Diplomarbeit

Effects of Immobilization on the Cardiovascular System and Orthostatic Tolerance

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Bujar Berisha

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Institut für Physiologie

unter der Anleitung von

Ass.-Prof. Priv.- Doz. Dr.med. Nandu Goswami PhD.
Univ.-Prof. Dr.med.univ. Helmut Hinghofer-Szalkay

Graz, 21.11.2014

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Graz, 21.11.2014 *Bujar Berisha eh*

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ABREVIATIONS

ACE	Angiotensin-converting enzyme
ANP	Atrial Natriuretic Peptide
ANS	Autonomic nervous system
AV	atrioventricular
BFV	Blood flow velocity
CBF	Cerebral blood flow
CNS	Central nervous system
CAR	Cardiac adrenergic receptors
CC	Cardiac contractility
CM	Chinese medicine
CMA	Cerebral arterial flow velocity
CO	Cardiac output
CPFR	Cardiopulmonary functional reserve
ESV	End-systolic volume
EDV	End-diastolic volume
EF	Ejection fraction
EX	Exercises
GFR	Glomerular filtration rate
GIT	Gastro-intestinal tract
HDBR	head down bed rest
HDT	head down tilt
HR	heart rate
HUT	Head upright tilt
L2	second lumbar vertebra
LBNP	lower body negative pressure
LV	left ventricle
M	men
MAP	Mean Arterial Pressure
NOEX	No exercises

MRI	Magnetic resonance imaging
N	number of subjects
Nut	Nutrition supplement group
PEPi	pre-ejection period
PVR	peripheral vascular resistance
RAS	Renin-angiotensin system
RAAS	Renin-angiotensin-aldosterone system
RR	Riva Rocci
RVE	resistive vibration exercise
SV	stroke volume
T1	first thoracic vertebra
TPR	Total Peripheral Resistance
TYP	Taikong Zangxin Prescription
VO_{2max}	maximal oxygen consumption;
w	women
↑	increase
↓	decrease

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ABSTRACT

Bed rest immobilization is known to cause cardiovascular changes. This thesis explores the physiology of cardiovascular regulation, and then discusses current literature that shows the relationship between cardiovascular system and immobilization. The aim of this thesis is to search the existing literature and provide current state of the art knowledge with regards to how cardiovascular system is regulated, paying particular attention to the role of the heart as well as blood vessels and how they are affected by the fluid shifts that occur during immobilization. Post-immobilization orthostatic intolerance is also discussed here. The relationship to differences in methodologies, subject/patient selection, types of interventions as well as differences in protocols are discussed.

To obtain the relevant literature related to my topic I used PubMed as primary database. I explored only articles written in English and publicized from 1997 till 2014. Furthermore, Web of Science Database as well as the List of References were also used to find articles related to this thesis. To save and organize the references I used RefWorks.

After literature search, I obtained 20 articles appropriate for my thesis and I classified them into three groups, based on the period of bed rest: 1) Less than 21 days (short term): These studies suggested significant amount of vascular deconditioning evidenced by decreases in endothelial function, increases in inflammation and arterial stiffening. 2) Between 21 and 60 days (medium term): These findings suggested an increase in heart rate and decrease in blood pressure and stroke volume contributing in this way to the development of orthostatic intolerance. 3) This group of studies evidenced an increase in heart rate and cardiac contraction, aimed to be induced by an elevated norepinephrine release as well as elevated sensitivity of cardiac adrenergic receptors after long term bed rest (up to 60 days).
The knowledge gained from this work is particularly relevant for doctors working in the area of cardiology, immobilization, syncope as well as space flight research.

Keywords—Immobilization, Cardiovascular System, Orthostatic Tolerance, head-down bed rest, Spaceflight

ZUSAMMENFASSUNG

Es wird angenommen, dass die Bettruhe und Immobilisation das Herz-Kreislauf System beeinflusst. Diese Diplomarbeit erforscht die Physiologie der Kreislaufregulation und diskutiert dann über die aktuelle Literatur, die den Zusammenhang zwischen Immobilisation und Herz-Kreislauf-System recherchiert. Zweck dieser Arbeit ist es, die vorhandene Literatur zu recherchieren und den aktuellen Wissensstand bezüglich der Regulierung des Herz-Kreislauf Systems zu erwerben. Besonderes Augenmerk wird auf die Rolle des Herzens und der Blutgefäße gelegt, und wie sie von der Flüssigkeitsverschiebung beeinflusst werden. Außerdem wird auch die orthostatische Intoleranz nach der Immobilisierung diskutiert. Ebenfalls werden die Unterschiede in der Methodik, Protokolle, Art der Intervention und Auswahl der Subjekte behandelt.

Um die relevante Literatur zu erhalten, habe ich primär die Pubmed-Datenbank benutzt. Es wurden nur die englischen Artikel verwendet, die im Zeitraum zwischen 1997 und 2014 veröffentlicht wurden. Weiters wurden die Web-of-Science-Datenbank sowie die Liste der Referenzen verwendet. Um die Referenzen zu organisieren und zu speichern, wurde die Software RefWorks herangezogen.

Nach der Literatursuche erhielt ich 20 passende Artikel für meine Diplomarbeit. Basierend auf der Zeit der Bettruhe habe ich sie in drei Gruppen klassifiziert: 1) Weniger als 21 Tage (kurzfristig): Diese Studien deuteten eine signifikante Dekonditionierung der Gefäße, bewiesen durch eine Minderung der Endothelfunktion, erhöhte Entzündungsparameter und arterielle Versteifung, an. 2) Zwischen 21 und 60 Tagen (mittelfristig): Diese Erkenntnisse beruhen auf einer Erhöhung der Herzfrequenz, eines Abfalls des Blutdruckes und des Schlagvolumens, und dadurch wird die Entwicklung der orthostatischen Intoleranz begünstigt. 3) Diese Gruppe von Studien zeigt eine Erhöhung der Herzfrequenz und der Herzkontraktion, induziert durch eine erhöhte Noradrenalin Freisetzung, sowie erhöhte Empfindlichkeit der Herz-adrenergen Rezeptoren nach langer Bettruhe (bis zu 60 Tage), an.

Die Erkenntnisse aus dieser Diplomarbeit können besonders wichtig für die Ärzte sein, die im Bereich der Kardiologie, Immobilisierung, Synkopen und Raumfahrt forschen.

I. INTRODUCTION

1.1. Physiology of cardiovascular system

Organs are part of the systems and only together and coordinated they can fulfill their functions. Cardiovascular system is a closed elastic system with an important function that can be categorized in three main groups: transportation, regulation and protection. Cardiovascular system supplies our body with essential nutrients and removes waste (such as urea) from the cells. It also transports hormones between the tissues and regulates the temperature of the body. Furthermore, this system protects against diverse pathogens due to immune function of the leukocytes. Cardiovascular system persists of: heart, blood vessels and blood.

1.1.1 Heart and its function

Heart is a muscular organ of vital importance that through its rhythmical contractions furnishes the body with blood. The heart wall persists of three layers. Epicardium is the outer layer of the wall of the heart (visceral layer of pericardium); the muscular middle layer is known as Myocardium. This is the thickest part of the wall. Endocardium is the inner layer of the heart (one layer epithelium). Heart is organized in two separated pump systems. Each of them contains one atrium and one ventricle.

Blood flow- Right atrium becomes the systemic blood continually from vena cava superior, vena cava inferior and the coronary sinus. From the right atrium flows blood in the right ventricle, this pumps the blood in the pulmonary trunk. Then goes the blood in to the small circulation, get reached with oxygen in the alveolar capillary level and reaches the left atrium through pulmonary veins. Left atrium than pumps it into the left ventricle. The last one pumps the oxygenated blood through Aorta in the whole body. The one direction blood flow in heart is possible thanks to heart valves. The tricuspid and bicuspid valve let the blood flow in ventricles whereas the pulmonary and aortic valve let the blood flow out of the ventricles. This blood flow through the heart chambers makes possible the coordinated contractions of heart muscle.

Heart contraction- Heart muscle is an involuntary striated muscle made of cells known as cardiac myocytes or myocardiocytes. Myocytes contain one nucleus in the center, myofibrils and many mitochondria. The Myofibrils are made of sarcomeres. The arrangement of actin and myosin filaments in sarcomeres is the same as in skeletal muscle. Myocardial cells are connected parallel with each other through gap junctions, which allow the free diffusion of Ions in intracellular fluid of neighbor cells and with it also the spreading of action potential. This feature makes cardiac cells act together as a unit and is known as functional syncytium. The heart insists of two syncytium: the atrial syncytium and the ventricular syncytium. They are connected by a conductive system called the A-V bundle (1).

Like all tissues in the body, cardiac muscle cells need to be supplied with oxygen and nutrients and released from the waste products. This makes possible the coronary arteries.

1.1.2 Blood vessels

The blood vessels are also important structures of the cardiovascular system that transport blood through the body. Blood leave the heard through arteries and return back through veins. The blood pressure in the arteries is around 120mmHg systolic and 80mmHg diastolic. Between these two types of blood vessels, there are capillaries, which make possible the exchange of nutrients and chemicals between the blood and the tissues. The arteries and veins consist of 3 layers: tunica intima (endothelial cells), tunica media (rich in smooth muscle) and tunica adventitia (connective tissue).

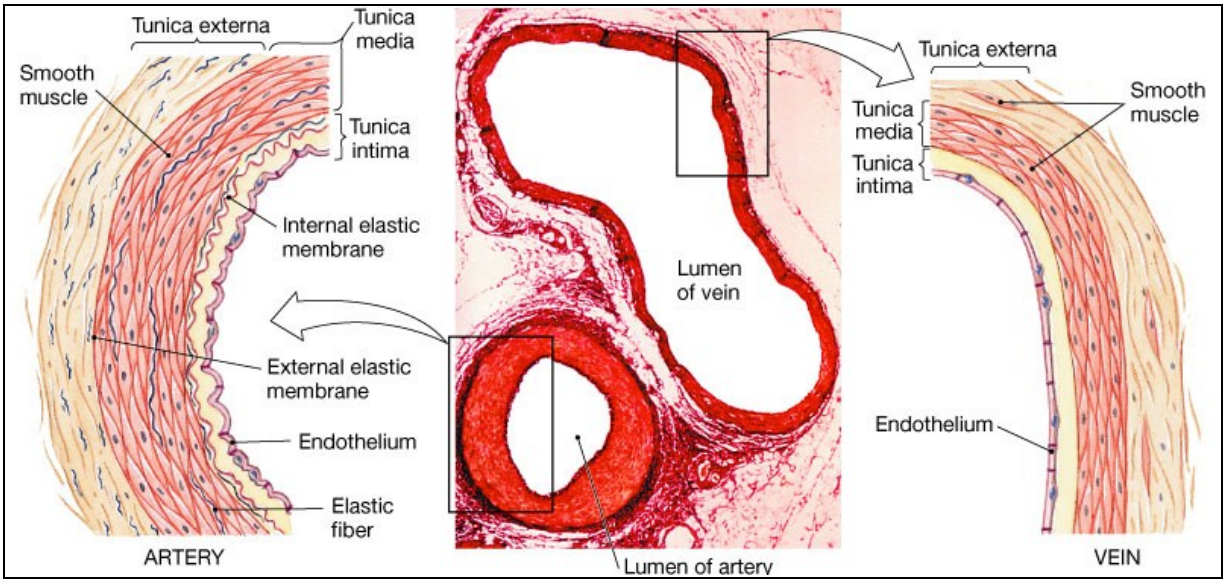

Figure 1: Characteristis of arterial and venous wall (2)

Thanks to tunica media and its smooth muscle fibers, blood vessels change the diameter and in turn influence blood flow to the organs. Vasoactivity and permeability are important characteristics of blood vessels (3).

Vasoactivity is a feature of blood vessels mainly controlled from the autonomic nervous system. Due to ability to dilate and contract the vessels have a huge impact in blood pressure. Thus, an increase of sympathetic activity case vasoconstriction and in turn increases the blood pressure in the vessel while a sympathetic inhibition case a vasodilation and a decrease in blood pressure. Through this mechanism, the body can shift large amounts of blood from blood vessels to the heart and increase heart pumping. Due to this mechanism, the body can compensate till to 25% of the total blood volume in case of hemorrhage and keep the circulation near to normal (4).

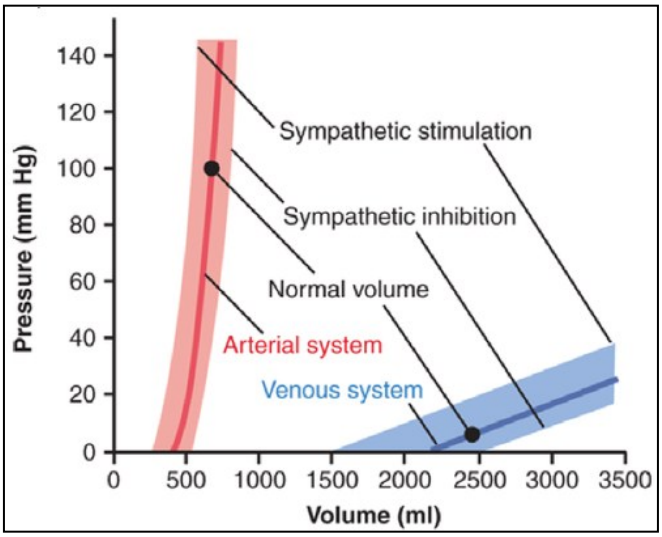

Figure 2: Impact of vasoactivity in blood pressure (5)

Permeability is another characteristic of blood vessels, especially capillaries that make possible the transfer of nutrients from vessel lumen to the tissue. This feature is increased in case of inflammation and induce the symptoms of inflammation.

Blood- as a fluid tissue flows around the body and enables the metabolism and the interconnection of the organs. This specialized connective tissue performs many functions that can be categorized in:

- Transport of oxygen and nutrients to the tissues and removal of metabolic waste at the opposite direction (transport and interconnection function)
- Protect against external and internal pathogens (immunological function)
- Hemostasis (stops bleeding in case of open wound)
- Homeostasis (optimizes body temperature, pH, ion concentrations, osmolality)

Two main components of the blood are plasma and cells dissolved in the plasma. An adult man has an average blood volume of 5 liters or 6-8% of the body weight.

1.2 Regulation of blood pressure

The main function of the heart is to pump blood and supply all body tissues and organs with oxygen and nutrition as well as to remove cellular waste. Of the same importance is also that the supply with blood happens under a normal pressure in vessels (around 120/80mmHg). Before we talk about the mechanisms that regulate the blood pressure, let me talk about some important parameters that help us evaluate the heart performance.

1.2.1 Cardiac output and mean arterial pressure

Blood pressure can be regulated by modifying parameters like cardiac output and resistance of blood flow in the vessels.

Cardiac output is defined as the amount of blood pumped in one minute by the heart. To calculate the CO we multiply the stroke volume and the heart rate (6).

Heart rate (HR) is defined as number of heart beats pro minute. It can change based on body's physical needs and the normal rate in rest is 60-100 bpm. Heart rate is rhythmically regulated by sinoatrial node (7). Furthermore, also inputs from sympathetic and parasympathetic nerves influence it. The cardiovascular center is localized in medulla oblongata, leading to increased heart rate via sympathetic activity and decreasing it via vagus parasympathetic stimulation. While a person is in rest both sympathetic as well as parasympathetic centers provide slight heart stimulation thus maintaining the heart autonomic tone (8).

Stroke Volume (SV) - is the difference between end systolic volume (ESV) and end diastolic volume (EDV). Under physiological conditions EDV contains approximately 120 ml blood while the ESV about 50 ml.

Cardiac output (CO) = SV x HR

Stroke Volume (SV) = EDV – ESV

Heart Rate = Beats per Minute

For a young men, an average resting cardiac output is 5.6 L/min and for a woman is 4.9 L/min. Because our cardiovascular system is a closed system, the heart can pump out only the amount of blood that returns back to it. This statement is very important, because the blood return is

from different body conditions influenced (bed rest immobilization, space flight), and in turn also the cardiac output.

To make this blood amount flow into the systemic circulation, the heart must pump against the resistance of the vascular bed, known as **Total Peripheral Resistance (TPR)**. It is affected primarily by changes in the diameter of the vessels.
Together with the CO they determine the **Mean Arterial Pressure (MAP)**, which is the driving force of blood flow:

Flow = Pressure/Resistance

CO = MAP/TPR

MAP = CO x TPR

MAP = HR x SV x TPR

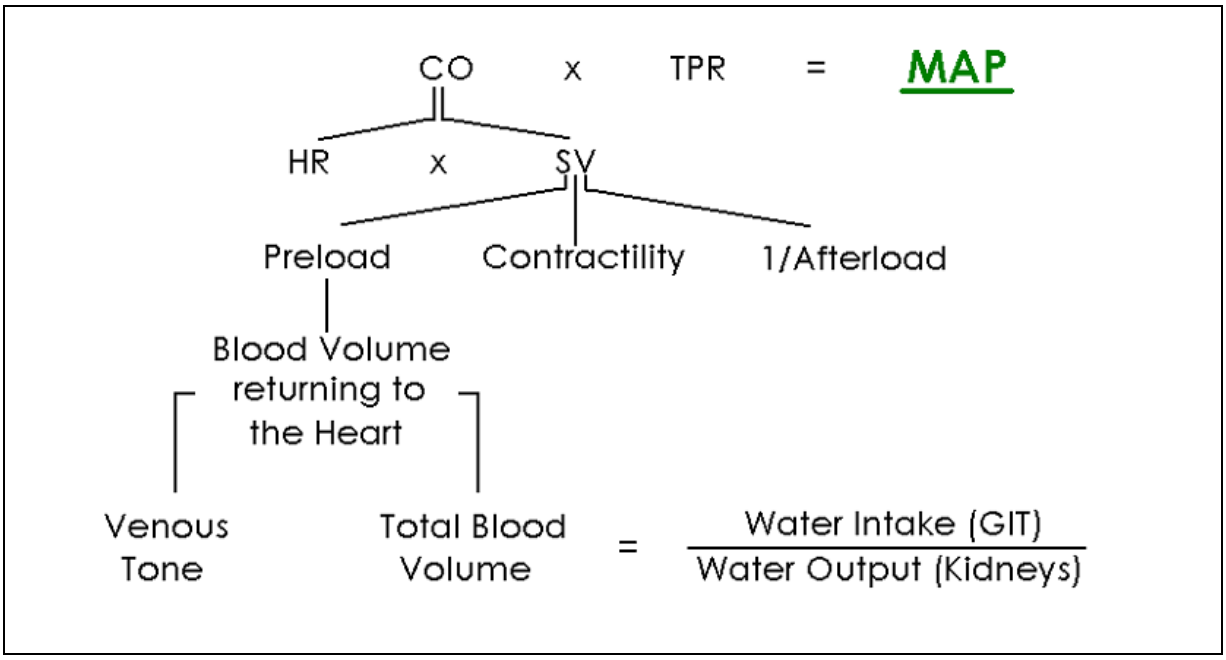

Figure 3: Cardiac output and mean arterial pressure (9).

This means that MAP is determined by HR, SV and TPR. Changes in any of this parameters affect MAP casing hypotension and in turn underperfusion which is especially critical for the brain or hypertension and its consequences (6).

1.2.2 Mechanisms of blood pressure regulation

Tissues have various needs for Blood amounts in different loading conditions. It is essential that the circulatory regulation mechanisms supply the organs always optimally with Blood. This is possible due to:

- Short term mechanisms in regulation of blood pressure
- Long term mechanisms in regulation of blood pressure
- Local mechanisms (1)

1.2.2.1 Short term regulation of blood pressure

These mechanisms of blood pressure control are able to regulate the arterial pressure in seconds.(10) If there is needed an increase of blood pressure than the nervous system affects vasoconstriction and cardioacceleration together and at the same time inhibits parasympathetic signals to the heart. Neuronal control mechanisms consist of:

a) Cardiovascular control centers in Medulla
b) Effector pathways (Autonomic nervous system) and
c) Afferent signals to the centers in central nervous system (CNS).

a) Cardiovascular control centers in CNS

Vasomotor center in CNS- is placed in retinacular substance of medulla and sends its fibers between T1 and L2. The parasimpathetical fibers go to the heart through vagus nerves, otherwise the peripheral sympathetic nerves and spinal cord innervate all arteries and veins. Important areas of this center are: a vasoconstrictor area, vasodilator area and a sensory area.

Cardio Acceleratory Center- sends sympathetic fibers down the spine to T1-T5 where they exit to periphery. When activated, it increases the heart rate and myocardial contractility.

The third center is **Cardio Inhibitory Center,** which originate in Medulla and it sends parasympathetic fibers through vagus nerve (1).

b) The autonomic nervous system (ANS)

Autonomic neuronal system through its sympathetic and parasympathetic activity affects arteries, veins and heart and makes a great job in rapid control of blood pressure. The main regulating functions of the neuronal mechanisms in cardiovascular system are: increase of the heart rate, rapid control of arterial pressure, redistribution of blood amounts to different parts

of the body. Principally, sympathetic nerve fibers increase the heart rate and contraction and parasympathetic nerves case the opposite. Sympathetic nerves contain mainly vasoconstrictor fibers. At the endings of this nerves is secreted Norepinephrine, which acts on α-adrenergic receptors and affects smooth muscle contraction.

These centers send their signals to the organs and tissues through effector pathways of autonom nervous system. An important part of the neuronal mechanisms are also the feedbacks from periphery to the center. This is possible primarily due to baroreceptors and chemoreceptors.

This part of nervous system is responsible for the main visceral functions of the body. The autonomic nervous system plays a huge role in control of cardiovascular system. For example it can double the heart rate in 3-5 seconds, in 10-15 seconds it can increase or decrease the blood pressure twice normal. ANS centers are located in the hypothalamus, brain steam and spinal cord. They come in contact with organs they innervate through sympathetic nervous system and parasympathetic nervous system.

Sympathetic nervous system- The fibers of this system originate in the spinal cord (between cord segments T1-L2) and then they get into the sympathetic chain. From here they travel to the target tissues. Principally, the sympathetic nervous fibers are composed of 2 neurons. The first neuron is called preganglionic neuron and connects ANS centers in the CNS and peripheral ganglia. (1) The axon of the preganglionic neuron through rr. communicantes albi reach the postganglionic neuron in the ganglion area and make a synapse between. The body of the postganglionic neuron lies on the ganglia of the sympathetic chain and from here sends postganglionic axons to the effector organs.

Parasympathetic nervous system- run away from the CNS through cranial nerves (III, VII, IX and X) and sacral spinal roots. The parasympathetic nervous system reaches the cardiovascular system by means of vagus around four fifths of parasympathetic fibers reach thoracic and abdominal organs by means of vagus. This system has also its pre- and postganglionic neurons. The ganglions of parasympathetic system are mostly located in the wall of the organ.(11)

The sympathetic and parasympathetic preganglionic fibers secrete acetylcholine, which is also a transmitter in the parasympathetic postganglionic fibers. All these fibers that secrete acetylcholine are called cholinergic fibers. Conversely, almost all of the sympathetic postganglionic fibers secrete norepinephrine and are said to be adrenergic.

Usually, have postganglionic nerves at their ends an enlargement (varicosities) where they store the transmitter vesicles filled with acetylcholine or norepinephrine. (12) Under the effect of action potential release the nerve endings their transmitter in to the effector organs.

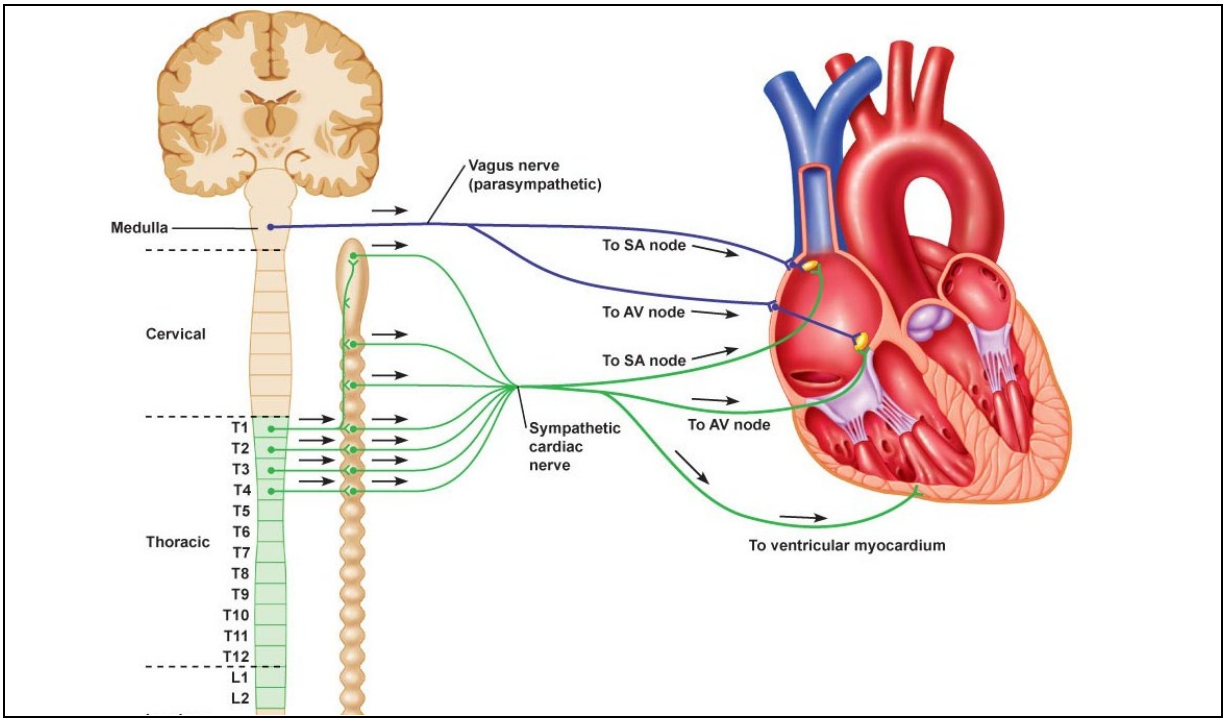

Figure 4: Role of autonomic nervous system in cardiovascular system (13).

The transmitters act on specific receptors on the effector organs. There are two types of receptors for acetylcholine: muscarinic and nicotinic receptors. Nicotinic receptors are located in the autonomic ganglia (between first and second neuron) and the muscarinic receptors are found in the effector organs and cells. There are also two types of adrenergic receptors: alpha receptors and beta receptors and their subtypes alpha$_{1,2}$ and beta $_{1,2}$ receptors. In alpha receptors binds mainly norepinephrine and one of the actions is the contraction of blood vessels. In beta receptors binds norepinephrine and epinephrine. Beta$_1$ receptors are

responsible for cardioacceleration and increased myocardial strength, while beta$_2$ receptors case vasodilation (14). Detailed information to receptors are listed in Table 2.

Table 2: Effects of different receptors in cardiovascular system (1).

Target	Sympathetic (adrenergic)	Parasympathetic (muscarinic)
cardiac output	β1, (β2): increases	M2: decreases
SA node: heart rate (chronotropic)	β1, (β2): increases(15)	M2: decreases
Atrial cardiac muscle: contractility (inotropic)	β1, (β2): increases(15)	M2: decreases
AV node	β1: increases conduction increases cardiac muscle activity	M2: decreases conduction Atrioventricular block(15)
Ventricular cardiac muscle	β1, (β2): inotropic, increases cardiac muscle contractility(15)	

c) Afferent signals

Baroreceptor reflex- Baroreceptors are located in the aortic sinuses, carotid sinuses and in the right atrial walls. The baroreceptor reflexes adjust the cardiac output and peripheral resistance being this way the best known nervous mechanisms in control of blood pressure. The baroreceptors respond in fraction of second in change of arterial pressure. They are most sensible in blood pressures around 100mmHg, where it is most needed. Additionally, they respond better to acute changes of blood pressure than to stationary pressure.

A rise in blood pressure dilates the vessel wall and stretches the baroreceptors. This stimulates the baroreceptors and make them to transmit signals in central nervous system. Signals that come from carotid sinuses are conducted through N. glossofaryngeus to the tractus solitarius of medulla oblongata. Signals from aortic sinuses are conducted through N. vagus in cardiac and vasomotor centers within medulla oblongata. This signals than inhibit the vasoconstrictor center and excite the vagal parasympathetic center.(16) These centers than send efferent impulses and affect vasodilatation of the arterioles and veins and decrease the heart rate and contraction. Conversely, in case of low pressure, baroreceptors are inhibited and their impulses to the brain are decreased. This induces decreased parasympathetic activity and increased sympathetic activity. In consequence we have: an increased heart rate and

contraction, increased vasoconstriction and release of epinephrine and norepinephrine which enhance heart rate.(11) As a result we have an increased blood pressure. Furthermore, baroreceptors are a pressure buffer system. They oppose increases and decreases in blood pressure reducing the variation of it.

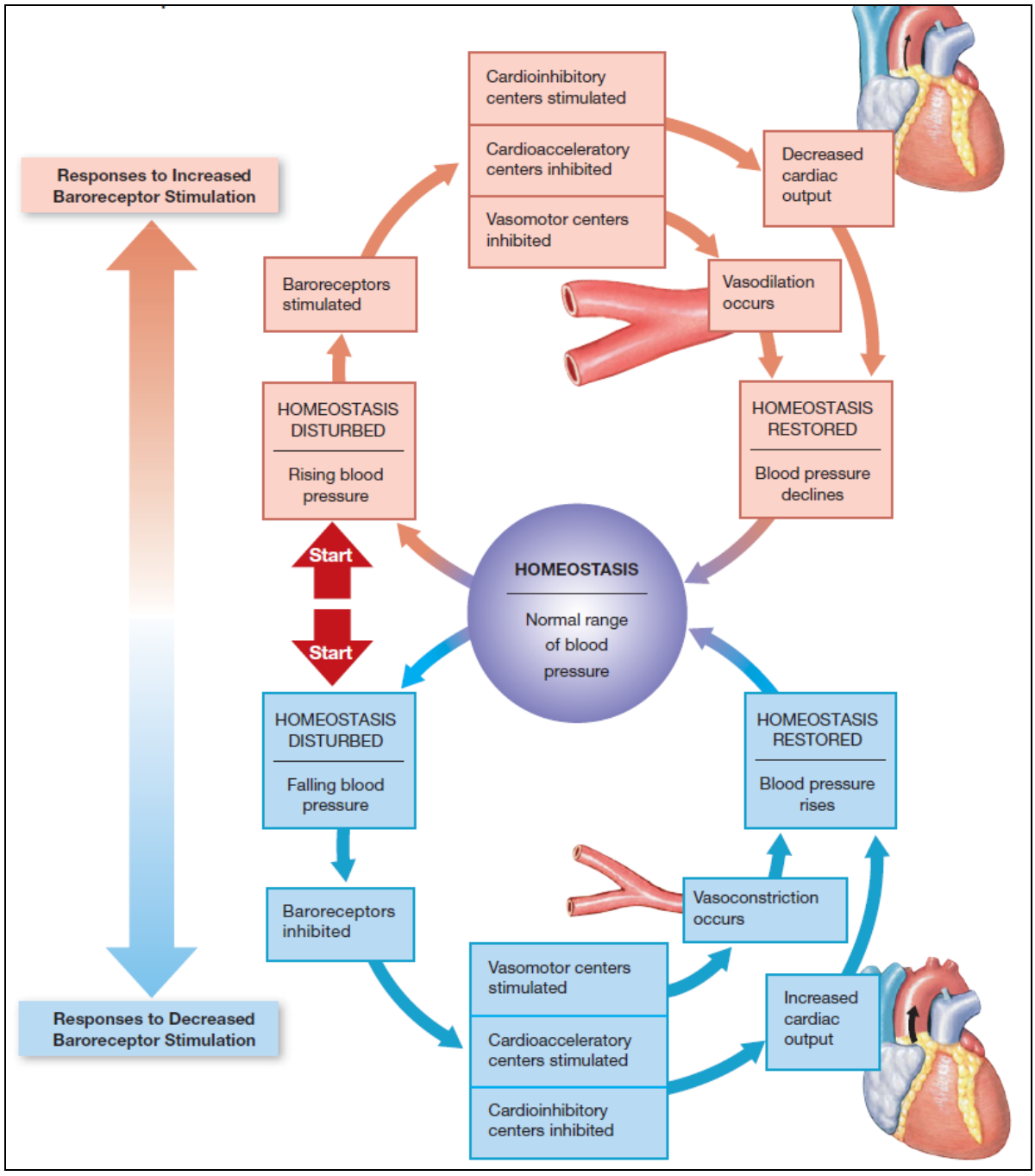

Figure 5: Role of Baroreceptors in Homeostasis (12).

Chemoreceptor reflex- Chemoreceptors are a group of chemosensitive cells placed in aortic and carotid sinuses and in this way exposed continually to arterial blood. Carotid bodies are placed in the bifurcations of the common carotid arteries. They send afferent nerves to N. glossopharingeus and from here to the dorsal respiratory area of medulla oblongata. Chemoreceptors are specialized in detecting following changes in blood:

- drop of Oxygen
- rise of carbon dioxide and
- drop of pH-values (14)

Any of these changes activate chemoreceptors and induces the activation of cardioacceleratory and vasomotor centers and in consequence, increase of cardiac output and vasoconstriction. The chemoreceptors play an important role in hypoxia and hypotension. Chemoreceptors are strongly stimulated first when the blood pressure falls under 60mmHg and in this way helps, when most important, to gain the further fall in blood pressure. There are also central chemoreceptors in medulla oblongata that control cerebral spinal fluid composition.(17)

1.2.2.2 Long term regulation of blood pressure

This mechanisms have a delayed onset in regulation of systemic blood pressure. Kidney with its **renal body fluid mechanism** play the main role in long term regulation of blood pressure. It is also supported from aldosterone system and renin-angiotensin system.

Long-term mechanisms for the regulation of systemic blood pressure, unlike the short-term regulatory mechanisms, have a delayed onset but do not adapt, providing a sustained regulatory effect on systemic blood pressure. The renal-body fluid system plays a predominant role in long-term control of systemic blood pressure because it controls both the cardiac output and systemic vascular resistance. This crucial role is supplemented by accessory mechanisms, including the renin-angiotensin system, aldosterone, and arginine vasopressin.

Renal-body fluid system- is the most important mechanism in long-term regulation of blood pressure. Due to this mechanism an increase in arterial blood pressure induces an increase of the diuresis and natriuresis and this continue till the mean arterial pressure returns to its native set (18).

Renin-angiotensin system (RAS)- is a hormonal mechanism that helps in regulating arterial pressure. A decrease in blood pressure or loss of blood volume activates juxtaglomerular apparatus in the kidney. It releases the hormone renin which in turn activates angiotensinogen to angiotensin I. Angiotensin I converts with the help of an enzyme known as angiotensin-converting enzyme (ACE) in Angiotensin II. Than this final product of RAS increases blood pressure through two pathways: it contracts the blood vessels in the body including here also the blood vessels of the kidneys and it stimulates the aldosterone secretion from the adrenal cortex. By constricting blood vessels Angiotensin II reduces the amount of blood that flow through kidneys and in this way decrease the diuresis, thus increasing blood volume. Aldosterone secreted due to angiotensin II action contribute also in retaining water and sodium raising blood pressure.(19)

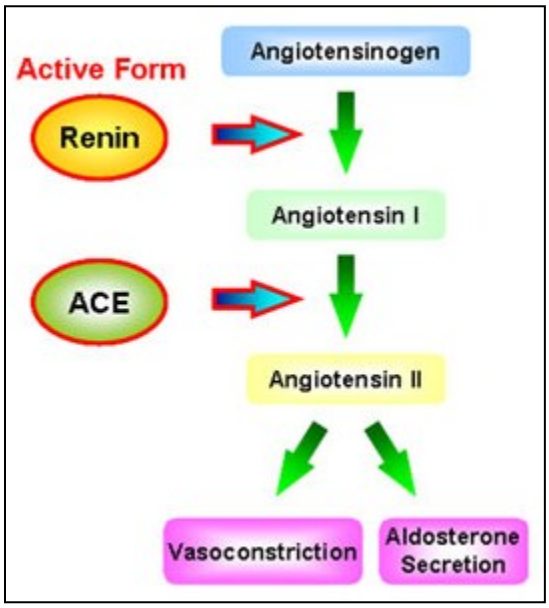

Figure 6: Renin-angiotensin system (20)

1.2.2.3 Local control mechanisms

Organs regulate their blood flow through mechanisms known as local regulation. Local regulation of blood flow occurs by vasoconstriction and vasodilation.

Metabolic mechanisms

These mechanisms try to regulate the blood flow in according to the metabolic needs of the tissue. Thus, when the oxygen amounts to the tissues decrease, the blood flow to this tissue increases markedly. Also an increase in metabolism of the tissue affects the blood flow to increase. There are two theories that try to explain this correlation between the regulation of local blood flow and the rate of tissue metabolism or the amount of oxygen.

Vasodilator theory for acute local blood flow regulation- According to this theory, when the rate of metabolism increases or the availability of oxygen decreases to a tissue, increases the release of vasodilator substances in the tissue. The vasodilators diffuse to pre-capillary

sphincters and case vasodilation. Important vasodilator substances are: adenosine, histamine, K^+ Ions and H^+ Ions.

Oxygen lack theory for local blood flow control- While oxygen is required in muscle contraction, according to this theory, the blood vessels will dilate in lack of oxygen. Oxygen lack theory is explained in relation to the pre-capillary sphincters, which regulate the amount of the blood flow to the tissue or organ. The higher the oxygen concentration in a tissue, the stronger is the contraction of the pre-capillary sphincters and in this way the less is the amount of blood flow respectively oxygen to the tissue. (1) An example of metabolic control of blood flow is hyperemia.

Myogenic mechanisms

Increase of intraluminal pressure stretches the smooth muscle of the vessel. This in turn affects a reactive contraction mediated by stretch-activated Calcium channels in the vascular smooth muscle cells. This myogenic contraction reduces blood flow nearly normal. An example of metabolic and myogenic mechanisms is the autoregulation.

Autoregulation of blood flow- is the intrinsic mechanism that keeps relatively stable the blood flow despite changes of arterial pressure. Thanks to this mechanism, the blood flow can be hold relatively constant even though the arterial pressure is elevated. Autoregulation is for a long time argumented by metabolic and myogenic mechanisms.

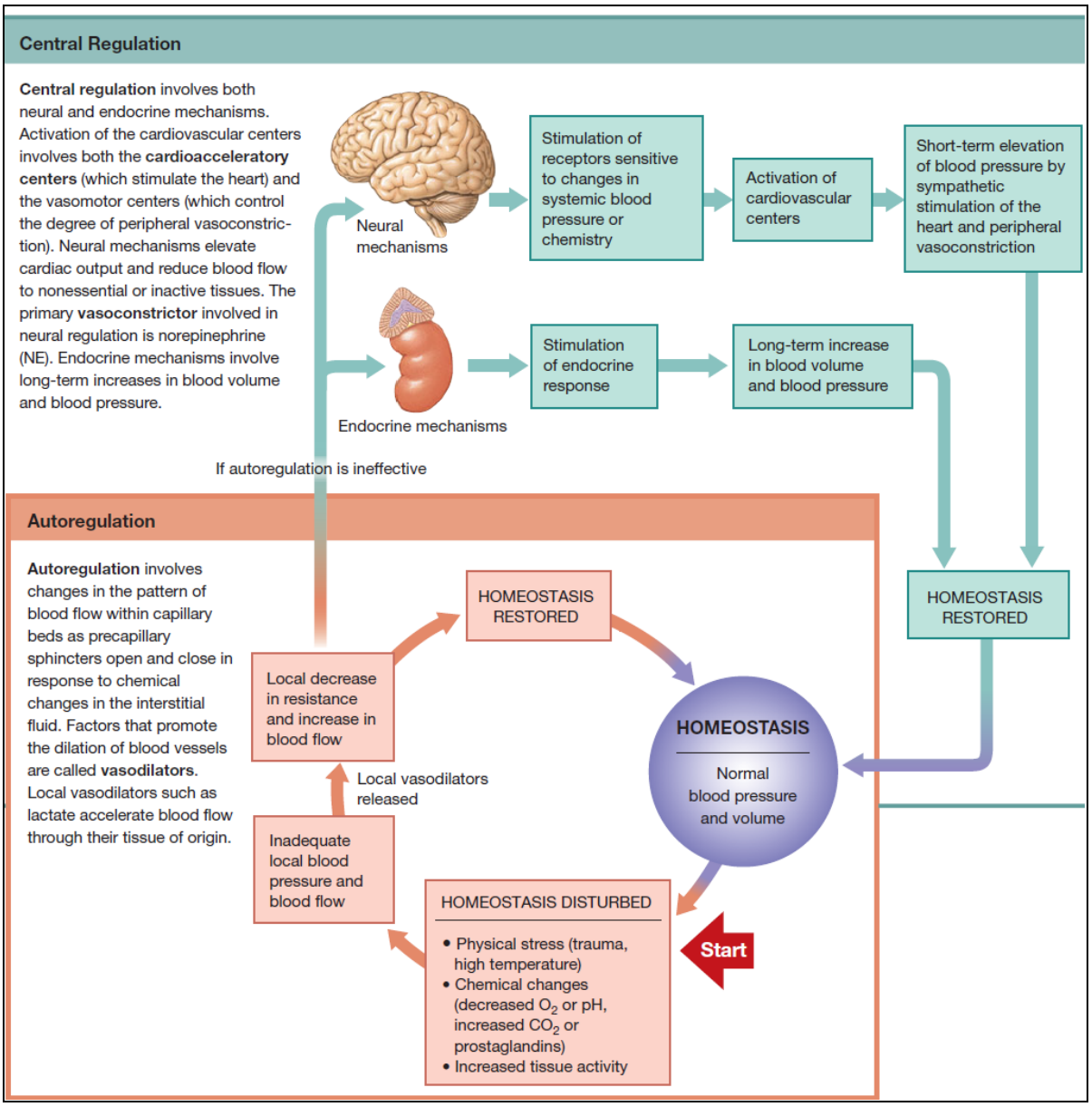

Figure 7: Central regulation and autoregulation of cardiovascular system (12).

1.2.3 Hormones that influence blood pressure

There are many hormones and other substances in the body fluids that affect circulation, which can be grouped in:

- Vasoconstrictors: catecholamine, angiotensin II and vasopressin.
- Vasodilators: kinines, atrial natriuretic peptide and histamine
- Ions and other chemicals: calcium, potassium, hydrogen, carbon dyoxid ions…

a) Vasoconstrictors

Epinephrine- is a hormone released immediately in stress situations from adrenal medulla. It stimulates alpha- and beta-receptors, increases heart rate and blood pressure. Adrenalin stimulates alpha-adrenoreceptors in small blood vessels that affects a vasoconstriction. Parallel stimulates adrenalin also $beta_2$-adrenoreceptors in central vessels effecting a vasodilatation. Due to its effect in $beta_1$-adrenozeptors increases the epinephrine the heart rate. It's important to note that chronically increased adrenalin levels in blood case hypertrophy of heard.

Norepinephrine- has a greater impact in alpha- than in beta-receptors. For this reason it acts a generalized vasoconstriction.

Angiotensin-II- is an effector hormone of the renin-angiotensin system. It is produced by kidneys in response to low blood pressure. Angiotensin-II is a strong vasoconstrictive peptide and through its effect in central neural system the release of Aldosterone from adrenal cortex. Aldosterone increases the reabsorption of water and sodium in kidneys thus increasing the volume of fluids in the body and also blood pressure (4).

Antidiuretic Hormone (Vasopressin) - is a peptide hormone with a very short half-life time (16-24min.) produced in Hypothalamus and stored at the posterior pituitary. It increase water absorption in the collecting ducts and distal convoluted tubule, retaining in this way the water in body. In high concentrations affects also vasoconstriction, which in turn increases blood pressure. It is released in response of increased plasma solute concentration, decreased blood pressure or blood volume and affects also the homeostasis, by regulating the amount of water, salts and glucose in the body.(21)

b) Vasodilators

Atrial Natriuretic Peptide (ANP)- is a peptide hormone secreted from the right atria cells in response to high blood pressure and plays a role in homeostatic. It is released in response to stretch of atria walls, sympathetic stimulation of beta-receptors, hypernatremia, Angiotensin II and Endothelin. ANP reduces blood pressure through different mechanisms: loss of water and sodium, inhibition of sympathetic stimulation of adrenal medulla and vasodilation. This hormone bins to its specific receptors and aim its goal in blood control affecting many organs or systems of organs. When ANP released induce water and sodium waste by increasing blood flow to the kidneys. This in turn increases the GFR; decreases the reuptake of sodium and

inhibits RAAS system. In vessels, relaxes the smooth muscle cells by elevation of GMPc and in heart inhibits cardiac hypertrophy.(12)

Kinins are polypeptides that in specific concentrations act to dilate the blood vessels. There are two forms of Kinins: Bradykinin, found in the plasma and Lysylbradikinin, found in body tissues. This vasoactive substances are expected to play a role in regulating blood flow especially to skin, GIT glands and salivary glands. They are also formed during active secretion of this glands.(1)

Bradykinin is a peptidhormone, synthetized from the kinin-kallikrein system by protheolythic cleavage of circulating kininogen. It connects to its bradykininrecceptors (B_2 receptors-responsible for the vasoactive effects) in vessel walls, which in turn cases dilation and increased permeability of the vessel. As a result decreases the blood pressure. Based on its effect in lowering blood pressure there are made also medicaments against high blood pressure (ACE-inhibitors) that increase the bradykinin levels and thus in turn decrease blood pressure.

Histamine- is a biogenic amine, involved in many physiological and pathological processes and especially in the inflammatory response. It is produced and stored in mast cells and basophils. Histamine is released when complement components C3a and C5a interact with specific membrane receptors or when antigens bind to mast cell fixed-IgE.

This amine is classified to the tissue hormones and exerts its actions due to specific receptors in target cells. Histamine cases through H_1 receptors a dilation and increase of the permeability of blood vessels. This leads to an edema of the skin and mucosal membrane. Stimulation of the same receptors in the bronchial walls case smooth muscle contraction. H_2 receptors primarily case smooth muscle dilation, but also stimulate the parietal cells of stomach to secret gastric acid (14).

1.3 Bed rest and Immobilization

In the early phases of medicine bad rest has been used as a treatment strategy for many disorders but studies have shown that in healthy humans, bed rest induces global changes collectively referred to as- body deconditioning. This fact enhanced the need of minimization of the bed rest period during hospitalization, physical exercises and adequate hydration and nutrition. Physiological changes during bed rest immobilization and lack of gravity have been evidenced also by people flying on space. Based on this fact, the studies dealing with bed rest are also useful for space flight investigations (22).

Figure 8: Bed rest effects by people lying in bed and astronauts (23,24).

Prolonged bed rest produces profound changes in most of the organ systems. It is supposed that cardiovascular, skeletal and muscular system is also impacted from this condition.

The muscles are going to atrophy and reduce 50% of their strength in 3-5 weeks of immobility, the bones loss density, the joints begin to deteriorate. Most involved in this process are the antigravity muscles. Important is that the loss of muscle mass will be regained in some weeks but the bone mass needs months longer to be regained, further contributing to higher risk of fractures, which in turn prolongs the immobility (25).

It is supposed that immobilization effects also hemostasis. The mechanisms acting in this process are thought to be: an increase in blood viscosity due to plasma volume reduction,

decrease in oxygen demand because of muscle atrophy (26) as well as a hemostatic dysbalance between pro and anti-coagulator factors which can lead to pathological formation of thrombus. Due to bed rest immobilization the lungs reduce their forced vital capacity as well as bronchociliar activity. These increase the risk of respiratory infections (26). Constipation, skin ulcers, body fat increase, mental disorders, loss of minerals and electrolytes some other consequences of immobility.

During bed rest, the body fluids shift from extremities to the thorax. This stimulates in atriums the release of ANP hormone, in response to high blood pressure. ANP reduces blood pressure through different mechanisms: loss of water and sodium, inhibition of sympathetic stimulation of adrenal medulla and vasodilation leading to decreased stroke volume. To counteract this effect, the body increase the heart rate (26). Decreased vagal activity and noradrenalin release are thought to be the mechanisms that cause this heart rate increase (27). Furthermore the heart muscle undergo atrophy. The cardiovascular changes due to bed rest immobilization will impact the body also when a person starts to move. During this remobilization period the blood pool to the lower limbs and because the cardiovascular system is already deconditioned, it cannot be quickly corrected from it. As a result it comes to orthostatic hypotension, which decreases cerebral perfusion and thus in turn leads to dizziness and a tendency to fall (26). Furthermore bed rest decreases also the maximal oxygen consumption (VO2max).

The correlation between cardiovascular system and bed rest immobilization is the main point of my thesis and is explored below.

1.4 Orthostatic Tolerance

Orthostatic tolerance is defined as ability of the body to maintain consciousness during postural changes (29). Postural changes (standing up) induce orthostatic stress, which causes shift of blood volume from chest to dependent body parts (lower extremities). This blood translocation reduces venous return as well as induces pooling of blood and extravasal fluid to lower extremities. During upright standing 750 ml of chest blood is going to shift downward (30). Vein blood reservoirs below the heart are going to be filled, heart venous return impedes and because of the hydrostatic blood pressure changes, cerebral perfusion is going to be reduced. Upright standing is associated with approximately 6-10 % reduce of cerebral perfusion due to hydrostatic change between brain and heart. Furthermore also the cardiac output decreases approximately 25% while heart rate increases (30). The splanchnic circulation is the largest venous reservoir, followed by low extremities. Similarly to orthostasis also hemorrhage induces akin loss of central blood volume. In these conditions, intact compensatory mechanisms are required to maintain cerebral perfusion, consciousness and blood pressure. An important mechanism for the brain is the cerebral blood flow autoregulation (30).

1.4.1 Compensatory mechanisms of orthostatic tolerance

Our body use this mechanisms to keep in normal range the cerebral perfusion, consciousness and blood pressure. Important compensatory mechanisms are going to be discussed below.

Cerebral blood flow autoregulation maintains constant blood flow to the brain by vasodilation in response to hypotension, and vasoconstriction in response to hypertension. This mechanism was for the first time described by Bayliss in 1902 (31). The cerebral arterioles and venules normally constrict or dilate themselves in order to maintain a constant blood flow to the brain. The problem is that autoregulation works only by mean arterial pressure (MAP) between 60mmHg and 160mmHg (32). Beyond these boundaries, the compensatory response of cerebral autoregulation is inadequate. At the breakthrough of the upper or the lower limit of autoregulation, the cerebral blood flow (CBF) increases or decreases proportional to MAP.

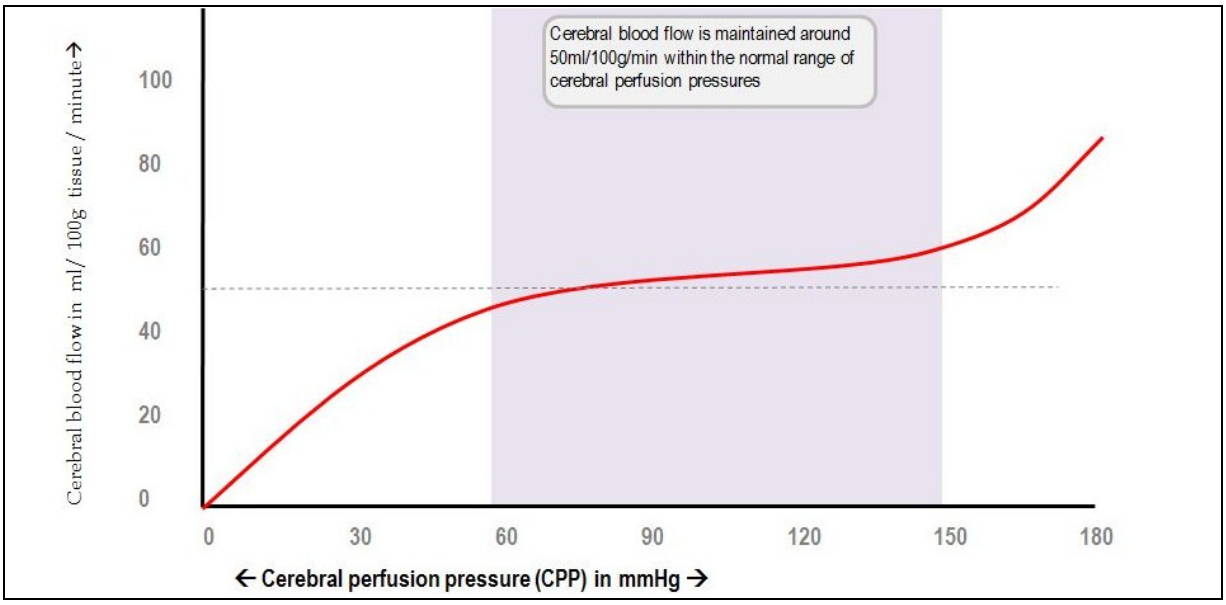

Figure 9: Autoregulation maintains a constant blood flow by MAP 50-150mmHg (33).

Muscle Pump effect is the first compensatory mechanism that counteract blood pooling. The muscles of leg and gluteal region contract and this propel the pooled blood to the heart. Muscle pump impacts also the lymphatic drainage of the low extremities and through chemoreceptors can be also involved in neurogenic compensatory system. Exactly this mechanism is crucial by people lying in bed for a long time and by astronauts. Because the muscle pump undergo atrophy during physical inactivity and/or less of gravity, this persons are vulnerable toward orthostatic stress.

The second line that counteract orthostatic intolerance is the **neurovascular respond**. Vasoconstriction of the arteries promote passive empting of the splanchnic and extremity circulation. This effect is associated with norepinephrine spillover from the nerve endings. The reflective compensatory mechanism that occurs during orthostatic stress are primarily controlled from baroreceptors in the carotid arch, sinus carotids and proximal coronary arteries. Through these high pressure baroreceptors occurs vasoconstriction and changes the heart rate. Some other mechanisms included on the compensation are: metabolic, local myogenic and arteriovenous responses. Also the inflammatory molecules, neuropeptides, prostacyclin, nitric oxide are thought to play an important role on this defense response.

Neurohumoral response is important during later stages of orthostasis. It counteract the orthostatic effect due to activation of RAAS, which in turn releases epinephrine and vasopressin. The neurohumoral effect is a long term response of the body against orthostasis. It affects tonic sympathetic vasoconstriction. Furthermore, epinephrine surge accompanies vasovagal syncope therefore it may also have an instrumental role in the mechanism of syncope onset.

As we can see, to stand successfully upright is required an interaction of physical, vascular, humoral, and neurologic components as well as blood volume. When this compensatory response to orthostatic stress is inadequate, occurs the orthostatic intolerance during standing upright. With the aim of exploring physiological responses to postural changes, the researchers use specific tests to induce this responses.

1.4.2 Test techniques used to induce orthostatic stress

These techniques induce a physical inactivity by subjects to negate the muscle pump effects. The researchers use specific tests to study physiologically responses to positional changes and their induced orthostatic stress. Most of these tests induce upright stress or negate the muscle pump effect (30).

Standing test is a simple physiological stressor of orthostatsis, although it is difficult to use on all ages and body conditions, especially by patients that cannot stand up and children. By standing we aim to negate the muscle pump and in this way to make more evident the neurovascular aspects of orthostatic control (34).

Head upright tilt table testing (HUT) is a commonly used orthostatic stress test. Since 1980 it is used as a medical procedure to diagnose syncope, but it is also used from investigators to provoke orthostatic stress and then to explore the symptoms and reactions in this condition. The subject lie flat on a special table which is mechanically driven in offset 60-90° from the horizontal for 10-45minutes. In upright positions over 30° activate the sinoaortic baroreflex, is important in regulation of arterial pressure and brain perfusion while standing (34). There occurs an enhance in heart rate from 10 to 25 beats/minute in normal persons, while persons with postural tachycardia syndrome develop higher heart rates associated with orthostatic intolerance and sometimes hypotension (30).

Lower Body Negative Pressure (LBNP) Test is a research method used often in the area of cardiovascular research. It stimulate gravitational stress as well as hemorrhage. Using this model enabled the examination of physiological responses to orthostasis. Furthermore, it is used also for studies by heart failure patients, astronauts and elderly. This model can be used also in combination with other test techniques like HUT or exercises. LBNP combined with HUT are used together from many investigators to induce a stronger orthostatic stress effects to the subjects and in this way also to experience the orthostatic intolerance.(35)

To make LBNP test, subjects lie on supine position with legs and lower abdomen placed in LBNP device (Chamber). Inside the chamber is the air pressure reduced (negative), created by vacuum pump. This negative pressure shifts the blood from the upper body toward the legs. Under physiological conditions, the body can compensate this reaction mainly by vasoconstriction and heart rate increase. Otherwise, by inadequate physiological response the blood pressure decreases leading to symptoms till ultimately syncope.

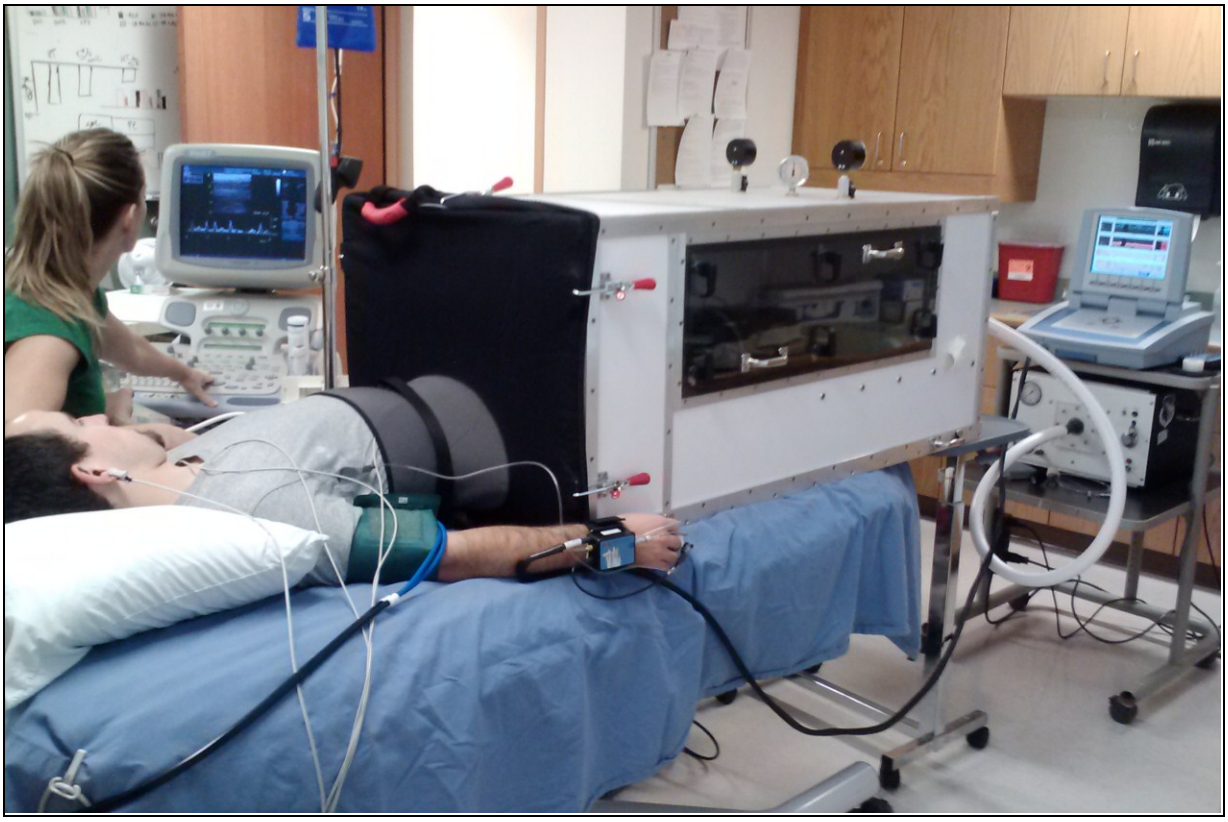

Figure 10: Low body negative pressure box (36)

II. AIMS AND OBJECTIVES

Based on the literature review, I will hypothesize what happens during bed rest immobilization with the cardiovascular system. The main question is how cardiovascular system is affected by bed rest immobilization. Subjects that undergo bed rest have different fluid distribution, as compared to say during standing up, the responses of the heart and the vessels will be accordingly adjusted.

This work will also focus on current knowledge regarding blood pressure regulation as well as effects of immobilization on the cardiovascular system. It is known that immobilization can lead to symptoms (vertigo) by standing up. For this reason will be explored also the mechanisms for orthostatic intolerance after that are responsible for immobilization period. An eventually impact of bed rest length on study-results is going to be discussed.

Differences in methodologies, selection of subjects, types of interventions as well as differences in protocols are also going to be discussed. When possible, the gender differences correlating to bed rest responses will be also investigated.

Based on the actually knowledge that physiological changes during bed rest immobilization occur also by space flight astronauts, I will discuss some papers that investigated the relationship between cardiovascular system and space flight. The results of these studies are going to be compared with bed rest studies and the similarities eventually differences are going to be elucidated.

The aim of this thesis is to update the existing literature correlated to bed rest immobilization and cardiovascular regulation. The knowledge gained from this work is particularly relevant for doctors working in the area of cardiology, immobilization, syncope as well as space flight research.

III. METHODOLOGY

The subject of my research was "Effects of Immobilization on the Cardiovascular System and Orthostatic Tolerance".

To get the relevant publications for my research, I made a searching strategy. At first I identified the essential subject by using keywords: **cardiovascular system, immobilization, orthostatic (in) tolerance**. Next I found the synonyms for my keywords: **"immobilization" synonym "bed rest", "cardiovascular system" synonym "circulatory system", "orthostatic tolerance" synonym "postural hypotension".**

At last I used MESH Database to find it out which of the above mentioned terms were represented in Pubmed.

Pubmed databases enabled me to find most of the publications relevant for my research.

To obtain my data from Pubmed, I used the strategy explored below.

Limiting criteria of my research- In order to limit my research criteria I use **AND** or **OR** or **NOT**. This way I focus on my interest field. To be concrete I take some examples: cardiovascular system AND Bed rest; cardiovascular system OR Orthostatic intolerance, Orthostatic Intolerance AND Immobilization. Also using quote (``) for the keywords found I helpfully in finding publications relevant to my topic.

Refining my search criteria- The above mentioned step gave me the opportunity to obtain many publications, but not all of them were relevant to my topic. To avoid the unnecessary studies I refined the criteria of my research. For this purpose I used the word **NOT** as filter: (Cardiovascular System NOT cardiovascular system, treatment) AND bed rest.

As second filter I defined the publication years of the researched articles (1950- 2014). Furthermore, I was interested on the articles written on English and/or Deutsch, therefore I defined the language of the publications as another refine search criteria.

The sources of my research- To explore my thesis, I used primarily **Pubmed database**. I found this database simple to use, up to data and I could find many publications related to my topic. As alternative to Pubmed, I used also **Web of Science database**. I found it particularly

good because you can see how many times a publication has been cited before. It serves as a filter to find out the most cited articles. Another tool of research that I found very helpful was **the list of References**. Sometimes the reference of one article was the publication relevant for my research. At last I used Internet (Google) particularly to find pictures and relevant Information for my Introduction.

Criteria for choosing my literature:

1. Articles relevant to my topic.
2. As primary literature I used Abstracts and full-text Articles.
3. Only the publications written in the last 64 years were explored.
4. As secondary literature I used Internet as well as Textbooks.
5. English and/or German publication were explored.

After literature search, I obtained 20 articles that were relevant for my thesis. Based on the time of bed rest period and the year of publication, I divided this articles into three groups:

1. The first group include the studies with a bed rest period of under 21 days. This articles offer different view perspectives of the relationship between cardiovascular system and immobilization based on the short term bed rest model.
2. Medium term bed rest studies include the studies with a bed rest period between 21 and 60 days.
3. The last group of studies examines the effects of prolonged bed rest (up to 60 days) on cardiovascular system. An eventually impact of bed rest length on study-results is going to be explored.

Furthermore, there are going to be discussed differences in methodologies, selection of subjects, types of interventions as well as differences in protocols. When possible, the gender differences correlating to bed rest will be also discussed.

Organizing and saving the References- I used **Refworks** to save and organize my references. I found it very useful, especially that I directly could import my references from the databases to my Refworks Account and from here to use these in my thesis.

IV. UPDATE OF THE LITERATURE

Based on my literature search, I obtained 20 articles that were relevant for my thesis.

Due to the time of bed rest period and the year of article publication, I divided this section of my thesis into three categories:

1. The first category include the studies that offer different view perspectives of the relationship between cardiovascular system and immobilization based on the short term bed rest model.
2. Medium term bed rest studies were also examine. Furthermore, an eventually impact of bed rest length on study-results is going to be explored.
3. The last category examines the effects of long term bed rest on cardiovascular system. The correlation to differences in methods, subject selection, intervention types and protocols will be also discussed.

4.1 Studies dealing primarily with short term bed rest period

Table 2: Short term bed rest studies; Legend: HDBR- head down bed rest; LBNP- lower body negative pressure; HDT- head down tilt; Ex- Exercises; ↑- increase; ↓- decrease; n- number of subjects; SV- stroke volume; LV- left ventricle; m- men; w- women;

Investigators	Subjects	Model	Time	Results
Levine B. et al 1997,24 mix	n=12	HDBR+LBNP	14 days	Distensible LV, ↓SV ↓Orthostatic tolerance
Bonnin 2001, 16m	n=8, bed rest group	HDBR	2x7 days	↑flow dependent vasodilation ↓Orthostatic tolerance
	n=8, control group (physical activity)	HDBR+ Physical activity		Non-significant
Bolea 2012, mix		HDBR	5 days	Impairment on ventricular repolarization
Nosova et al 2014,	n=5	HDBR	5 days	↑vascular inflammation ↓endothelial function

4m, 1w				↑arterial tonus&stiffnes ↓diastolic pressure
Jeong 2014, 21m	n=7, sedentary gr.	HDBR	18 days	↓transfer function gate Improved dynamic cerebral autoregulation
	n=14, exercise gr	HDBR+ Ex		↓transfer function gate Improved dynamic cerebral autoregulation
	.	Post HDT-infusion load		↑transfer function gate by sedentary group
Blaber	27 Astronauts	Standing test before and after space flight	10 min.	↓mean arterial pressure ↓cerebral blood flow
Norsk	Astronauts	Cardiovascular changes during space flight	2 weeks during and till 6months post flight	↓blood pressure 5-10mmHg ↓vascular resistance ↑CV, ↑SV Sympathetic activity high

Now let me discuss the above mentioned studies (Table 2) in detail.

Levine BD and his colleagues (37) hypothesized that the large fall in stroke volume after bed rest is a consequence of cardiac mechanic changes. They measured the mass of LV, end-diastolic volume of LV (LVEDV) and pressure of pulmonary capillars (PCWP). This parameters was followed for two weeks by 12 people (24+/-5 years), during LBNP, and two weeks pre- and post-6 degrees HDBR. Detailed information about differences before and after HDBR in the table below. As a result, 2 Weeks of HDBR led to LV distension and a shift of the P-V curve. This causes an excessive reduction of stroke volume during orthostasis which contributes to orthostatic intolerance.

Bonnin P and his colleagues (38) investigated the correlation between increased flow-dependent vasodilation after HDBR and orthostatic intolerance. For this study was used 16

voluntary men. Eight men was arranged into the control group and maintained its usual physical activity and eight men underwent two periods of 7 days HDBR (-6 degrees). Using echography and Doppler, the investigators measured blood flow velocity (BFV) and diameter of brachial artery. The results suggested an increase of flow-dependent vasodilation of large arteries after HDBR. As a conclusion, bed rest deconditioning enhances the flow-dependent vasodilation and may contribute to the orthostatic intolerance.

Bolea and his colleagues (39) explored the effects of microgravity on ventricular repolarization. Healthy adults underwent 5 days head down bed rest (HDBR). During the tilt table test were measured: QT to RR and QT (p) to RR hysteresis. Furthermore the differences between them have been explored. The results of the study suggested significant differences between QT and QTp before HDBR but not after it. Furthermore, different effect of HDBR on QT to RR and QTp to RR was evidenced. Based on the study results, impairment on ventricular repolarization dispersion due to HDBR has been suggested.

Nosova and her colleagues (40) investigated the effects of bed rest on cardiovascular system. They hypothesized that sedentary inactivity induce endothelial dysfunction, increase the vascular inflammation and lead to stiffness of the arteries. To prove their hypothesis, they took 5 healthy persons (4 men and 1 woman) those underwent 5 days of bed rest. They measured flow- mediated vasodilatation and applanation tonometry to investigate the vascular function. Furthermore they measured also the inflammation parameters. Isocaloric diet was applied for the period of inactivity.

The results suggested a decrease of the endothelial function, increase of the inflammation (15-hydroxyeicosatetraeonic acid was measured), decrease of the diastolic pressure and stiffing of the arteries. Based on the results, study- researchers speculate that physical inactivity encourages a vascular deconditioning state that leads to arterial stiffness and arterial tone increase.

Jeong and his colleagues (41) explored the effects of head down bed rest in brain circulation. 21 subjects took part on the study and they were organized in two groups. First group (sedentary group) included 7 participants which underwent 18 days bed rest. After bed rest the

participants became a volume infusion with dextran to restore reduced plasma volume. The second group (exercise group) included 14 participants who performed cycling HDBR. Furthermore, the exercise group is divided into two subgroups: the first subgroup became dextran infusion after HDBR. By the first subgroup was performed an infusion with dextran to load the volume (Ex+ Dex Group), while the second subgroup did not become the infusion. To estimate the cerebral dynamic autoregulation they analyzed transfer function changes in cerebral flow velocity and blood pressure. The results of the study suggested that after bed rest was reduced the gain of transfer function in both groups. As study conclusion came out that in both groups the dynamic cerebral auto regulation was improved or preserved after HDT bed rest. Furthermore, volume loading is shown to increase the transfer function gain leading to the suggestion that plasma volume changes are important for the dynamic cerebral autoregulation.

Blaber and his colleagues (42) explored the regulation of cerebral blood flow on astronauts before and after space flight. They hypothesized that there is a difference in cerebral autoregulation before and after flight by subjects that finished and the others that did not finished the stand test. 27 astronauts were included on the study, 19 of them finished the stand test while 8 did not. They were part of the shuttle mission which lasted 8- 16 days. The subjects underwent a 10 min stand test which is done 10 days before flight, 1-2 hours after landing and 3 days after landing. Parameters that were measured included: mean blood flow velocity of the middle cerebral artery (MCA), mean arterial pressure as well as cross spectral power, gain, phase, and coherence. The results of the study suggested that mean arterial pressure of the MCA was reduced by stand test. Differences between finishers and not finishers as well as over test days, were significant. The data taken before flight suggested a higher cerebral vasodilatation to the non-finishers compared with finishers. Furthermore is being evidenced that on the day of landing the non-finishers suggested a significantly decrease in cerebral mean blood flow velocity during stand test compared to finishers group. In this study is also evidenced an interaction effect of gender from supine to stand and over the days of study.

The study investigators concluded that their results indicate a mismatch of cerebral blood flow with blood pressure as cause of presyncope in astronauts. Furthermore, also the gender is suggested to be important in orthostatic intolerance after flight.

Norsk P (43) has written a review about the adaptive responses of cardiovascular system on the astronauts during space flight. Based on the data he explored, a reduction of brachial diastolic pressure by 5mmHg during the initial 2 weeks of space flight is being evidenced. Furthermore, from the first till the sixth month of flight, a blood pressure reduction of 10 mmHg has been found. At the same time systemic vascular resistance decreased, cardiac volume and stroke volume increased. These changes are found also on the persons being supine on the earth. During space flight the sympathetic activity nerves sympathetic activity is kept surprisingly high, similar to earth people seated upright. This result could not be predicted from simulation models thus indicating that the dilatation of arterial vessels during spaceflight is induced from another mechanism other than baroreflex induced sympathetic decrease. Furthermore explorations are needed to find the spaceflight mechanism that causes arterial dilatation, which can explain the high sympathetic activity, associated cardiovascular changes and blood pressure decrease.

4.2 Studies dealing primarily with medium term bed rest period

Table 3: Medium term bed rest studies; *Legend:* HDBR- head down bed rest; LBNP- lower body negative pressure; Ex- Exercises; ↑- increase; ↓- decrease; n- number of subjects; SV- stroke volume; LV- left ventricle; HR- heart rate; m- men; w- women; PEPi – pre-ejection period; PVR- peripheral vascular resistance; RR- Riva Rocci; NOEX- No exercises;

Investigators	Subjects	Model	Time	Results
Traon 1998, 7m	n=7	HDBR (Stand+LBNP)	42 days	↓vasomotor response ↑HR, ↓RR
Edgell H. et al 2007, 24w	n=8, control group n=8, nutrit. group n=8, exercise gr.	HDBR HDBR+ Nutrition HDBR+ Ex	56 days	↑HR, ↓SV, ↓PVR ↑HR, ↓SV, ↓PVR Non-significant
Hodges G. et al	n=7, control group	HDBR	56 days	↑PEPi

2010, f	n=7, exercise gr.	HDBR+ Ex		↑PEPi (less significant)
Carrick R. et al 2013, 24m, 3w	n=9, NOEX group n=18, EX group	HDBR+LBNP HDBR+LBNP+Ex	35 days	↓SV, ↓LV-filling ↓SV, ↓LV-filling (less significant)

Now let me discuss the above mentioned studies (Table 3) in detail.

Traon AP and his colleagues (44) explored the cardiovascular responses to orthostatic tests through an experiment with seven men participants and 42 days of HDBR (-6 degrees). In this experiment they simulated a long duration space flight. The subjects underwent stand tests and LBNP test. To measure the autonomic nervous system responses they analyzed heart rate and spontaneous baroreflex responses. The investigators found out that standing and LBNP tests induced a higher heart rate and a reduction of blood pressure related to reduction of vasomotor activity. Changes on the autonomic nervous system changes found in this study are related to the orthostatic intolerance, common by people undergoing bed rest and by astronauts after space flight.

Edgell H. and his colleagues (45) investigated the effects of 6 degrees HDBR in stimulation of adrenergic receptor and its effects on cardiovascular response. They also explored the effect of exercise to gain these changes. In this study took part 24 females, organized in these groups: control group, exercisers group and a nutrition supplement group (no exercise). HDBR elevated heart rate and d stroke volume in the control and nutrition groups, but it doesn't effect this parameters in the exercise group. Leg vascular resistance was reduced in control and nutrition group but greater in the exercise group. There happened changes in total peripheral vascular resistance (PVR) but at lower intensity. As a result the HDBR cased a reduced PVR, but no changes in sensitivity of response of PVR to adrenergic stimulation. Exercise was effective against HDBR effects.

Hodges, G J and his colleagues (46) tested if head down bed rest affects the relationship between left ventricular depolarization to the pre-ejection period (PEPi). There was also explored the effect of exercises in this process. In this study was followed fourteen women for

56 days of HDBR. The members of this study was divided into a Control (non-exercise) and Exercise (exercise) group, each group with 7 members.

The values of ECG and stroke volume before and after HDBR period told that there was an increase of PEPi after HDBR, especially in the group of control. But the HDBR period had no effect in the QRS interval and cardiac afterload.

Isoprenaline infusion reversed the HDBR-induced delay in the PEPi.

As a result HDBR cases a delay on systolic ejection onset. Because the low-dose Isoprenaline infusion reversed this PEPi delay appears that the mechanism of delayed onset of systole following HDBR is a consequence of the contraction of the LV and not of LV-depolarization.

Carrick Ranson and his colleagues (47) investigated the causes of upright stroke volume reduction leading to orthostatic intolerance after bed rest exposure. The core issue of the study was to find out if the diastolic filling and slow relaxation of left ventricle (LV) induce stroke volume reduction or does the exercise training while in bed contribute to these changes. To investigate this they took 27 healthy adults (24 men and 3 women) that underwent 5 weeks 6 degree head down bed rest (6° HDBR). They divided the participant into two groups: 18 of them performed near daily ergometry (EX Group) while the other 9 lied passive on bed (NOEX Group). To define the LV function they measured: mass of left ventricle, left ventricular end diastolic volume (LVEDV), pressure of pulmonary capillary, stroke volume and Doppler measures. These data were collected before and after HDBR, during bed rest, during LV filling (used saline infusion) and during decreased LV loading (used LBNP system).

The study results suggested that reduction of stroke volume (SV) as well as of left ventricular end diastolic volume (LVEDV) during bed rest and LBNP were greater by the non-exercise group compared with EX group after HDBR. By the EX group reduction was less prominent or unaltered. Furthermore, Doppler ultrasound measures during left ventricular unloading by LBNP after HDBR did not change significantly in either of the groups. During saline infusion all the variables restores to pre- HDBR level on both groups. The investigators found out that Doppler variables of dynamic left ventricular filling after HDBR were significantly reduced on both groups. These changes were prominently by the NOEX group compared with EX group. As study conclusion came out that upright stroke volume reduction after HDBR is much more

affected from changes in left ventricular loading conditions rather than diastolic suction and ventricular relaxation.

4.3 Studies dealing primarily with prolonged term bed rest period

Table 4: Long term bed rest studies; *Legend:* HDBR- head down bed rest; LBNP- lower body negative pressure; Ex- Exercises, ↑- increase, ↓- decrease, n- number of subjects; SV- stroke volume; LV- left ventricle; HR- heart rate; m- men; w- women; PEPi – preejection period; PVR- peripheral vascular resistance; RR- Riva Rocci; NOEX- No exercises; TYP- Taikong Zangxin Prescription; EF- ejection fraction; CM- Chinese medicine; CPFR- cardiopulmonary functional reserve; CMA- cerebral arterial flow velocity; CAR- cardiac adrenergic receptors; CC- cardiac contractility; CO- cardiac output; VO_2max- maximal oxygen consumption; RVE- resistive vibration exercise;

Investigators	Subjects	Model	Time	Results
Convertino V. et al (l. review) 1997		HDBR		↓SV, ↓CO, ↓ VO_{2max} ↑norepinephrine release ↑sensitivity of CAR ↑CC
Perhonen M. et al 2001, 5m	n=2 n=3 n=4 Astronauts	HDBR HDBR Space flight	42 days 84 days 10 days	Cardiac atrophy Cardiac atrophy Cardiac atrophy
Hughson et al 2007, 24w	n=12, non-exer. gr. n=12, exercise gr.	HDBR HDBR+ Ex	60 days	↑HR, ↓SV, Non-significant ↓Orthostatic tolerance
Ferretti 2009, 7 mix	n=17	HDBR	90 days	↓Cardiovagal activity ↓vascular sympathetic act. ↓HR, ↓RR
Yuan M. et al 2012, 21m	n=7, control group n=7, RVE group n=7, Herb group	HDBR HDBR+ Ex HDBR+ Herb	60 days	↑Vasodilation, ↑CMA ↑Vasodilation(less significant) ↑Vasodilation(less significant)

Arbeille (n=24) 2012, 24w	n=8, control group n=8, exercise group n=8, nutrition group	HDBR+LBNP HDBR+LBNP HDBR+LBNP+ Nutrition	60 days	↓Orthostatic tolerance Ex. preserved cardiovascular changes
Shi H.Z. et al 2014, m	n=7, control group n=7, CM group	HDBR HDBR + TYP	60 days	↑HR, ↓EF, ↓SV, ↓CPFR Non-significant
Convertino	Astronauts			↑HR, ↓SV, ↑Vasoconstriction ↑preload ↑Orhtostatic intolerance

Now let me discuss the above mentioned studies (Table 3) in detail.

Convertino, Victor A. and colleagues (28) by a literature review found out that there is a range of changes in cardiovascular system that can contribute to maintenance of $VO_{2max.}$ They made a distinction between central (cardiac) and peripheral consequences of bed rest.

The data suggest that due to bed rest comes to elevated norepinephrine release and elevated sensitivity of cardiac adrenergic receptors (CAR). These can be responsible for increased heart rate and increased cardiac contraction after bed rest. Despite these increased parameters, the stroke volume and in turn the maximal cardiac output are clearly reduced. Because the cardiac contractility (CC) is increased, the increased stroke volume appears to be a result of decreased cardiac filling, caused by decreased blood volume and central venous pressure. The consequence of these central mechanisms together with peripheral mechanisms such as: reduced red cell mass and muscle blood flow during physical inactivity, is the reduction of $VO_{2max.}$

Perhonen MA and her colleagues (48) tested the hypothesis that heart muscle atrophy after bed rest or spaceflight is an adaptation to loading conditions. Five healthy men underwent bed rest for 6 weeks and 3 of them completed 12 weeks of bed rest. Left and right ventricle mass as well as end diastolic volume were measured with the help of magnetic resonance imaging (MRI). In the study was tested also four Astronauts during 10 days of spaceflight. As a result

there was determined a cardiac atrophy by all of the members in this study. The authors suggested that this is a physiological adaptation of the heart to reduced myocardial load and demonstrates the plasticity of cardiac muscle.

Hughson RL and his colleagues (49) studied vascular responses to 60 days of bed rest in 24 woman volunteers. They were divided into an exercise and non-exercise group to find out if exercises are effective against bed rest consequences. They made a series of experiments and used drugs such as nitroglycerin and isoproterenol to stimulate responses.
Finally, they found a higher heart rate in the non-exercise group after HDBR, associated with lower stroke volume. The diameter of the leg arteries was reduced in non-exercise group. These changes in cardiovascular system contribute to orthostatic intolerance after HDBR.

Ferretti G. and his colleagues (50) tested if head down bed rest induce impairments in autonomic cardiovascular regulation. Seventeen healthy volunteers underwent for 90 days -6 degrees HDBR. As a measure of baroreceptor reflex activity, vascular sympathetic control, heart rate and blood pressure, they analyzed the efferent muscle sympathetic nerve activity. The data were obtained through noninvasive techniques in rest and simple activities like: moderate handgrip, LBNP and active standing. Their results suggested that inactivity in subjects (-6 degree HDBR) reduced cardio-vagal and vascular sympathetic activity. It also reduced the blood pressure and heart rate.

Yuan M. and his colleagues (51) quantified the peripheral arterial and venous response to 60 days of HDBR. In the study took part 21 males divided into three groups each with 7 subjects: control group, resistive vibration exercise group and Chinese Herb group.
Using echography and Doppler ultrasonography, they measured different parameters of arteries and veins in the subjects before and after HDBR. Arterial and venous parameters were measured 3 minutes before tilt and 1 minute after tilt.
Results suggested a vasodilation leading to significantly increased flow velocity of middle cerebral artery after 60 days of HDBR. Furthermore, resistive vibration exercise and Chinese herb helped against vasodilation in this areas, whereby RVE was more effective.

Arbeille and his colleagues (52) explored the arterial flow velocity and calf vein flow during orthostatic intolerance test after 60 days 6°HDBR. The structures that were assessed included: Cerebral, Femoral and Aortic arterial flow as well as Tibial and Gastrocnemius vein section. Echography and Doppler were used to assess the vessel flow. In the study were included 24 healthy women. They were divided in 3 groups: control group (Con), exercise group against LBNP (Ex-LBNP) and nutrition group (Nut). Before and after HDBR all participants underwent a 10 min 80° tilt. After that, followed a LBNP till presyncope. 13 participants could not finish the experiment because they developed presyncope symptoms, while the rest participants finished it. The majority of the persons that did not finish the experiment suggested a decrease on aortal flow, distension of Tibia vein and a lack of increase of Cerebral/Femoral ratio after HDBR+LBNP correlated to orthostatic intolerance. These abnormal changes were more evident in Control and Nutrition Groups compared with Exercise Group.

Their study suggests that HDBR did not impact the cardiovascular changes to orthostatic stress to the same extent in each participant. Furthermore, exercises within LBNP appear to preserve the cardiovascular changes to tilt; nutritional intervention alone is not enough. Aortic and cerebral/femoral ratio flows were most closely related to orthostatic intolerance.

Shi HZ and his colleagues (53) explored the changes in cardiopulmonary function induced by 6 degrees head down bed rest (HDBR) and the effects of Taikong Zangxin Prescription (TYP) as a countermeasure. Fourteen healthy males took part in the study. They were randomly divided into two groups (control group and Chinese medicine group) with seven members and both groups underwent 6 degrees head down bed rest for 60 days. The members of control group received daily placebo pills and the members of Chinese medicine (CM) group received TYP. Before and during the study was evaluated the heart rate, cardiopulmonary functional reserve and exercise capacity. Their results suggested that the heart rate (HR) increased gradually during HDBR in the control group ($P < 0.05$) but not in the CM group. The ejection fraction (EF), stroke volume (SV), stroke volume index (SVI) and left ventricular fractional shortening decreased over time in control group but not in the CM group. As a conclusion there was a distinct reduction in cardiac systolic and pumping functions as well as in cardiopulmonary functional reserve and exercise capacity for 60 days of 6 degrees HDBR in

the control group. The TYP improved significantly the cardiac and pumping functions in the CM group. It appears that some traditional Chinese Medicines may indeed have important countermeasure function. Relevant to my thesis are the results of control group, which underwent 60 days of -6degrees HDBR. In this group was reported a gradual increase in heart rate, reduced cardiopulmonary functional (CPFR) reserve and reduced exercise capacity.

Convertino (54) wrote another review that explored the adaptation of cardiovascular system to spaceflight. He underlined the fact that astronauts immediately after return from spaceflight develop an orthostatic hypotension. This process is supposed to be caused from reduction of stroke volume and lower reserve to increase the resistance of periphery vascular vessels. As consequence, the systemic blood pressure cannot be maintained despite heart rate increases. Furthermore, hypo-reactivity of receptors that control smooth muscles of arteries was suggested to impact the inadequate vasoconstriction while reduction in preload appears to cause the stroke volume reduction. Based on systematic evaluations, Convertino underlined also the importance of acute physical exercise as countermeasures against orthostatic hypotension. Moreover, he suggested that the pharmacological agents which target and restore blood volume as well as increase vasoconstriction reserve should be the focus for furthermore explorations of countermeasures against astronauts orthostatic intolerance.

V. SUMMARY

Bed rest immobilization has been suggested to affect cardiovascular system. Based on the explored studies in my thesis, there appears to be an impact of bed rest immobilization on the cardiovascular system and orthostatic tolerance.

Studies dealing with short-term bed rest reported significant changes of the vascular wall, such as: decrease of endothelial function, increase of the inflammation as well as stiffing of the arteries by subjects underwent HDBR. Based on these results appears that physical inactivity encourages a vascular deconditioning. Furthermore, these studies evidenced also a reduction of stroke volume during orthostasis, which contribute to development of orthostatic intolerance.

Studies dealing with medium term bed rest based on HDBR model reported an increase in heart rate and decrease in blood pressure by Standing and LBNP tests. This effects are suggested to be caused from reduced vasomotor response. Moreover, HDBR induced also reduction of the total peripheral vascular resistance and delayed onset of systolic ejection that relates on the impairment of LV contraction. Evident was also an upright stroke volume reduction caused primarily from a decrease in LV loading.

Studies dealing with long term bed rest reported an increase in heart rate and cardiac contraction. These changes are suggested to come from an elevated norepinephrine release as well as elevated sensitivity of cardiac adrenergic receptors. Otherwise, stroke volume and cardiac output are reduced. There was evidenced also a cardiac atrophy as a physiological adaptation to reduced myocardial load demonstrating in this way the plasticity of cardiac muscle.

In summary, the articles explored in my thesis suggest that bed rest immobilization induces cardiovascular changes, which contribute to the development of orthostatic intolerance. As counteracting mechanisms, exercises appear to be effective in reducing the physical inactivity changes as well as orthostatic symptoms. Similar changes were reported by astronauts, therefore the knowledge gained from this work is relevant also in the area of space flight research.

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