic, circulation, pumping oxygen-rich blood to all other tissues of the body, including the heart itself. While the small and large circuits pump the same amount of blood in the same time pressures vary greatly between them. The pressure in the left ventricle and consequent aorta averages at 100 - 120 mmHg, while the right ventricle and pulmonary artery normally reach only a fifth of that level at 20 - 25 mmHg (Speckmann et al., 2008).

Blood is not distributed evenly among the systems and circulations. 85 % are within the systemic and only 20 % in the pulmonary circulation. However only 20 % of the blood is within the systemic arteries, while about two thirds of the blood volume are pooled in the systemic veins. At approximately five liters of blood this amounts to circa 3,2 liters. The term pooled is used here because in upright position on earth about 500 ml of blood are pooled within the lower extremities of the body due to gravitational pull on it. Thus the veins and especially those of the lower extremities hold a blood reservoir that can easily be utilized if need be. e.g.: the leg-up-maneuver in orthostatic syncope.

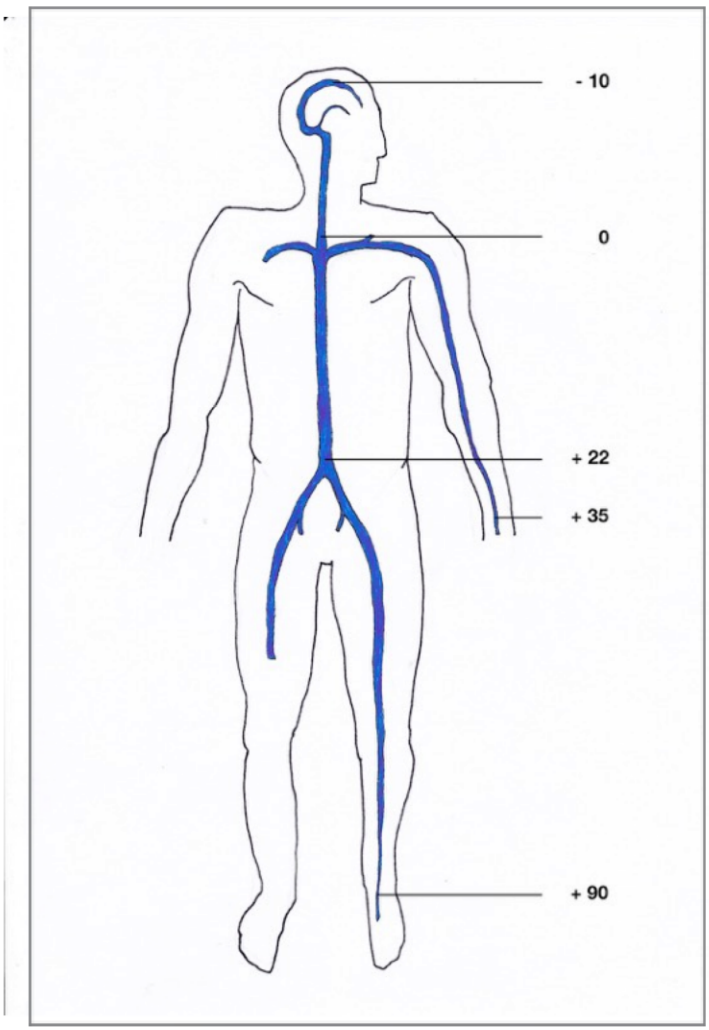

Figure 7: Venous pressure [mmHg]
in a standing person on earth (1g environment).

In upright position within the venous system there is a pressure gradient of about 90 mmHG between the right atrium and the feet. This is due to the gravitational pull on the blood column within the body (Hall, 2010).

To maintain a unidirectional blood flow towards the heart two systems are in place. The valves inside the veins allow for blood only to pass in one direction. Once bloods starts moving backwards, like when gravity pulls it towards the ground, the vales shut to prevent backflow. The veins of the arms and legs are topographically closely related to the muscles of the extremities. When one uses those muscles, as in walking or exercising, the tightening of the muscle compresses the adjacent veins pumping the blood. Much like in the heart the muscle pumps the blood and the valves allow for directed blood flow, in this case from more distal parts of the extremities to the center of the body. This principle is known as the muscle pump of the circulation (Hall, 2010).

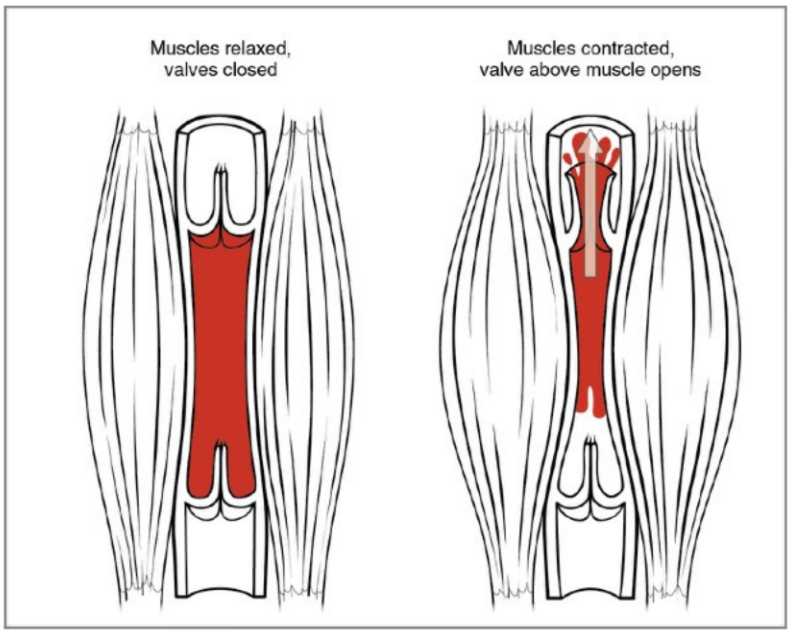

Figure 8: Muscle Pump

When the muscles contract they squeeze blood out of nearby veins. Valves only allow only unidirectional blood flow towards the heart. From (College, 2013), via commons.wikimedia.org, under Creative Commons Attribution 3.0 Unported license

All peripheral tissues and organs are capable of regulating their own blood flow depending on metabolic activity. As demand increases more O_2 is utilized and more CO_2 produced. This in turn feedbacks to local small arteries which reactively dilate, resulting in increased blood flow to the organ. This is illustrated by skeletal muscle blood flow when it is raised from a resting 20 % to 80 % of cardiac output during exercise. *Note*: Cardiac output at the same time increases as well - as mentioned before - depending on amount of activity and training level (Stanfield, 2017).

The time course of vascularization is best described by two quotes as stated by Hall (2010):

> "If the metabolism in a tissue is increased for a prolonged period, vascularity increases, a process generally called angiogenesis; if the metabolism is decreased vascularity decreases."
>
> "Vascularity is determined by maximum blood flow need, not by average need"

The body's circulation is capable to adapt to changing demand of the tissues by increasing and decreasing vascularization to the tissues. This effect is also made use of in physiological exercise. Blood pressure is a closely monitored and regulated vital parameter. Hence several different systems measure and adjust to maintain a steady pressure. Aside the heart and the vasculature itself there are a few more important players. On short term stretch sensitive baroreceptors at the aortic arch and the carotid sinus detect changes in blood pressure and via afferent nerves signal these changes to the coordinating center in the medulla. Via both the sympathetic and parasympathetic system the response effects both the heart and the systemic blood vessels. e.g.: a raise in blood pressure detected at the baroreceptors would result in both peripheral vasodilation and bradycardia (Boron and Boulpaep, 2017). Most blood pressure regulation in the long haul is controlled by the kidney and the Renin–Angiotensin–Aldosterone System (RAAS). Unlike the baroreceptors and the autonomic nervous system, this reactions take hours for significant responses. Kidney perfusion pressure and body salt to water ratio are maintained at a stable levels by this system (Hall, 2010).

9.4. Microgravity Environments

Gravity is a force that attracts two bodies with mass towards each other. This force is proportional to the product of their respective masses and reciprocally proportional to the distance between them squared. The gravitational pull experienced is equal for both objects independent of their mass, as Newton's Law of Universal Gravitation states.

$$F = G\frac{m_1 m_2}{r^2}$$

Figure 9: Newton's Law of Universal Gravitation

This is true for every two objects of mass, however mass needs to be significantly high enough. For example, to reduce the earth's gravitational pull to 1.000th of its surface level (9,81 m/s^2) one has to travel roughly half the distance to the moon. Gravity levels this low and lower will be in place on future missions into the solar system.

Current missions, almost exclusively to the International Space Station which orbits the earth at about 400 km, do not experience zero-gravity as gravity levels at that altitude are close to 90 % of that on earth's surface. The space station and everything on it are in perpetual free fall around the earth as a result of its high orbiting velocity of 27.600 km/h, letting it orbit the earth every 90 minutes. As a result the crew on board experiences no gravitational forces.

With just over five hundred people who have been to space in space exploration history data on physiological changes and adaptations to microgravity is limited.

As of 2018 the International Space Station is the only manned space station and there are no more than six crew members at a time and about ten every year. Their time on the space station filled with research in many different fields one of which are life sciences.

Figure 10: ISS crew in weightlessness

STS-123 mission, March/24/2008, photo by NASA, via commons.wikimedia.org

Almost all physiological systems have been describe to adapt to weightlessness and each does so within its own timeframe. **Figure 11** below sketches the timeline of some important systems and their adaptation to microgravity.

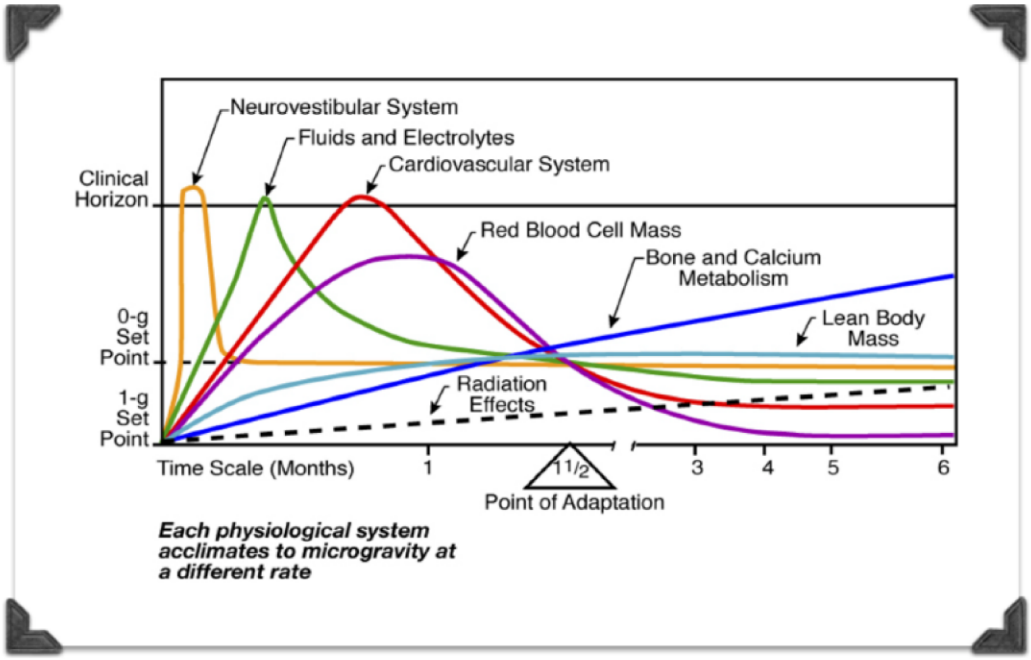

Figure 11: Microgravity effects on different organ systems

From the Physiology Slide Set of the American Society of Gravitational and Space Research

9.4.1. Neurovestibular System

The effects of microgravity on the vestibular system set in immediately upon entering earth's orbit. About 50 % of astronauts exhibit a variety of symptoms that are summarized as "Space Motion Sickness" (SMS). Similar to motion sickness on earth symptoms such as nausea, vomiting, vertigo, drowsiness, disorientation or trouble concentrating set in within the first hours or days in space. In most astronauts the symptoms weaken or disappear entirely during the first week as the neurovestibular system adjusts to the new environment. When the crew returns to earth similar symptoms sometimes can be observed with the addition of trouble standing upright or walking a straight line (McArdle et al., 2014). Medication such as Dimenhydrinate or Promethazine have been used to counter SMS symptoms in astronauts (Weerts et al., 2014).

9.4.2. Bone and calcium metabolism

One of the greatest concerns to future long term missions in space is loss of bone density resulting in space osteopenia. Ever since the first spaceflights in the 1960s and 1970s bone density loss has been documented and measured at up to 10 % even on short term flights. Reductions were decidedly higher in weight bearing bones i.e. the calcaneus while only little loss was measured in bones of the upper extremities (McArdle et al., 2014). More recent data have put the number at about 1-2 % loss in bone density per month in space. This is comparable to the loss a postmenopausal woman experiences every year (Ziambaras et al., 2005, Cappellesso et al., 2015).

Lost mechanical stress has been proposed as main reason for the observed osteopenia. Reduced calcium uptake, both nutritional and intestinal, changes to Vitamin D metabolism and endocrine influences are also discussed and investigated as influences on the observed phenomena. Medication - osteoporosis therapy with calcium and vitamin-D supplementation - and exercise training have yielded some success in preventing bone density loss, though a lot of research is still required (McArdle et al., 2014). Upon reentry into gravity on earth - or in future missions, possibly Mars - an increased risk of fractures is to be expected. Such fractures put the crew at high risk with possibly fatal outcomes.

The endocrine system and the immune system as well as microgravity effects on the central and peripheral nervous system have also been studied (McArdle et al., 2014).

9.4.3. Simulated Microgravity environments

Since only a very limited number of people can actually be sent into space and time is a limited and valuable resource for those sent into space, models to simulate the conditions and different aspects of spaceflight on earth needed to be implemented.

The two main parameters that need to be recreated the best of possibilities are:

- upward shift of blood inside the body
- disuse of the musculoskeletal system

A lot is already known about both these aspects in microgravity as described in chapters **Fluid distribution** and **Muscle in microgravity**.

9.4.4. Parabolic Flight

In parabolic flight an aircraft flies several parabolic curves at 45° ascent and descent. During the phase close to the apogee of the curve the passengers within the aircraft experience perceived microgravity lasting for about 20 seconds at a time

These maneuvers are normally flown somewhere between 5.000 and 10.000 meters in altitude. The difference between the lowest and highest point of the parabola is about 3.000 meters (McArdle et al., 2014). Parabolic flight not only is used to familiarize astronauts with the feeling of weightlessness but also to test equipment and procedures under these conditions.

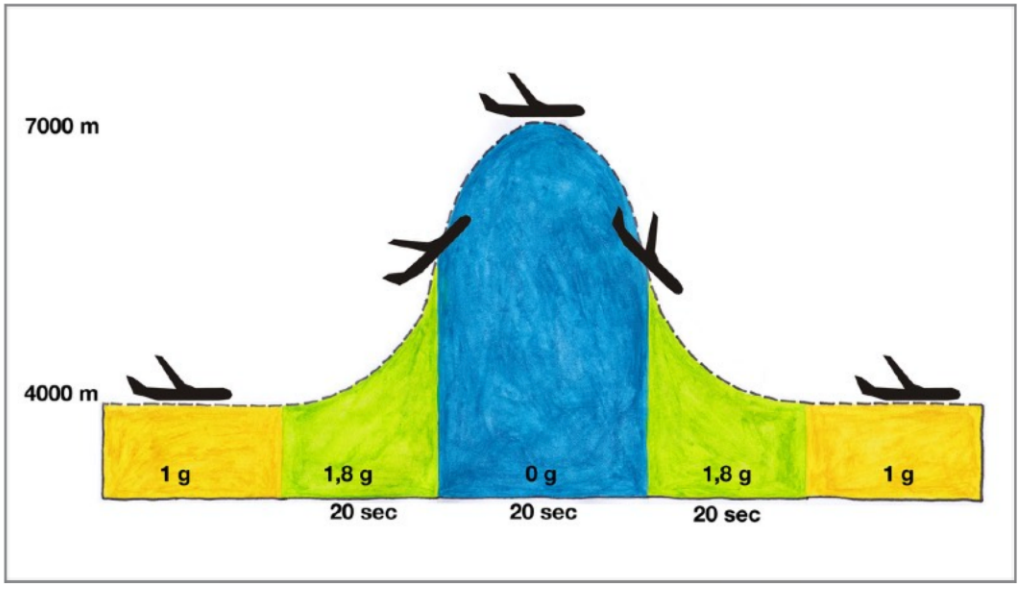

Figure 12: Parabolic flight

The different phases of parabolic flight. © Brottrager

9.4.5. Water immersion

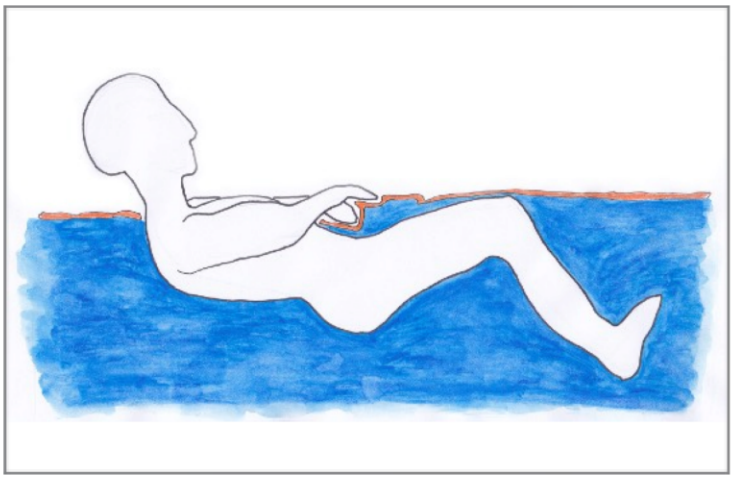

Figure 13: Water immersion

© Brottrager

When immersed in water the weight of the water pushes onto the skin as well as the connective tissue and muscles right below. This force squeezes liquid, mainly blood from these tissues to more central compartments of the body, especially the thorax. At the same time pressure within the blood vessels of the extremities is increased to to the external pressure. This results in baroreceptors signaling a reduction of vasoconstricting pathways such as vasopressin or the RAAS. As a result only the central pooling, not peripheral behavior, of blood in water immersion can be compared to microgravity, even if caused by different effects (Regnard et al., 2001). (see chapter **Fluid distribution**)

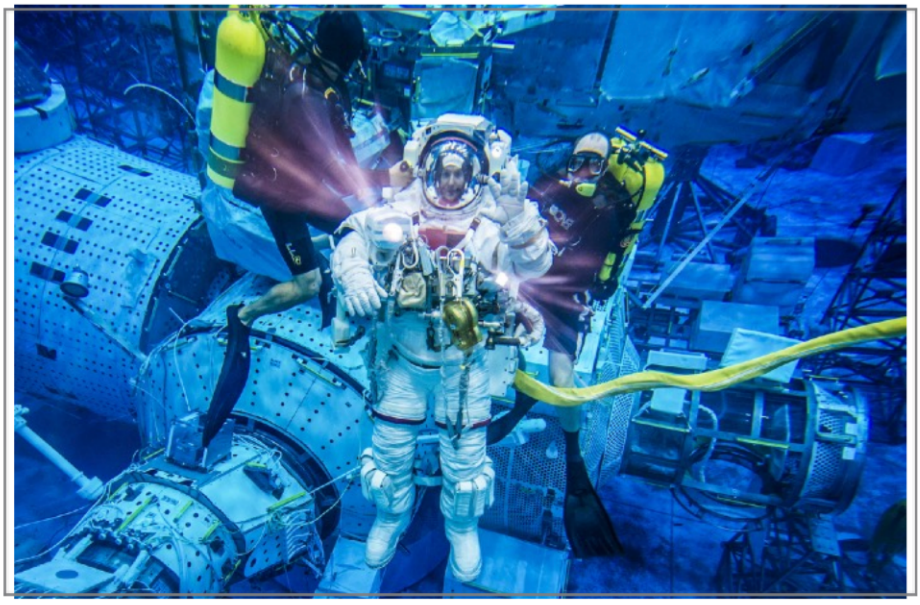

Figure 14: Underwater training

Astronauts in full gear practicing for extra vehicular activity on submerged models of the International Space Station, ESA/NASA (2013)

In Wet Water Immersion test subjects are immersed directly in water with usually only their head sticking out. Due to the effects long term water exposure has on the skin Dry Water Immersion was developed. In this the subjects immersed in water wear a waterproof elastic suit, protecting their skin (Watenpaugh, 2016). Long term trials and exercises while immersed have proven difficult, resulting in other simulation models gaining popularity. It is further important to note that in addition to water immersion, under water training is an indispensable setting for astronauts to train for activities in microgravity, i.e. Extra Vehicular Activities.

9.4.6. Unilateral Lower Limb Suspension (ULLS) and Casting

Several studies show both ULLS (de Boer et al., 2007) and casting (Sargeant et al., 1977) to have similar effects on muscle atrophy, cf. (Narici and de Boer, 2011), regarding muscle mass as seen in spaceflight. However Widrick et al. (2002) claim differences in muscle fibre types effected by ULLS compared to spaceflight and bed rest studies and propose the more extensive limitation in movement as possible cause. This emphasizes the limitations of these techniques. Fluid shifts are not present in casting and ULLS. Compliance to the regimen is also harder to observe.

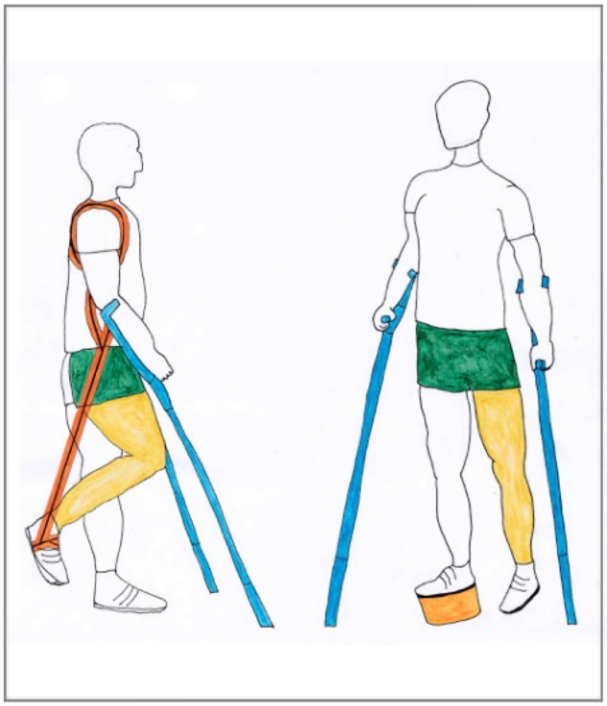

Figure 15: Unilateral Lower Limb Suspension
Left: classic unloading of one leg by suspending using a sling, Right: unloading using "platform shoe". After Tesch et al. (2016)

9.4.7. Head Down Bed Rest

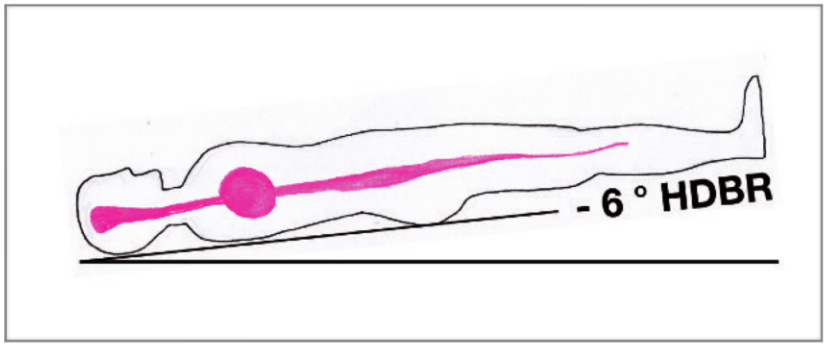

Figure 16: Head Down Bed Rest
showing the expected fluid shifts within the body, simulating microgravity.
© Brottrager

In Head Down Bed Rest (HDBR) -6° below horizontal have been established as a valid analog that closely simulated the fluid shifts within the body as seen in microgravity. Some studies have used various other inclinations, though the majority of studies uses -6°.
While pressure effects on the bodily tissues are close to upright levels, fluid shifts to the thoracic cavity and the head are applicable simulations for microgravity. As it is feasible to keep people in bed for up to several weeks at a time the model can also be used to study physical inactivity and its effects on the muscles and skeletal structures. This was both early and long term effects an be studied (Regnard et al., 2001). Some data is also taken from normal bed rest studies and from studies on people who have been immobilized for longer periods of time (Wall et al., 2013).

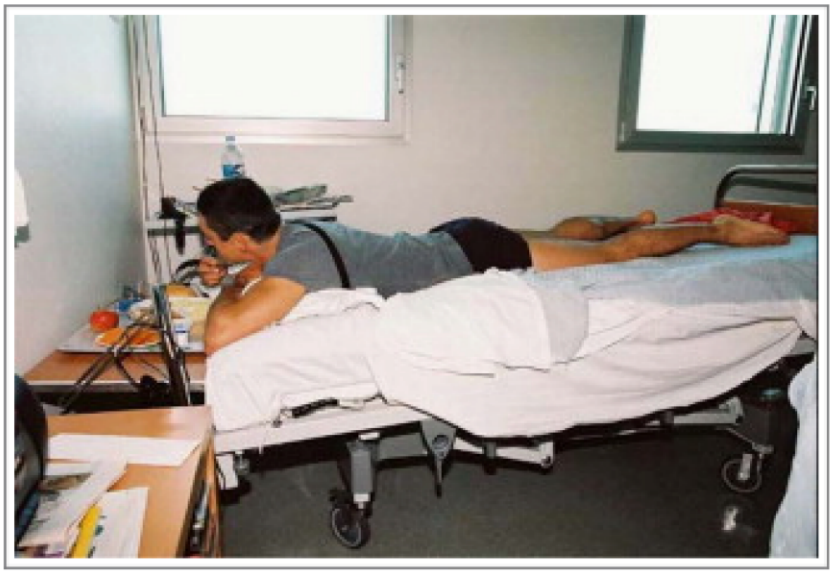

Figure 17: Head Down Bed Rest Study
from Tagayasu et al. (2014)

9.5. Fluid distribution / Plasma Volume

When humans enter the microgravity environment of space gravitational pull on all bodily tissues drops to near zero. This includes the the blood volumes within the vasculature, especially of the lower extremities. Lack of gravitation causes a redistribution of the blood more evenly across the body, resulting in increased blood volume within the headband thorax, while comparatively less blood is pooled inside the legs. Facial edema during first days in space has been observed as a result of this redistribution (Diedrich et al., 2007).
Even with the different distribution of blood towards the head in space central venous pressure does not rise. On the contrary it has been documented to decrease (Buckey et al., 1996a). Several studies have reported reduced plasma volume (10 to 15 %) within days of entering microgravity (Alfrey et al., 1996, Leach et al., 1996). These results have been successfully reproduced in ground based head down bed rest studies (Hirayanagi et al., 2004, Westby et al., 2016).

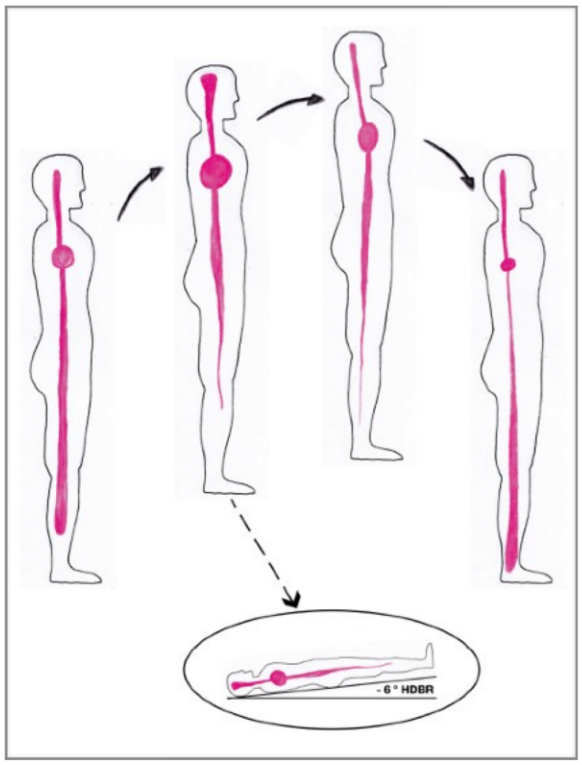

Figure 18: Changes of fluid distribution in microgravity
Lower Left: On earth, before take-off
Upper Left: Headwards shift of fluids early in spaceflight
Upper Right: Even distribution late in spaceflight, reduced plasma volume

While the endpoint – 15 % reduced plasma volume – is similar in spaceflight and in HDBR the underlying mechanism is now believed to be different. In HDBR within the first 24 hours subjects experience approximately 350 ml of increased urine output (Trappe et al., 2006). This same increase in urine output is not seen in spaceflight (Norsk, 2005). While most of the plasma change in bed rest has been attributed to central fluid load a different mechanism has been proposed for microgravity environments. With the lack of gravity the weight of the tissues on itself is also lifted causing a) a reduction in transmural pressure and b) a relaxation of tissues. When the tissues of the thorax relax the chest cavity increases in volume. This results in a decrease in central venous pressure despite the fluid shift to the thorax (White and Blomqvist, 1998). This model accounts for the observed phenomena in spaceflight as well as HDBR where the relaxation of tissues does not occur. Another factor contributing to diminished plasma volume in spaceflight is reduced fluid intake. Nutritional studies have found energy intake, accompanying a lower feeling of thirst and appetite, to be reduced by about one-third during missions. The effect is especially strong for the first two to three days in space when space motion sickness is strongest (Stein et al., 1999).

9.6. Muscle in Microgravity and Simulated Microgravity

The influence of microgravity on skeletal muscle has been known from observations on Skylab and MIR missions in the 1970s and 80s and since been confirmed by more extensive data from ISS missions. Load bearing muscles responsible to hold posture on earth are most extensively affected by the microgravity environment. This has been best documented for the muscles of the lower limb, namely the M. gastrocnemius and M. soleus but for muscles of the back, upper arm and thigh as well. Lower limb muscle cross sectional area can be expected to decrease up to 24 % on missions of six months of microgravity (Narici and de Boer, 2011, McArdle et al., 2014). Macroscopically, reductions in muscle volume and cross sectional area have been documented for spaceflight as well as simulated microgravity. This atrophy seems to develop in a non-linear way (Narici and de Boer, 2011).

Muscle strength (force generated) and power (strength over time) are both documented to decrease in microgravity with first effects showing within days of exposure (Lambertz et al., 2001). Alterations to coordination patterns have been documented as well, suggesting some kind of neuromuscular disfunction (McArdle et al., 2014). A study by Laughlin et al. (2015) tested functional fitness of different muscle groups of 32 crew members (e.g. squats, push-ups etc.) found reductions in upper and lower body muscle endurance as well as flexibility and agility.

A number of countermeasure regimens have been proposed to reduce or eliminate muscle deterioration in microgravity. These include artificial gravity, daily exercise, electrical stimulation, lower-body negative pressure, nutrition and pharmaceutical interventions. Regarding applicability, cost and risks a combination of nutrition and daily exercise has proven the most effective so far (Narici and de Boer, 2011, McArdle et al., 2014).

Systems currently in use on the International Space Station to measure and counter the microgravity effects on the musculoskeletal system (NASA):

- Combined Operational Load Bearing External Resistive Exercise Treadmill (COLBERT)
- Advanced Resistive Exercise Device (ARED)
- Cycle Ergometer with Vibration Isolation System (CEVIS)
- Percutaneous Electrical Muscle Stimulator (PEMS)
- and a number of diagnostic research and measurement systems

Despite the countermeasures in place a study on nine ISS crew members found reductions of calf muscle volume (-10 to -15 %) and performance (-14 to -30%) after six months in the space station measured within the first week after landing. A second measurement within the second week found some restoration towards pre-flight values, more so in volume than performance (Trappe et al., 2009).

On a the microbiological level there is still some dispute about muscle fibre types affected by microgravity as summarized by Narici and de Boer (2011) :

> "Thus, although the issue seems unsettled, there seems to be stronger evidence of greater susceptibility of human type I fibre to atrophy in response to simulated microgravity."

Trappe et al. have found in their study that Myosin Heavy Chain (MHC) profiles in their astronauts' calf muscles changed from slow to fast twitch fibers i.e. percentage of type I fibers was reduced while percentage of type IIa fibers was increased after spaceflight. (2009) This is in accordance to previous findings in rodents (Talmadge et al., 1996) and humans (Zhou et al., 1995). Similar findings in muscle biopsies have been found by Fitts et al. in their study on ten ISS crew members. (2013) Both studies concluded the countermeasures taken during the missions had shown some effect in protecting against atrophy and the shift in MHC skeletal muscle profiles. (Trappe et al., 2009, Fitts et al., 2013)

10. Aims and Objectives

The heart is a muscle and with all the knowledge that has been gained and established about striated-skeletal-muscle in spaceflight over the last decades the question that arise are:

Can microgravity and the resulting disuse of the musculoskeletal system have similar deteriorating effects on the heart? Can we expect heart atrophy upon return from long term space missions? Is there evidence that functional deficits are to be suspected after such missions and could they endanger future missions to Mars or further into the solar system?

The purpose of this diplomarbeit is to search literature, primary sources, secondary sources and text books, on these questions, on heart anatomy and functionality and how they are effected by microgravity and simulated microgravity exposure.

Adaptations and changes to cardiovascular structure and performance will be confronted with standard knowledge of human anatomy and physiology and training physiology. In the introduction chapter cardiovascular physiology is revised as well as established knowledge on space science research in microgravity and simulated microgravity. In the review chapter all the data gathered from the studies will be categorized and analyzed to allow for applicable conclusions. Where possible spaceflight data will be compared to simulation data to evaluate practicality of said simulation techniques for different cardiovascular parameters. The time course of changes to the heart and its performance parameters will also be examined where sufficient data is available.

One main theory about cardiovascular changes stems from a 1990s review on human physiology in spaceflight:

> "These flight data were similar to those of groundbase data [51] and and support the notion that blood volume reduction rather than deterioration of myocardial function plays the leading role in the decrease of left ventricular end-diastolic and stroke volumes during rest and exercise in weightlessness." (Convertino, 1990)

11. Methodology

For this thesis current literature about the heart's physiology and anatomy in microgravity were searched and compared to textbook literature and understanding of the underlying mechanisms. Standard textbooks were used for the anatomy and physiology of the heart, as well as training physiology, and compared to each other in the introduction.

Pubmed, the MeSH-database and Google Scholar were used as digital sources for literature on the topic. The following terms where used in various combinations:

"space", "space flight", "microgravity", "heart", "weightlessness", "weightlessness simulation", "Blood vessels", "muscular atrophy", "exercise test", "orthostatic intolerance", "stress test", "Myosin Heavy Chains", "blood pressure", "sonography", "ecg", "electrocardiogram", "osteoporosis", "ecg", "Electrocardiography", "Electrocardiogram", "osteopenia"

Only articles written in English or German were included when at least an abstract of the paper was available.

All the results were checked for various other criteria:

- The studies found should focus mainly on quantifying and investigating changes to anatomy and physiology of the heart and the correlated remodeling processes.
- Studies on patients with preexisting conditions (heart disease, diabetes etc.) were excluded
- Studies looking at genetic diseases were excluded.
- Studies on ischemia, inflammation, pericardial effusion, tumors or traumatic incidents were excluded.
- Studies on hypo- or hyperbaric effects on the cardiovascular system were excluded.
- Studies on molecular and biochemical markers were only included if closely related to anatomical or physiological remodeling during weightlessness or simulated weightlessness.
- Hypergravity studies (> 1 G, i.e. Centrifugation) studies were excluded.
- Studies on radiation effects were excluded.
- Neurological and neuromuscular effects were only included if closely related to anatomical and physiological remodeling.

- Studies looking mainly at the psychological effects of microgravity exposure were excluded.

With the exception of studies on “Myosin Heavy Chains”, animal studies were excluded from the search as the effects on human physiology and anatomy are the focus of this review. As basis for this thesis studies, trials and case reports were included as primary sources as well as reviews as secondary sources. Relevant references within the papers where followed and included if applicable to the extent of this review.

For the introduction various standard textbooks were used and compared to review the basic anatomy and physiology of the heart. There are only few textbooks that already mention spaceflight and microgravity effects on the various systems of the body. For these chapters the books were complemented by review literature to summarize the current understanding on microgravity effects on these systems.

References where managed with Endnote X8.2 (license provided by Medizinische Universität Graz). All papers, textbooks, reviews and web sources combined make up to 100 sources used for this review.

Some of the illustrations where created in collaboration with Stefanie V. Brottrager, MA BA. The illustrations were generously provided to be used in this diplomarbeit.

As text processing software Pages™ 7.1 was used.

12. Review of the Literature

This research resulted in 81 papers on the topic. In addition to that nine reviews were included in this thesis and nine textbooks used for the the introduction chapter. At some points additional resources such as image were used. The sources were categorized and classified by the cardiac parameters they looked at. These were:

- Heart Rate (HR)
- Blood Pressure (BP)
  - systolic, diastolic and mean blood pressure
- Stroke Volume (SV)
- Cardiac Output (CO)
- Ejection Fraction (EF)
- Oxygen Consumption (VO_2)
  - Maximal Oxygen Consumption (VO_2max)
- Plasma Volume (PV)
- Heart Filling Dimensions
  - here both ml and cm^2 were used by the primary papers
- Left Ventricular Mass (LVmass)
- Total Peripheral Resistance (TPR)
- Strain and Strain Rate
- Tissue Velocity

Seven studies looked at orthostatic intolerance from various angles, including some standing tests, and were also included in this review. Some papers looked at other parameters or variables that can possibly influence cardiac remodeling in weightlessness such as nutrition during the studies or countermeasures applied. Changes to vasculature and the endothelium were investigated in four papers. For a more complete understanding of the matter and to round out the picture these were included in this thesis as well.
Of the 81 papers reviewed in this thesis 26 discuss data from ground based simulated microgravity studies. Zero-gravity data from parabolic flight, short-term or long-term spaceflight is obtained from 26 studies. One study discusses a mathematical model for computer simulation of microgravity effects. 10 were found for in depth information.

12.1. Heart Rate

Heart Rate is the best observed and documented cardiac parameter. In almost 60 years of spaceflight the heart rate of crew members of various missions has been observed before, during and following up the missions. This numbers are supported by a number of studies that simulated weightlessness the occurring fluid shift or the physical inactivity of spaceflight or both. There seems to be a trend towards increased HR in both spaceflight and simulation. The time course of these adaptations has been documented by various studies over the years both in bed rest and space flight studies. Prior to 2013 (first manned flight, cargo flights started using the route in 2012) flights to the International Space Station took approximately 50 hours, even longer for earlier space stations. Only in 2013 the flight has been shortened to only about six hours.

Table 1: Studies investigating heart rate in spaceflight
SF: spaceflight, PF: parabolic flight, HDBR: head down bed rest, BR: bed rest, R-0: landing day while still in (simulated) microgravity

Study		Duration	R+1 %		Counter measure
Aubert et al., 2010	SF	10-11 d	+7		
Buckey et al., 1996b	SF	9-14 d		**R+0**: +13 % supine test	
Bungo et al., 1987	SF	5-8 d		**R+0**: +31 % 7 subjects **R+7-14 d**: +8 % 17 subjects	FL
D'Aunno et al., 2003	SF	short duration		**R-0**: +25 %, follow up +0 %	
D'Aunno et al., 2003	SF	4 month		**R-0**: -2 %, follow up +20 %	
Gundel et al., 1999	SF	long duration		+99 ms RR interval, in flight measurement	
Herault et al., 2000	SF	6 months	+9	**R+7**: +22 %	Bracelets
Levine et al., 1996	SF	9-14 d	-1	**R+0**: -1 % measurements taken at maximal exercise	
Moore et al., 2014	SF	91-192 d	+0	measurements taken at maximal exercise	Exercise
Moore et al., 2015	SF	48-219 d		**R+5**: +9 % measurements taken at various exercise levels	Exercise
Perhonen et al., 2001a	SF	10 d		**IF-5d**: +15 %	
Trappe et al., 2006	SF	17 d	+10	at 150 Watts exercise	
Verbanck et al., 1997	SF	10 d		**R+2**: +14 % trend to normalization within 9 days of return	
Verheyden et al., 2009	SF	10 d - 180 d		-18 % in-flight compared to pre-flight upright measurement	

Table 2: Studies investigating heart rate in simulated microgravity
Legend as in Table 1

Caiani et al., 2004	PF			-5 % zero-G vs. upright position +7 % zero-G vs. supine position	
Caiani et al., 2007	PF			-17 % no LBNP zero-G vs. upright position -5 % LBNP zero-G vs. upright position	LBNP
Fortrat et al., 2001	HDBR	42 d		**R-0**: +12 %	
Hirayanagi et al., 2004	HDBR	14 d	+11	**R-0**: + 6 %	
Hung et al., 1983	BR	10 d	+ 10 - 21 bpm	"at submaximal and peak upright effort after bed rest"	
Levine et al., 1997	HDBR	2 weeks	+1	after 2 weeks of HDBR	
Perhonen et al., 2001a	BR	12 weeks		**Wk-12**: +15 %	
Perhonen et al., 2001b	HDBR	18 d	+4	-3 % in hypovolemia protocol	
Platts et al., 2009	HDBR	90 d		**R+3**: +6 %	
Shi et al., 2014	HDBR	60 d		**R+3**: +27 %	
Shiraishi et al., 2003	HDBR	120 d		"significantly increased" post bed rest	
Trappe et al., 2006	HDBR	17 d		**R+3**: +9 % at 150 Watts exercise	
Westby et al., 2016	HDBR	60 d	+27	**R+13**: +13 %	

Due to historically longer flights to get to the space stations only little life science data is available for the first hours of spaceflight and microgravity adaptations. Verbanck et al. (1997) found that "early inflight" HR dropped around 20 %. This is in accordance with parabolic flight studies, which simulates the first 30 seconds of microgravity adaptation where Caiani et al. (2004, 2007) found a 5 to 12 % drop in HR compared to preflight upright values. Similar changes have been found in early head down bed rest data. In their study on 12 men Hirayanagi et al. (2004) found HR to be lowest after six hours of -6° head down bed rest and reached pre-HDBR values again 24 hours into bed rest. Even earlier, after less than an hour into head down tilt Levine et al. (1997) reached the lowest values of HR before settling at about starting values three hours into bed rest.

The time course of HR changes during prolonged unloading has been better studied and suggests that after the initial adaption phase heart rate stabilizes at close to normal level. Studies to both the MIR space station (Herault et al., 2000) and the ISS (Verheyden et al., 2009) have concluded that compared to pre-flight supine values HR does not increase

during long term space flight missions. Both studies included stays in orbit of up to six months.

Compared to that, head down bed rest studies such as Platts et al. (2009) or Westby et al. (2016) found minor (Platts + 5 % on day 90 of bed rest, Westby +9 % on day 60 of bed rest) increases in HR. Both claimed their results though to be not statistically significant and are in accordance with Shiraishi et al. (2003) who had no changes in HR during their 120 day bed rest study.

On day one after both bed rest and spaceflight studies have shown different results. Most studies point to a more pronounced increase of HR on the day of landing and the first day after spaceflight compared with in-flight measurements. Comparing studies on space missions of different length shows short-term missions to lead to bigger increases in HR than long term missions. This has been shown by Buckey et al. (1996b), in their study on eleven male and one female astronaut who flew space shuttle missions of nine to 14 days who showed HR to be increased by 13 % on landing day.

More recently this rise in HR has been stated by Aubert et al. (2010) who studied five astronauts after short term flights (ten to eleven days) to the International Space Station. Bungo et al. (1987) even found HR to be increased by 31 % on landing day even with one liter of isotonic fluid loading right before return to earth on their study on seven space shuttle astronauts. For their follow up they could gather data from 17 astronauts who still had an average of +7 % in heart rate even after a seven to 14 day recovery period on earth. HR does return to closer to preflight values within one to two weeks post-flight (Bungo et al., 1987, Verbanck et al., 1997, D'Aunno et al., 2003).

D'Aunno et al. (2003) looked at the differences between short term and long term spaceflight, by averaging RR-intervals on lead II and lead V_2 of the ECG measurements. Similar to the previously mentioned studies, they found HR to be increased after short term spaceflight (+25 %) but normalization on follow-up. Six astronauts studied after long term spaceflight showed no changes in heart rate on landing day, but, contrarily to short term data, an increased HR on follow-up measured eleven and 39 days after landing.

A rise in HR after long term missions has also previously been postulated by Herault et al. (2000) who investigated six MIR cosmonauts. They found a moderate rise of 9 % on day one after landing which was accentuated (+22 %) on day R+7. Simulation studies, while

showing trends towards higher HR after bed rest similar to spaceflight, do not point to this difference between short and long term duration. Increases are moderate in both short term (Levine et al., 1997, Hirayanagi et al., 2004) and long term bedrest studies (Fortrat et al., 2001, Platts et al., 2009) ranging from +1 % (Levine) to +11 % (Fortrat). Westby et al. (2016) in their bed rest study on three women and four men contradict the aforementioned spaceflight data. They found HR after 60 days to be raised by over 26 %. heart rate remained raised on day R+13 by still 13 %.

Early after spaceflight an increase in HR could be expected, given the previously observed decreased in plasma volume (Watenpaugh, 2001). This combined with the redistribution towards the legs upon entering the 1-G environment on the ground accounts for a decrease in preload and consequently in stroke volume. To maintain cardiac output heart rate needs to increase in response.

In case even more compelling data pointing to higher increases of HR after long term idleness and unloading would present, this could turn out to be a point of concern in itself as it has been theorized increased resting HR is a risk factor for cardiovascular disease and dysfunction in itself (Fox et al., 2007).

Especially on days early after return into the the 1-G environment on the ground a redistribution of plasma volume to the legs could also account for an increase in HR. However this would not explain the differences in short and long term space flight as plasma volume has been documented to decrease within as little as the first 24 hours of space flight (Williams et al., 2009). The differences between short and long term effects could point to functional changes in the heart, induced by the long term stay in microgravity.

There have been some studies done on exercise performance both after space flight and microgravity. It is interesting to note that maximum heart rate, with stress tests done at maximum exercise capacity, does not undergo any changes after space flight (Levine et al., 1996, Moore et al., 2014). However at sub-maximal exercise levels, such as shown by Moore et al. (2015) in 37 ISS crew members (+9 %), or Trappe et al. (2006) (+10 %, N=8), heart rate is increased space flight. This is in accordance with simulation studies. In 2006 Trappe et al. compared four space shuttle crew members and eight subjects in bed

rest, both for 17 days. They found very similar changes in HR after both protocols (SF, +10 %; HDBR, +9%).

The similarities on bed rest and space flight studies in both resting heart rate and heart rate in exercise indicate that simulation is a valid model for HR changes, though the differences in long term heart rate changes need further looking into. In addition it is important to note that while relatively big changes have been documented in various studies, in absolute numbers HR has never changed enough to fit clinical criteria for tachycardia.

12.2. Stroke Volume

Stroke volume is the amount of blood pumped by the heart with every single beat. At rest stroke volume is expected to be 60-70 ml per beat. In exercise and stress SV can be increased to meet raised physiological demand up to two fold. Trained athletes have a higher resting state stroke volume as well as a much higher maximal stroke volume when compared to untrained individuals (McArdle et al., 2014).

As described by the Frank-Starling-Law-of-the-Heart, "**The heart can only pump what it gets"**, this is a highly preload and plasma volume dependent parameter.

Changes in stroke volume always need to be seen in the context of these changes.

Table 3: Studies investigating stroke volume in spaceflight
Legend as in Table 1

Study		Duration	R+1 %		Counter measure
Buckey et al., 1996b	SF	9-14 d		**R+0**: -36 %	
Herault et al., 2000	SF	6 months	-6		Bracelets
Levine et al., 1996	SF	9-14 d		**R+0**: -22 % all measurements at maximum exercise	
Perhonen et al., 2001a	SF	10 d		**in-flight**: -29 %	
Verbanck et al., 1997	SF	10 d		"[…] shows a large (~40%) increase early in flight, but SV is reduced by late in flight to a level not significantly different from preflight controls."	

Table 4: Studies investigating stroke volume in simulated microgravity
Legend as in Table 1

Study		Duration	R+1 %		Counter measure
Caiani et al., 2006	PF		+19	in zero-G	LBNP
Caiani et al., 2007	PF		+32	in zero-G	LBNP
Caiani et al., 2009	PF		+14	in zero-G, +1,7 % in zero-G with LBNP	LBNP
Hirayanagi et al., 2004	HDBR	14 d	-15		
Levine et al., 1997	HDBR	2 weeks	-12	after bed rest	
Perhonen et al., 2001a	BR	12 weeks		**Week 12**: -21 %	
Perhonen et al., 2001b	HDBR	18 d	-14	-14 % in hypovolemia protocol	
Platts et al., 2009	HDBR	90 d		**Day 49**: -3 %	
Shi et al., 2014	HDBR	60 d		**R+3**: -6 %	
Westby et al., 2016	HDBR	60 d		**R+0**: -15 %	

Measurements of SV in microgravity have a peculiar time course. Upon entering microgravity, due to the reduced gravitational pull on the blood column in the veins preload is raised, leading to SV increases of 13 - 31 % (Caiani et al., 2006, 2007, 2009).
At the end of spaceflight flight and bed rest, on the days R+0 and R+1, changes in SV seem to be similar but space flight seems to have an even bigger effect (HDBR avg. -14 % vs. SF avg. -22 %). Especially on landing day, back in 1-G environment, SV is substantially lower than pre-flight measurements, both at rest and in during exercise (Buckey et al., 1996b, Levine et al., 1996). Simulations protocols of similar length, ten days to two weeks, show comparable results as space flight data (Levine et al., 1997, Hirayanagi et al., 2004).
It appears that both long duration bed rest, as shown by Shi et al. (2014) (-6 %) and Westby et al. (2016) (-15 %), and spaceflight (-6 % (Herault et al., 2000)) point to a less pronounced decrease in SV.
The time course of the increases in stroke volume immediately upon entering microgravity to the lowered SV at the end of spaceflight is not yet fully understood and needs further investigation. Bed rest data has shown stroke volume to decrease much slower than plasma volume. In long term bed rest studies such as Platts et al. (2009) or Westby et al. (2016) it takes almost one month to get to 10 % decreases of SV. As plasma volume is decreased

already after one day, this could point to compensating mechanisms in place early on, that later deteriorate, possibly in line with cardiac remodeling and dysfunction. This time course, especially how SV develops during and after long term space flight, needs further investigation to determine the effects and causes of the SV changes that have been observed so far.

12.3. Heart Dimensions

Table 5: Studies investigating the heart's filling dimensions
LVDV: left ventricular end diastolic volume, LVSV: left ventricular end systolic volume, EDA: End diastolic area [mm2], ESA: End systolic volume, LVDdia: Left ventricular end diastolic diameter [mm], LVSdia: Left ventricular end systolic diameter [mm], Rest of legend as in Table 1

Study		Duration		R+1 %		Counter measure
Caiani et al., 2006	PF		LVDV	+19	zero-G	LBNP
Caiani et al., 2006	PF		LVSV	+23	zero-G	LBNP
Caiani et al., 2007	PF		LVDV	+21	zero-G	LBNP
Caiani et al., 2007	PF		LVSV	+14	zero-G	LBNP
Corsi et al., 2002	PF		EDA	+11	zero-G	
Corsi et al., 2002	PF		ESA	+11	zero-G	
Corsi et al., 2004	PF		EDA	+14	zero-G	
Corsi et al., 2004	PF		ESA	+11	zero-G	
Dorfman et al., 2007	HDBR	60 d	LVDV		R+0: -20 %	Exercise Nutrition
Herault et al., 2000	SF	6 months	LVDV	-5		Bracelets
Hung et al., 1983	BR	10 d	LVDV		R+0: -17 %	
Kozàkovà et al., 2011	HDBR	5 weeks	LVDVI	-10		
Levine et al., 1997	HDBR	2 weeks	LVDV	-7	after bed rest	
Perhonen et al., 2001b	HDBR	18 d	LVDV	-20	-7 in hypovolemia protocol	
Platts et al., 2009	HDBR	90 d	LVDdia		Day 49: -4 %	
Platts et al., 2009	HDBR	90 d	LVSdia		Day 49: -9 %	
Shi et al., 2014	HDBR	60 d	LVDV		R+3: -10 %	
Shi et al., 2014	HDBR	60 d	LVSV		R+3: -15 %	
Summers et al., 2005	SF	9-16 d	LVDV		R+0: -7 %	FL
Westby et al., 2016	HDBR	60 d	LVDV		R+0: -15 %	
Westby et al., 2016	HDBR	60 d	LVSV		R+0: -13 %	

In accordance with the headward shift of blood volume upon entering microgravity left ventricular volume in systole and diastole increase (Corsi et al., 2002, Caiani et al., 2007). These filling volumes appear to follow plasma volume changes as measurements early in head down bed rest show reductions in end-diastolic and end-systolic volumes of around 10 % after one week of bed rest (Platts et al., 2009, Westby et al., 2016). In their study on space shuttle astronauts Summers et al. (2005) showed left ventricular diastolic volume to be 7 % decreased after spaceflights of only nine to 16 days.

On day R+1 Herault et al. (2000) found LVDV to be five percent decreased in six cosmonauts after long term space flight. After sedentary bed rest heart dimensions and filling volumes have been shown to be even greater. Westby et al. (2016) in their study on four men and three women had systolic volume decreased by 13 % and diastolic volume by 15 % on day R+0. However, LV volumes in systole and diastole rebound in accordance with plasma volume recovery and are restored to baseline levels in both space flight R+3 (Summers et al., 2005) and bed rest R+3 and R+13. (Westby et al., 2016)

Dorfman et al. (2007) compared in their study sedentary bed rest to two types of counter measures, nutritional protein supplementation and exercise. They studied 24 young women and separated them into the three groups of eight subjects each. The study shows comparable results in LV diastolic volume in sedentary bed rest (-20 %) and the protein supplementation group (-22 %). The exercise protocol however did not show “significant reduction in LV volume”. Summers et al. (2005) who tried for fluid loading on landing day, using 15 ml/kg of isotonic saline solution, could not prevent significant changes in LV end-diastolic volume using this measure.

12.4. Cardiac Output

Cardiac Output (CO) is the product of stroke volume and heart rate and thus represents the amount of blood that can be pumped by the heart within one minute.

$$CO[ml/min] = SV[ml] * HR[1/min]$$

Figure 19: Cardiac Output

In spaceflight where a drop in stroke volume is to be expected due to the reduction in preload and plasma volume HR needs to increase to compensate and maintain cardiac output at a stable level.

Table 6: Studies investigating cardiac output in spaceflight
Legend as in Table 1

Study		Duration	R+1 %		Counter measure
Buckey et al., 1996b	SF	9-14 d		**R+0**: 0 %	
Herault et al., 2000	SF	6 months	+3	+13 % on one week follow-up	Bracelets
Levine et al., 1996	SF	9-14 d		**R+0**: -23 % all measurements at maximum exercise	
Perhonen et al., 2001a	SF	10 d	-29	in flight measurement	
Verbanck et al., 1997	SF	10 d		"[Cardiac Output] was elevated early in flight (n = 2) and returned to preflight control by late in flight."	

Table 7: Studies investigating cardiac output in simulated microgravity
Legend as in Table 1

Study		Duration	R+1 %		Counter measure
Caiani et al., 2007	PF		+15	in zero-G	LBNP
Hirayanagi et al., 2004	HDBR	14 d	-4		
Levine et al., 1997	HDBR	2 weeks	-10	after bed rest	
Perhonen et al., 2001a	BR	12 weeks		**Week 12**: -7 %	
Perhonen et al., 2001b	HDBR	18 d	-13	-11 % in hypovolemia protocol	
Platts et al., 2009	HDBR	90 d		**Day 49**: +6 %	
Shi et al., 2014	HDBR	60 d		**R+3**: +18	
Westby et al., 2016	HDBR	60 d	+2	**R+0**: +2 % +18 % on day 13 follow-up	

Caiani et al. (2007) have shown that CO initially in spaceflight increases. This is mostly due to the increase in stroke volume when gravitational pull ceases and blood pools in the center of the body. In part this is countered by a lowered heart rate, though not enough to account for the increase in SV to keep CO at a stable level.

Perhonen et al. (2001a) compared in-flight data from German Spacelab missions to bed rest and found similar results. On flight day five HR was increased by 15 % while SV decreased by 29 %, resulting in a net decrease of CO of 19 %. Similarly, when they compared this to bed rest data, after two weeks of bed rest CO had dropped by 18 %. Even after twelve weeks of bed rest CO was 9 % lower than pre bed rest.

A similar time course was shown by Platts et al. (2009), though less dramatic in their HDBR study on five women and eight men. The tendency to rebound to CO values closer to pre bed rest data was there in both studies, even without any special counter measures like diet or exercise. The in-flight time course of CO changes in space is not yet well understood and is at need for further investigation future studies.

On day R+0, R+1 and following-up after bed rest and space flight there is some conflicting data available. Herault et al. (2000) and Verbanck et al. (1997) found little changes after space flight. After 18 days of head down bed rest Perhonen et al. (2001b) found cardiac output to be 13 % reduced in seven male subjects and Levine et al. (1997) found CO to be 10 % reduced after two weeks of bed rest in eleven men and one woman.

These moderate changes can be explained by the loss in plasma volume which in turn causes the decrease in SV. To maintain cardiac output level heart rate increases, keeping CO at a sustainable level. The differences in results following bed rest and space flight could be explained by different study protocols. Levine et al. and Perhonen et al. measured cardiac output in standing position, while Verbanck had their subjects sitting upright. Herault et al., unfortunately, do not give that kind of information, but in summary standing measurements would account for sustained reduction in CO after spaceflight where supine position could mask such changes as demonstrated by Buckey et al. and discussed below.

Levine et al. (1996) looked at cardiac performance in four men and two women after 9-14 days of spaceflight on Spacelab missions. The subjects were tested at maximum exercise two weeks before and on several days after returning from space. On day of landing maximum cardiac output was reduced by 23 %. In the following days (measurements made on days R+1, R+2 and R+6-9) cardiac output at maximum exercise returned to preflight levels. This is a strong indicator that maximum exercise is strongly dependent on plasma volume as stroke volume during exercise could not increase as much as before space flight.

Buckey et al. (1996b) demonstrated cardiac output to be maintained after 9-14 days in space if tested in supine position. However a stand test demonstrated CO to be significantly decreased and to a point where nine out of 14 participants could not complete the stand test on landing day. This indicates cardiac dysfunction after space flight and consequently reduced orthostatic tolerance.

12.5. Total Peripheral Resistance

Total Peripheral Resistance, or Systemic Vascular Resistance (SVR), in human circulation is defined as the resistance the heart has to overcome to be able to pump blood to and through all blood vessels and tissues of the body.
In technical terms it is paraphrased from Ohm's law of electrical conduction as stated by Mann and Braunwald (2015, p. 378):

> Vascular resistance calculations are based on the hydraulic principles of fluid flow, in which resistance is defined as the ratio of the decrease in pressure between two points in a vascular segment and the blood flow through the segment. Although this straightforward analogy to Ohm's law represents an oversimplification of the complex behavior of pulsatile flow in dynamic and diverse vascular beds, calculation of vascular resistance based on these principles has proved to be of value in several clinical settings.

Calculation of TPR requires knowledge of Cardiac Output as well as pressures at the start and end point of the discussed segment of vasculature, in this case the entire systemic circulation. This means pressure in the aorta (Ao_p) as well as the right atrium (RA_p) need to be identified.

$$TPR[dyne*sec*cm^{-5}] = \frac{80 * (Ao_p - RA_p)}{CO}$$

Figure 20: Total Peripheral Resistance

Peripheral resistance highly influences arterial pressure, therefore investigation of how it changes in spaceflight is vital in understanding blood pressure changes. Normal range for TPR is between 700 and 1.600 dyne*sec*cm^{-5} with a mean of 1.100 (Mann and Braunwald, 2015).

Table 8: Studies investigating total peripheral resistance
Legend as in Table 1

Study		Duration	R+1 %		Counter measure
Buckey et al., 1996b	SF	9-14 d		**R+0**: +17 % - standing	
Bungo et al., 1987	SF	5-8 d		**R+0**: +31 % +2 % on follow-up 7 to 14 days after return	FL
Hirayanagi et al., 2004	HDBR	14 d	+15		
Levine et al., 1997	HDBR	2 weeks	+16	after bed rest	
Perhonen et al., 2001a	SF BR	10 d	+26	in-flight measurement -6 % on week 12 of HDBR	
Perhonen et al., 2001b	HDBR	18 d	+14	+12 % in hypovolemia protocol	
Herault et al., 2000	SF	6 months	-9	calculated resistance index -5 to -11 all through flight (femoral artery)	Bracelets

Data obtained on landing day after space flight show that peripheral resistance in supine position increases only slightly (+7 %) while standing upright the increase is more pronounced (+17 %). It has been shown that performance in orthostatic stand tests after spaceflight depends on the subjects ability to increase TPR even further. Stand test *finishers* increased their peripheral resistance at the end point of the stand test by 32 % after space flight while *non-finishers* showed little change (-1 %). Nine out of the 14 subjects tested where in the *non-finisher* group. This is an indication that the finishers could compensate for lowered stroke volume, consequence of lowered plasma volume, by increasing their peripheral resistance. While both *finishers* and *non-finishers* experienced similar drops in SV and compensatory increase in HR, it appears that peripheral resistance adaptability seems the determining factor for post-flight stand text performance (Buckey et al., 1996b).

Bungo et al. (1987) found similar changes in TPR on landing day (31 %). They showed in their study, looking at follow up exams in 17 astronauts, that vascular resistance returns to normal levels (+2 %) seven to 14 days after spaceflight. These early results where successfully replicated and confirmed by bed rest studies later. Hirayanagi et al. (2004) found that only 14 days of HDBR in their study on twelve men increased TRP

significantly. At only 6 h post-HDBR vascular resistance was increased by 15 %. However this value returned to normal, close to baseline levels, on day R+1. This could be mirroring the rebound in plasma volume and reestablished regulation of the autonomic nervous system.

Similar results, after 18 days of bed rest, were reported by Perhonen et al. (2001b). They showed similar changes in peripheral resistance in seven men who first completed two weeks of bed rest (TPR +14 %) and a minimum of one year later were recruited again for an acute hypovolemia protocol (TRP +12 %). In this protocol hypovolemia was induced by administration of 20 mg of furosemide.

In a long term space flight study by Herault et al. (2000) they looked at the resistance index of various big arteries. This resistance index is calculated from systolic and diastolic Doppler velocity amplitudes and changes in proportion to changes in systemic resistance. This method has shown some promising results previously (Aaslid et al., 1982, Maulik et al., 1989) however because absolute values are gathered from Doppler sonography, the numbers have to be evaluated with care.

In their study, Herault et al. (2000) found a trend towards decreased resistance index day R+1 after long term space flight albeit non significant. All throughout the flight resistance index in the femoral and the renal artery was significantly decreased. If indeed resistance index changes proportionally with vascular resistance these results contradict other studies, as discussed earlier.

12.6. Blood pressure

Blood pressure is the result of the amount of blood pumped by the heart over time and the resistance within the vasculature. Corresponding to Ohm's law (U=R*I) mean arterial pressure is defined as:

$$MAP = CO * TPR$$

Figure 21: Mean Arterial Pressure

In addition to mean arterial pressure systolic and diastolic blood pressures are often measured, as it is easily measured using sphygmomanometry, a blood pressure cuff.

Standard unit blood pressure is millimeters of mercury [mmHg] above surrounding air pressure.

As true MAP is dependent of the wave form of blood pressure over time, MAP is usually estimated, most commonly using the formula:

$$MAP \simeq DBP + \frac{1}{3}(SBP - DBP)$$

Figure 22: Clinical approach to Mean Arterial Pressure

A standard BP reading is given “systolic over diastolic pressure”. At 120 / 80 mmHg this results in a MAP of 93,3 mmHg.

This emphasizes that, while an easy to measure vital sign, blood pressure is a result of interaction of complex cardiovascular conditions. In orthostatic intolerance it is a drop in blood pressure that causes impaired cerebral perfusion, in turn leading to symptoms of presyncope and syncope such as lightheadedness, cold sweats, nausea, blurred vision or loss of consciousness.

Because blood pressure measurements are easily attainable numerous studies have had a look at BP changes in microgravity and simulated microgravity. Neither spaceflight nor simulation studies so far showed significant blood pressure changes both long and short term, suggesting that homeostatic reflexes regulating BP are well maintained in such conditions. BP remains stable despite the loss in plasma volume (Westby et al., 2016).

Table 9: Studies investigating blood pressure
Legend as in Table 1

Study		Duration	BP Value	R+1 %		Counter measure
Aubert et al., 2010	SF	10-11 d	Sys	+20	increases were persistent at 25 day follow-up	
Aubert et al., 2010	SF	10-11 d	Dia	+11		
Aubert et al., 2010	SF	10-11 d	Mean	+3		
Buckey et al., 1996b	SF	9-14 d			**R+0 (supine)** Sys: +5 % Dia: +6 % Mean: +6 % **R+0 (end stand test)** -7 % +0 % -2 %	
Bungo et al., 1987	SF	5-8 d	Mean		**R+0**: +11 %	
Herault et al., 2000	SF	6 months	Sys	+10	increases were persistent at 7 day follow-up	Bracelets
Herault et al., 2000	SF	6 months	Dia	+8		
Herault et al., 2000	SF	6 months	Mean	+9		
Levine et al., 1996	SF	9-14 d	Sys		**R+0** Sys: -1 % measurements taken at maximum exercise	
Moore et al., 2015	SF	48-219 d	Sys		**R+5** Sys: -2 % Dia: -6 % changes persisted on R+30	Exercise
Moore et al., 2015	SF	48-219 d	Dia			
Perhonen et al., 2001a	SF	10 d	Mean		**in-flight**: +6 %	
Verheyden et al., 2009	SF	10 - 180 d			Sys: -7 % Dia: -6 % Mean: +1 %	
Fortrat et al., 2001	HDBR	42 d	Sys		**R+0**: +16 %	
Hirayanagi et al., 2004	HDBR	14 d	Sys	+4		
Hirayanagi et al., 2004	HDBR	14 d	Dia	+6		
Hung et al., 1983	BR	10 d	Sys		"Systolic blood pressures […] were not significantly different after bed rest."	
Kozàkovà et al., 2011	HDBR	5 weeks	Sys	-5	carotid SBP	
Levine et al., 1997	HDBR	2 weeks	Mean	+5	"after bed rest"	
Perhonen et al., 2001a	BR	12 weeks	Mean		Week 12: -13 %	
Perhonen et al., 2001b	HDBR	18 d	Mean	+5	-2 % in hypovolemia protocol	
Platts et al., 2009	HDBR	90 d	Sys		**R+3** Sys: -8 % Dia: 0 %	
Platts et al., 2009	HDBR	90 d	Dia			
Shiraishi et al., 2003	HDBR	120 d	Sys		no significant changes in BP were found during or after bed rest	
Westby et al., 2016	HDBR	60 d			**R+0** Sys: 0 % **R+0** Dia: 0 % **R+0** Mean: +1 %	

Stand test data, obtained on day R+0 after HDBR (Fortrat et al., 2001) and spaceflight (Buckey et al., 1996b) - both standing and supine -, show a significant increase in BP after space flight. Both studies show some subjects not to be able to the stand test after HDBR and spaceflight respectively. In those subjects the expected drop in BP and/or presyncope symptoms occurred before the ten minute mark of the stand test protocol. A trend towards increase in blood pressure on day R+0 and R+1 after spaceflight was also shown by Bungo et al. (1987) (MAP +11 %) and replicated in simulation studies (Levine et al., 1997, Hirayanagi et al., 2004). Aubert et al. (2010) and Herault et al. (2000) had found similar increases in their studies which were also persistent at up to 25 days follow up examinations.

In another bed rest study on ten male subjects Kozakova et al. (2011) looked specifically at carotid systolic BP and found a decrease (-5 %), albeit non-significant, when comparing pre- to post-HDBR (R+0) blood pressure. This is the only study showing such changes. However this allows for speculation if carotid blood blood pressure regulation was shown to be impaired after microgravity or simulated microgravity, this in turn could play a major role in development of orthostatic intolerance. This ties in with a study by Tuday et al. (2007) who found arterial compliance to be lower in orthostatic tolerant compared with orthostatic intolerant astronauts after space flight. The missions lasted only five to 18 days and OI is not an effect of long-term adaptation to spaceflight even if it might be more pronounced after longer missions. They speculate “a stiffer, or less compliant, arterial bed will allow for less accumulation of blood volume in the arterial circulation and consequently shift the extra volume to the venous side, aiding in venous return.” This helps explain the better performance of these astronauts in post-flight stand tests.

12.7. Left Ventricular Mass

Muscle atrophies as consequence of desuetude and unloading. This is regularly observed on earth in sick and injured patients, or even when regular exercise is stopped. The same phenomenon has been shown to be true for skeletal muscle in spaceflight as well (Fitts et al., 2000, Mujika and Padilla, 2001).

There has been some speculation whether muscle atrophy affects the heart muscle in similar fashion and if cardiac performance is restricted as well. While skeletal muscle

atrophy in spaceflight has long been known (Leonard et al., 1983) effects on the cardiac muscle have only been investigated and reported much later.

Table 10: Studies investigating left ventricular mass
Legend as in Table 1

Study		Duration	R+1 %		Counter measure
Dorfman et al., 2007	HDBR	60 d		**R+0**: -10 % +18 % in exercise control group	Exercise Nutrition
Kozàkovà et al., 2011	HDBR	5 weeks	-13		
Levine et al., 1997	HDBR	2 weeks	-5	after bed rest	
Perhonen et al., 2001a	SF	10 d	-12	after 10 d of SF	
Perhonen et al., 2001a	BR	12 weeks	-16	after 12 weeks of bed rest -8 % in the group that completed 6 weeks of bed rest	
Platts et al., 2009	HDBR	90 d		**Day 49**: -8 %	
Summers et al., 2005	SF	9-16 d		**R+0**: -9 % +3 % on day 3 follow-up	FL
Westby et al., 2016	HDBR	60 d		**R+0**: -14 % -5 % on day 13 follow-up	

Levine et al. (1997) found left ventricular mass decreased by 5 % after only two weeks of bed rest without exercise counter measures. They speculate that the observed shifts in Starling curves are not only result of changed plasma volume (-17%) but might be result of cardiac remodeling and possibly atrophy as well. However they conclude: “There is no evidence that this adaptation represents a pathological response of the myocardium.”
Perhonen et al. (2001a) found similar results in both spaceflight and bed rest. Left ventricular mass was reduced by 8 % after six weeks of bed rest. In the three subjects who completed the entire twelve weeks of the study left ventricular mass declined further by an extra 8 %. Mean wall thickness of the left ventricle was significantly reduced by 4 % as well. They compared this to space flight data where after only ten days in space caused left ventricular mass to decrease by 12 % vs pre flight. Both bed rest and spaceflight groups where investigated using MRI measurements.
In newer bed rest studies, done by Platts et al. (2009) or Kozakova et al. (2011) these results were confirmed. Similarly, Summers et al. (2005), investigating eleven men and 27 women on shuttle missions lasting nine to 16 days, found left ventricular mass 9 %

reduced after space flight. Left ventricular mass reductions where no longer present in echocardiographic follow-up measurements on day R+3. They compared these results to a ground based study where the relationship between dehydration and left ventricular mass was explored and found comparable decreases in both data sets. Thus, they hypothesize left ventricular mass to be affected by shifts in body fluids, even with fluid loading before reentry protocols.

All this information is especially interesting in the context of a study by Dorfman et al. (2007). They looked at 24 decided into three groups: sedentary bed rest as control and exercise and nutrition-protein as two treatment groups. All subjects stayed in bed for 60 days. The control group showed a decrease in left ventricular mass (-10 %). This was not the case in both treatment groups. In the nutrition protocol the subjects' LV mass was preserved while in the exercise protocol an increase of 18 % could be attained. The exercise protocol consisted of 40 minutes of supine treadmill running in a lower body negative pressure chamber and resistive training for the legs two to four times a week. This underlines the protective role exercise takes in cardiac function and remodeling and its applicability to simulated microgravity. A similar follow up study, on long term space station mission would be advisable to validate these findings in spaceflight as well.

12.8. Ejection Fraction

When the heart contracts to pump blood into the pulmonary and systemic vascular system not all blood is ejected from the heart's ventricles. The share of blood ejected accounts for about ⅔ of end-diastolic-volume or 66 %.

$$EF = (EDV - ESV)/EDV$$

Figure 23: Ejection Fraction

Clinical recommendations have put the cut-off value at ≥ 55 % for normal EF and ≤ 50 % for (mildly) abnormal EF (Lang et al., 2005). Whether or not the 50 to 55 % range should be considered borderline-abnormal is still under debate (Mahadevan et al., 2008).

Raised levels of ejection fraction are observed in cardiac hypertrophy. Most commonly observed causes for cardiac hypertrophy are "athlete's heart" (i.e. hypertrophy as

physiological response to exercise), hypertension and some forms of genetically inherited hypertrophic cardiomyopathies (Bonow, 2012). Ejection fraction is clinically used as a marker to indicate left ventricular function. So far no studies in microgravity or simulated microgravity have suggested a decrease in EF big enough to meet the cut-off of clinically relevant left ventricular disfunction.

Table 11: Studies investigating ejection fraction
Legend as in Table 1

Study		Duration	R+1 %		Counter measure
Bungo et al., 1987	SF	5-8 d	-6	**R 7-14**: +6 %	FL
Caiani et al., 2006	PF			+0 in zero-G	
Caiani et al., 2007	PF		+8		
Caiani et al., 2009	PF			+0 in zero-G +5 % in zero-G + LBNP	LBNP
Herault et al., 2000	SF	6 months	-3	**R+7**: -2%	Bracelets
Hung et al., 1983	BR	10 d		**R+0**: +11 %	
Kozàkovà et al., 2011	HDBR	5 weeks	-1		
Martin et al., 2002	SF	long	-11	compared with +6 % in short duration spaceflight	
Platts et al., 2009	HDBR	90 d		+7 % on day 49 of bed rest	
Shi et al., 2014	HDBR	60 d		**R+3**: +6 %	
Summers et al., 2008	SF	9-16 d	+5		
Westby et al., 2016	HDBR	60 d		**R+0**: +0 %, **R+13**: +3 %	

The biggest drop in EF has been documented by Martin et al. (2002) with -11 % in long duration spaceflight. Decreased EF, -3 % on day one after six months on the MIR space station, has also been found by Herault et al. (2000) and Bungo et al. (1987) (-6 % after 5 to 8 days on space shuttle missions).

Contrary to Bungo, in a study on space shuttle astronauts on missions of similar length, Summers et al. (2008) found a increase of 4 % in EF which they deemed “clinically inconsequential”. Unfortunately, Summers et al. do not mention the setting of their measurement but it appears their fractions at 79 % preflight and 83 % postflight are high, comparable to other studies done during exercise, such as Hung et al. showed in their bed rest study. (1983)

Ejection fraction has also been documented to slightly increase after head down bed rest, most recently by Shi et al. (2014) (+6 % on day 3 after bed rest) and Westby et al. (2016) (+3 % on day 13 after bed rest). Both studies had a duration of 60 days. An increase in EF base level could point towards a diminished capacity to further augment EF during high demand exercise post

Both microgravity and simulated microgravity studies so far have shown that changes in EF are well within normal clinical boundaries with no indication of left-ventricular disfunction and pointing towards normal cardiac contractility.

12.9. VO_2max and VO_2peak

VO_2peak is defined as the maximum level of O_2 consumption a subject can reach in a given test or exercise. VO_2max is defined as the maximum level of O_2 consumption achievable for a subject. Even with higher effort or work rate VO_2 will not increase significantly (Whipp). O_2 consumption in the body is determined by how much oxygen can be supplied to be consumed and how much oxygen those tissues are able to metabolize. An increase in metabolizing rate can, if possible, only be achieved through long lasting training regimens. Thus the oxygen supply through the blood stream is considered the more determining factor with regard to maximum oxygen capacity. Supply changes with cardiac output, blood volume or erythrocyte quality. Diseases impairing normal pulmonary function also affect oxygen uptake into the blood stream. Generally, a drop in VO_2max or VO_2peak on a certain test can be seen as a drop in exercise performance.

Table 12: Studies investigating peak and maximum O2 capacity
Legend as in Table 1

Study		Duration	R+1 %		Counter measure
Hung et al., 1983	BR	10 d	-15	**VO_2max** after bed rest	
Levine et al., 1996	SF	9-14 d		**VO_2max** R+0: -23 % -9 % on day 6-9 follow-up	
Moore et al., 2014	SF	91-192 d	-15	**VO_2max** -2 % on 30 day follow-up	
Shi et al., 2014	HDBR	60 d		**VO_2max** was significantly lowered on day R+3	
Trappe et al., 2006	SF HDBR	17 d		**VO_2max** -2 – -6 % at 1 week follow-up	
Westby et al., 2016	HDBR	60 d		**VO_2peak** -14 % on day 14 after bed rest **VO_2peak** -33 % on day 60 of bed rest	

Moore et al. (2014) studied effects of long term spaceflight on VO_2max[4] on nine male and five female astronauts during and after their ISS missions. Cycle tests where performed several times during the mission and on return days R+1, R+10 and R+30. There was a significant reduction in VO_2max both in space (-10,8%) and on day R+1 (-15%). Accordingly, maximum obtainable power, in watts, preflight vs R+1, on the cycle test declined by 19 %. These performance drops where present despite extensive countermeasures on the International Space Station, consisting of both aerobic and resistive exercise on 4-6 days / week. On day R+1 one subject could not complete the test protocol as "dizziness" occurred, which could be interpreted as a sign of orthostatic intolerance. Performance levels rebounded to pre-flight levels by R+30, but were still present on R+10. In the paper the authors attribute the fall in exercise performance to more likely be caused by reduced plasma volume and red blood cell mass than cardiac disfunction. This is in accordance with Levine et al. (1996) who after only nine to 14 days in space found VO_2max to be reduced by 23 % on landing day. Lowered VO_2max was still present on 6-9 day follow up tests. No regular countermeasures where performed during this mission.

Westby et al. (2006) compared results from a a Spacelab mission lasting 17 days to 17 days of head down bed rest. Both groups completed the same amount of exercise during the study. During spaceflight VO_2peak at 150 watts was more decreased (-9 %) than during bed rest. While VO_2peak was stable on all recovery tests for the bed rest group it is worth pointing out the spaceflight group had a significantly reduced VO_2peak only on day R+8. Contrarily, VO_2max rebounded towards preflight numbers by day R+8 after spaceflight and R+7 after bed rest, even though still significantly decreased. There is no good explanation why VO_2peak at 150 watts was progressively decreasing after space flight.

[4] In the original paper Moore et al. use the term VO_2peak, but their in-text definition overlaps far more with the general VO_2max definition, thus this is used in this review.

12.10. Tissue and Flow Velocity

Table 13: Studies investigating tissue and flow velocity
Legend as in Table 1

Study		Duration		R+1 %		Counter measure
Caiani et al., 2004	PF		E peak	+57	in zero-G	
Caiani et al., 2004	PF		A peak	+13	in zero-G	
Caiani et al., 2004	PF		E/A peak	+40	in zero-G	
Caiani et al., 2007	PF		S’	-2	in zero-G	LBNP
Caiani et al., 2007	PF		E’	+51	in zero-G	LBNP
Caiani et al., 2007	PF		A’	+38	in zero-G	LBNP
Caiani et al., 2007	PF		E’/A’	-7	in zero-G	LBNP
Summers et al., 2008	SF	9-16 d	E/A		**R+0**: -12 %	
Summers et al., 2008	SF	9-16 d	E’/A’		**R+0**: -8 %	
Westby et al., 2016	HDBR	60 d	E’		**R+0**: -10 %	
Westby et al., 2016	HDBR	60 d	E/A		**R+0**: -39 %	

Flow velocities in the heart throughout the cardiac cycle are measured echocardiographically and described as velocities in systole (S), early diastole (E) and late diastole (A). Correspondingly, mitral annulus velocities are described as systolic (S’), early diastolic (E’) and late diastolic (A’).[5]

Early in spaceflight, as shown in parabolic flight, both flow velocity and mitral annulus velocity increase in diastole as a consequence of volume load on the heart as has been reported by Caiani et al. (2004, 2007). Early inflow velocity strongly increased due to volume loading. This accounts for the rise in E/A ratio. E’/A’ ratio appears much less affected by parabolic flight showing a small, non significant, decrease (-7%) in zero g. This hints at a possible application of E’/A’ ratio as a load independent marker for cardiac function. However in the paper they already claim this would need a lot more investigation before put to regular use. Summers et al. (2008) studied data from 27 shuttle astronauts after nine to 16 days in space and evaluated diastolic function. Both E/A (-8 %) and E’/A’ (-12 %) dropped after the mission. As in clinical practice an E/A ratio < 1.0 is seen as

[5] A and A’ are derived from the *atrial contraction* and its subsequent filling of the ventricles.

indicator for impaired relaxation, continuously decreasing values after spaceflight will have to be monitored in the future.

One long-term bed rest study by Westby et al. (2016) investigated the effects of 60 days of supine head down bed rest on diastolic function. No counter measures where performed in this study. Similar as in spaceflight they found E/A to be diminished. Starting from a baseline of 1,72 , E/A ratio dropped to 1,05 on day R+0, a decrease by 39 %. This is borderline to clinically relevant impairment and needs further investigation in missions of even longer duration. Even 13 days after bed rest, while trending back towards pre-bedrest values, E/A ration was still significantly decreased.

12.11. Strain (%) and Strain Rate (s^{-1})

Strain and Strain Rate represent how much and how fast a tissue is deformed. In cardiac muscle this is a marker for systolic contractility and diastolic compliance.

Table 14: Studies investigating strain and strain rate
Legend as in Table 1

Study		Duration		R+1 %		Counter measure
Caiani et al., 2009	PF		Sε	+42	in zero-G	LBNP
Caiani et al., 2009	PF		S'SR	-15	in zero-G	LBNP
Caiani et al., 2009	PF		E'SR	+42	in zero-G	LBNP
Caiani et al., 2009	PF		A'SR	-21	in zero-G	LBNP
Kozàkovà et al., 2011	HDBR	5 weeks	ε	-6	longitudinal Strain	
Kozàkovà et al., 2011	HDBR	5 weeks	S'SR	-10	longitudinal Strain Rate	

Caiani et al. (2007) in a parabolic flight study studied the changes early in microgravity. and load dependency of strain and strain rate. Parabolic flight showed strain to increase by 42 % in microgravity. The strain rate however was increased only in early diastole, while both late diastole and systole showed strain rate decreased. These observations fit the headwards shift of blood volume early in microgravity. Increased blood inflow explains early diastolic filling, creating the increased strain rate numbers. Systolic strain rate is decreased, possibly the effect of increased stroke volume and decreased heart frequency. Systolic strain is significantly increased, due to the increased filling of the heart, in accordance with the Frank-Starling law of the heart. They conclude, strain and strain rate

can be used as additional future markers for cardiac properties like stiffness or compliance and its complex interactions.

In a different study Kozakova et al. (2011) looked at long term effects after head down bed rest on strain and strain rate. They observed both Strain (-6 %) and Strain Rate (-10 %) to be decreased after five weeks of bed rest. They conclude this to be connected closely to preload and afterload, observed changes in left ventricular mass and possibly other remodeling processes.

12.12. ECG Changes

The interactions between a quickly changing environment when moving to microgravity and the physiological and psychological stress associated with it have been stated as a possible risk for cardiac arrhythmia. This would be observable on ECG readings and upon medical examination. Despite some anecdotes (Dietlein, 1983, Fritsch-Yelle et al., 1998) there have been numerous ECG testings on crew members that have yielded mixed results. Sides et al. (Sides et al., 2005) conclude in their review "Available data provide little evidence to suggest that spaceflight in and of itself is a cause for serious cardiac dysrhythmias, thus posing a high risk to the health and well-being of astronauts." Contrary to that Tagayasu et al. (2014) identify electrolyte imbalances, radiation effects and QT interval prolongation as considerable risks to develop arrhythmia in space.

The QT segment of the electrocardiogram represent cardiac depolarization and repolarization the latter being known as especially vulnerable to induce cardiac dysrhythmia. An increase in QT time has been shown in both spaceflight and bed rest studies (D'Aunno et al., 2003, Bolea et al., 2012).

Further, Microvolt T-Wave Alternans i.e. variation in shape and amplitude of the T-wave in ECG, have been shown to be induced by head-down bed rest (Grenon et al., 2005). This is another indication that repolarization patterns are possibly effected by microgravity.

All this points to the need of further investigation of ECG alterations, as arrhythmia could pose a threat to health and safety of future long term spaceflight missions.

12.13. Counter Measures

To counteract the effects of microgravity on the physiological systems of the body a number of measures have been tested and put into place. Fluid loading, i.e. drinking of isotonic saline solution - usually about one liter - just before returning to earth has routinely been used in spaceflight. While a slight effect might be in place this has not been enough to prevent the significant drops in stroke volume and the diminished orthostatic stress test performances. The question arises if this is simply because the amount ob substituted fluid has not been enough to effectively counteract these outcomes upon reentering the 1g environment of earth. Possibly, not only plasma volume loss but reduced red blood cell mass might account for some of the observations (Alfrey et al., 1996).

Different exercise protocols have been in place for many years in both astronauts and cosmonauts and have become a literal daily routine on the International Space Station nowadays. While these exercises have shown effective in partly reducing the unloading effects on the musculoskeletal system, the effects on the cardiovascular system are not yet well understood. Dorfman et al. (2007) conclude in their bed rest study cardiac atrophy can be prevented by exercise protocol. Their exercise group even showed a significant increase in left ventricular mass when compared to the non-exercising control. Moore et al. (2015) also similarly conclude that the current exercise protocols on the ISS are effectively maintaining cardiac performance levels. In their opinion “relative hypovolemia that exists due to microgravity exposure obscures this upon return to Earth.”

Crew members of space missions tend to eat far less calories in space than on Earth, leading to a net energy deficit of up to 1.500 kcal daily, even after the initial problems with space motion sickness fade away. This happens via a loss in both thirst and appetite, the first of which is seen as the main factor in plasma volume reduction. Consequentially, body weight drops and a metabolic shift towards a ‘hunger-state’ can be observed. (Stein et al., 1999). In the future it will be necessary to monitor energy intake in astronauts.

Dorfman et al. (2007) investigated how a specified diet - high in protein - would compare to sedentary bed rest and exercise in preventing cardiac atrophy. While the exercise group even had increases in heart size and mass the nutrition group was able to maintain pre-bedrest levels. The group without special diet or exercise saw both size and mass of the

left ventricle decreased after 60 days of head down bed rest. This clearly indicates the possibly big role a specified diet can have for future space flight missions.

Lower body negative pressure has shown an effective measure in that it counters the shift of blood towards the center of the body. By applying negative pressure to the lower extremities blood is sucked back down, mimicking the gravitational pull on the blood column within the circulation. If application of lower body negative pressure proves viable - possibly applied when sleeping - this could help counter effects of microgravity on the circulatory system.

Pharmacological counter measures to counter space flight effects physiological systems have yet to be further investigated. Space motion sickness is routinely treated by premedicating astronauts using substances such as Promethazine and bone density loss is countered with treatment similar to osteoporosis medication (McArdle et al., 2014).

This option option for the cardiovascular system - such as Erythropoietin substitution to maintain red blood cell count - has not yet been much explored but always need to withstand a serious risk/benefit assessment.

13. Conclusions

Microgravity and simulated microgravity effect all physiological systems of the human body to some extent. The cardiovascular system and specifically the heart is no exception to that. While little direct effects of microgravity on the cardiovascular system have been shown, the two major indirect forces can be identified. The unloading and lack of use of the musculoskeletal system and the reduction of blood and blood plasma volume.

As the body adapts to the new microgravity environment all cardiovascular parameters show changes in response. Most notably stroke volume is reduced as a consequence of reduced plasma volume and cardiac preload. To maintain cardiac output heart rate and peripheral resistance are increased. While a stable state can be established during spaceflight a major concern regards how these changes and readaptation to a 1-g environment would ensue. Orthostatic intolerance is the main concern here and has been well documented over the years to be a result of spaceflight and bed rest (Buckey et al., 1996b, Fortrat et al., 2001). In the end it is not the heart but the lack of cerebral perfusion causing syncope and orthostatic intolerance. Thus there is need of additional investigation of cerebral vasculature response to microgravity and blood flow regulation (Blaber et al., 2011). While not specific focus of this research a number of studies have implied a sex difference in the development of orthostatic intolerance, showing that women are more prone to presyncope symptoms than men, due to lower vascular resistance (Waters et al., 2002). This ties in with Tuday et al. (2007) who propose arterial compliance as a deciding factor in development of orthostatic intolerance. Just over ten percent of people who have been to space have been women (Wikipedia, accessed 11.07.2018). This suggests the need for further studies to understand these differences and the underlying mechanisms in both sexes in post-spaceflight orthostatic intolerance.

Some research has suggested, in addition to plasma volume loss, cardiac remodeling processes as contributors to the development of orthostatic intolerance (Levine et al., 1997, Perhonen et al., 2001a, Westby et al., 2016). This claim has long been point of discussion and some theorize that the observed cardiac atrophy is an artifact of the plasma volume reduction (Summers et al., 2005). With conclusive answers still missing more research to understand possible cardiac remodeling processes is indicated.

So far echocardiography has been the main tool to study the heart during and after spaceflight. Future research should explore the possibilities of new MRI and CT imaging technologies. However since these technologies are far away from being available in space, they can only provide additional pre- and postflight information, complementing cardiac sonography.

Some changes for skeletal muscle expression of myosin heavy chain patterns have been documented, namely a relative shift from type I to type II MHC fibers (Fitts et al., 2013). Rodent studies imply similar changes to take place in the heart with shifts in the cardiac specific MHC types (Goldstein et al., 1992, Yu et al., 2000). While similar human data likely will remain unobtainable, for ethical reasons regarding the risks of cardiac biopsies, a deeper understanding of these developments and interactions with cardiac performance is desirable.

Cardiac performance has not been extensively tested post-spaceflight. Exercise and cardiac stress tests and the incorporation of newer cardiac performance indices such as Cardiac Index or Myocardial Performance Index, could certainly help get a more complete picture of cardiac performance changes during and after spaceflight missions.

Cardiac ultrasound is a cheap, quick and non-invasive technique to examine the heart and evaluate its function. Therefore it will remain the most important technology in cardiac spaceflight research in the foreseeable future. More extensive in-flight and postflight protocols should be recommended. In clinical practice echocardiographic measurements of systolic and diastolic function are gaining significance and should be introduced as a standard exam in spaceflight research as well.

Summarizing, it can be stated that certain effects and adaptations of the cardiovascular system are undeniable and inevitable. Functionality and cardiac performance are conserved to a degree that it is highly unlikely these changes will endanger mission goals or the crew members themselves. A more complete understanding of the mechanisms in place is however irrefutably necessary to comprehend interaction between the cardiovascular and other physiological systems. As stated earlier, all systems are involved in spaceflight adaptations and the risks posed there e.g. through bone density loss, skeletal muscle atrophy or changes to the immune system, are threatening mission success to a bigger extent (Demontis et al., 2017). Measures to counteract or even prevent deleterious effects

on the human body, firstly exercise and a balanced diet, will need to be researched and in place in all future spaceflight missions.

A comprehensive understanding of the response of all physiological systems is even more important as future space missions are getting longer with more psychological and physical stress on the spaceflight crew.

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