

Diplomarbeit

**Cardiovascular Control During Tilt-Table Testing in Patients
with Histories of Syncope: Case Studies**

eingereicht von

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zur Erlangung des akademischen Grades

**Doktor(in) der gesamten Heilkunde
(Dr. med. univ.)**

an der

Medizinischen Universität Graz

ausgeführt am

Institut für Physiologie

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Declaration

I hereby declare that I have authored this thesis independently, that I have not used other than the declared sources/resources, and that I have explicitly marked all material that has been quoted either literally or by content from the used sources.

Graz, February 15th, 2018

Laura Lunzer eh.

Acknowledgements

First of all, I would like to thank my supervisor Prof. Priv.-Doz. Dr. med. Nandu Goswami for his support throughout the thesis work. Furthermore, I would like to thank my co-supervisor Prim. Dr. Giorgio Giacomini and the team of the LKH Knittelfeld for their provision of the data and their support.

Special thanks go to my parents, my sister, and my aunts.

Abstract

Background: Orthostatic dysregulation is a very common problem, especially in older people and young women. The orthostatic dysregulation/syncope is a dysregulation/syncope caused by a malfunction of the orthostatic reaction. In healthy people, the orthostatic reaction ensures that the cardiovascular system works correctly in an upright position. In the case of a deficient regulation, the orthostatic regulation does not work as it should after standing up, and orthostatic dysregulation occurs. The symptoms of orthostatic dysregulation appear after a rapid change in position, especially from that of lying down to standing up. These complaints force those affected to sit or lie down. In some cases, syncope may also occur. [2]

Aims and objectives: This diploma thesis aims to examine the physiology of cardiovascular regulation and the physiology of orthostatic dysregulation as well as its diagnosis and therapy. Furthermore, this diploma thesis provides a brief insight into the most common differential diagnoses of orthostatic dysregulation.

Methodology: The data presented here are from LKH Knittelfeld, where tilt-table testing was performed to diagnose an orthostatic intolerance. Due to the Data Protection Act and patient confidentiality, only two patients (one with orthostatic intolerance and one without) were included in this thesis. They both underwent tilt-table testing for a diagnosis. The haemodynamic data were measured using a Task Force Monitor (CNSystems, Graz).

Results: Both patients were males and above 80 years of age. One of these patients had a positive tilt test and was therefore diagnosed with orthostatic intolerance, while the other had a negative tilt test. The patient suffering from tilt-table-induced syncope experienced a decrease in the systolic blood pressure (from about 152 mmHg to 110 mmHg) at the beginning of the tilt test. Simultaneously, the heart rate increased slightly. Eighteen minutes after the passive head-up tilt was started, the systolic blood pressure decreased to 75mmHg. At this point, the heart rate decreased as well, and the patient experienced syncope. In comparison, the patient without orthostatic intolerance (i.e. whose tilt test was negative) had quite a constant blood pressure and heart rate throughout the test.

Discussion: The data showed the differences in cardiovascular responses between the patient who experienced syncope during tilt-table-testing and the patient who did not. These case studies show that the compensatory mechanisms involved in blood-pressure regulation during tilt-table testing are inappropriate in persons with a positive tilt test. In addition to ageing, several factors increase the risk of orthostatic intolerance. While the case studies presented here are only based on two patients, the strength of this study lies in that differences can be seen in the cardiovascular response between persons suffering from and not suffering from orthostatic intolerance during tilt-table testing even when only examining two patients. This study can be used as a base for future studies in which a larger number of patients could be assessed during tilt-table testing, particularly to understand the underlying mechanisms that predispose some patients to syncope but not others.

Zusammenfassung

Hintergrund: Orthostatische Dysregulation ist ein sehr häufiges Problem, insbesondere bei älteren Menschen und jungen Frauen. Die orthostatische Dysregulation/Synkope ist eine Dysregulation/Synkope, die durch eine Fehlfunktion der Orthostase-Reaktion verursacht wird. Die Orthostase-Reaktion sorgt bei gesunden Menschen dafür, dass das Herz-Kreislauf-System in aufrechter Haltung einwandfrei funktioniert. Im Falle einer Fehlregulation nach dem Aufstehen funktioniert die Orthostase-Reaktion nicht wie sie sollte, und orthostatische Dysregulation tritt ein. Die Symptome der orthostatischen Dysregulation treten nach einem schnellen Wechsel der Position auf, insbesondere vom Liegen zum Stehen. Diese Beschwerden zwingen die Betroffenen zum Sitzen oder Liegen. In manchen Fällen kann auch eine Synkope auftreten. [2]

Zielsetzung: Das Ziel dieser Diplomarbeit ist es, die Physiologie der kardiovaskulären Regulation und die Physiologie der Orthostase-Intoleranz sowie ihre Diagnostik und Therapie zu erforschen. Des Weiteren gibt diese Diplomarbeit eine Übersicht über die häufigsten Differentialdiagnosen der orthostatischen Dysregulation.

Methodik: Die hier angeführten Daten stammen vom LKH Knittelfeld, wo Kipptisch-Tests durchgeführt wurden, um eine Orthostase-Intoleranz zu diagnostizieren. Aufgrund des Datenschutzgesetzes und der Patientenvertraulichkeit wurden in diese Studie nur zwei Patienten eingeschlossen (einer mit Orthostase-Intoleranz und einer ohne). Beide wurden einer Kipptischuntersuchung unterzogen. Die hämodynamischen Daten wurden mit einem Task Force Monitor gemessen (CNSystems, Graz).

Ergebnisse: Beide Patienten waren männlich und über 80 Jahre alt. Einer der beiden Patienten hatte eine positive Kipptisch-Untersuchung und daher wurde bei ihm eine orthostatische Dysregulation diagnostiziert, während der andere Patient eine negative Kipptisch-Untersuchung hatte. Es hat sich gezeigt, dass der Patient mit Orthostase-Intoleranz zu Beginn der Untersuchung eine Abnahme des systolischen Blutdrucks (von etwa 152 mmHg auf 110 mmHg) erfuhr. Gleichzeitig nahm die Herzfrequenz leicht zu. 18 Minuten nach Beginn der passiven Aufwärtsskipung sank der systolische Blutdruck auf 75 mmHg. An diesem Punkt nahm auch die Herzfrequenz ab und der Patient erlitt eine

Synkope. Im Vergleich dazu hatte der Patient ohne Orthostase-Intoleranz über die Zeit der Untersuchung hinweg einen konstanten Blutdruck und eine konstante Herzfrequenz.

Diskussion: Die Daten wiesen die Unterschiede in der kardiovaskulären Regulation bei einem Patienten, bei dem eine Synkope während des Kipptischtests auftrat, im Vergleich zu einem Patienten, bei dem keine auftrat, auf. Diese Fallstudie zeigt, dass die kompensatorischen Mechanismen, die bei der Blutdruckregulierung während des Kipptischtests beteiligt sind, bei Personen mit positivem Kipptischtest fehlreguliert sind. Es ist zu beachten, dass es mehrere Ursachen gibt, die das Risiko einer Orthostase-Intoleranz mit dem Alter erhöhen können. Während die hier vorgestellten Fallstudien nur von zwei Patienten stammen, liegt die Stärke dieser Studie darin, dass Unterschiede beobachtet werden können in der kardiovaskulären Regulation zwischen Personen, die an orthostatischer Intoleranz leiden, und solchen, die während der Kipptischuntersuchung nicht darunter leiden. Diese Studie kann als Grundlage für die Planung zukünftiger Studien herangezogen werden, in denen eine größere Anzahl von Patientinnen und Patienten einer Kipptischuntersuchung unterzogen werden könnten, insbesondere, um die zugrundeliegenden Mechanismen zu verstehen, die einige Patientinnen und Patienten zur Synkope prädisponieren und andere nicht.

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List of Abbreviations

mmHg	millimetre of mercury
CO	cardiac output
SVR	systemic vascular resistance
CVP	central venous pressure
CPR	cerebral perfusion pressure
TPR	total peripheral resistance
PVR	pulmonary vascular resistance
ANS	autonomic nervous system
Ach	acetylcholine
NO	nitric oxide
EDHF	endothelium-derived-hyperpolarizing factor
ACE	angiotensin-converting enzyme
ANP	atrial natriuretic peptide
ECG	electrocardiogram
ICD	implantable cardioverter-defibrillator
POTS	postural orthostatic tachycardia syndrome
HUTT	head up tilt test
CNAP	continuous non-invasive arterial pressure
HDL	high-density lipoprotein
LDL	low-density lipoprotein
TIA	transient ischemic attack

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1 Introduction

1.1 Cardiovascular Regulation

1.1.1 Regulation of blood pressure

1.1.1.1 Short-term regulation

Blood pressure is defined as the pressure of the circulating blood on the walls of the blood vessels. Usually, the term blood pressure is used for the pressure present in the large arteries of the circulatory system. Normally, it is defined as systolic and diastolic pressure and is measured in mmHg. The normal value is about 120/80 mmHg. Blood pressure that is lower than the normal value is called hypotension, and blood pressure that is higher than the normal value is called hypertension. Long-term hypertension is a risk factor for many diseases, e.g. heart attack or metabolic syndrome. It is more frequent than long-term hypotension. There is a whole range of factors which influence the arterial blood pressure, such as cardiac output, total peripheral resistance, arterial stiffness, emotional state, and physical activity. The mean arterial pressure describes the average blood pressure. It is defined as: $MAP = (CO \times SVR) + CVP$

If cardiac output increases due to an increase in heart rate or stroke volume, the mean arterial pressure will also increase if the vascular resistance stays the same. On the other hand, if the cardiac output decreases, the mean arterial pressure will also decrease if the vascular resistance remains the same. The measurement of mean arterial pressure is very important in estimating organ perfusion, e.g. in patients with sepsis or under treatment with catecholamines. Furthermore, it is necessary for calculating the cerebral perfusion pressure (CPR).

Central venous pressure is defined as the pressure in the vena cava. It is a value used to estimate the blood returning to the heart and the ability of the right heart to pump blood into the arterial system. The central venous pressure is measured using a central venous catheter. Normally, the pressure lies between 0-9 mmHg. It is used to determine the central venous oxygenation. As an indicator for an intravascular volume state, it is obsolete nowadays.

Vascular resistance is the resistance that the blood must overcome to create a flow. Systemic vascular resistance (SVR) is the vascular resistance generated by the systemic circulation. It is also called total peripheral resistance (TPR). Pulmonary vascular resistance (PVR) is the vascular resistance generated by the pulmonary circulation. Systemic vascular resistance is used for the measurement of blood pressure, cardiac function, and blood flow.

$$SVR = 80 \times (MAP - MVP \text{ or } CVP) : CO$$

Factors that impact vascular resistance are the vascular compliance determined by muscle tone, hormones, and cell signalling molecules, which induce vasodilatation or vasoconstriction. When a vasoconstriction occurs, the systemic vascular resistance increases, and when a vasodilatation occurs, the systemic vascular resistance decreases.

Cardiac output is the blood volume pumped by the heart per time unit. Mostly, it is represented in L/min. The cardiac output is an important indicator of whether the heart can deliver enough blood to the different parts of the body. A reduced cardiac output is an indicator of a reduced pumping function of the heart, a disease in the heart's valves, or hypothyroidism. An increased cardiac output is an indicator of fever, hyperthyroidism, anaemia, septic shock, or pregnancy.

$$Cardiac\ output = stroke\ volume \times heart\ rate$$

The stroke volume and thus, the cardiac output is mainly affected by the preload and afterload. The volume in the atria at the end of the diastole is defined as the preload. The preload can be affected by various causes. Important factors that change preload are the heart rate and the hydration status. If the heart rate becomes faster, the atria do not have that much time to fill, and the preload becomes less. The stroke volume increases when the blood volume increases. A greater amount of blood stretches the heart walls and leads to an increased contraction of the heart. Therefore, more blood gets pumped through the aorta. This mechanism is known as the Frank-Starling mechanism.

Afterload is defined as how much pressure the heart must build up to eject the blood at the systole. It is mainly influenced by the vascular resistance. A stenosis of the heart valves can influence afterload, too, because then, the heart must generate a higher pressure for ejecting the blood.

Other factors that influence the stroke volume are the heart size, the fitness level, gender, the contractility, and the duration of contraction (**Figure 1**, below). There are also many drugs that change the contraction. Positive inotropes, for example, are high blood calcium and drugs such as Digoxin. Negative inotropes, for example, are high blood potassium, acidosis, hypoxia, and drugs such as beta blockers and calcium-channel blockers. Factors that have an impact on the heart rate are autonomic nervous innervation, hormones, the fitness level, and age. Sympathetic innervation influences the heart in a positive ionotropic way, and parasympathetic innervation in a negative one.

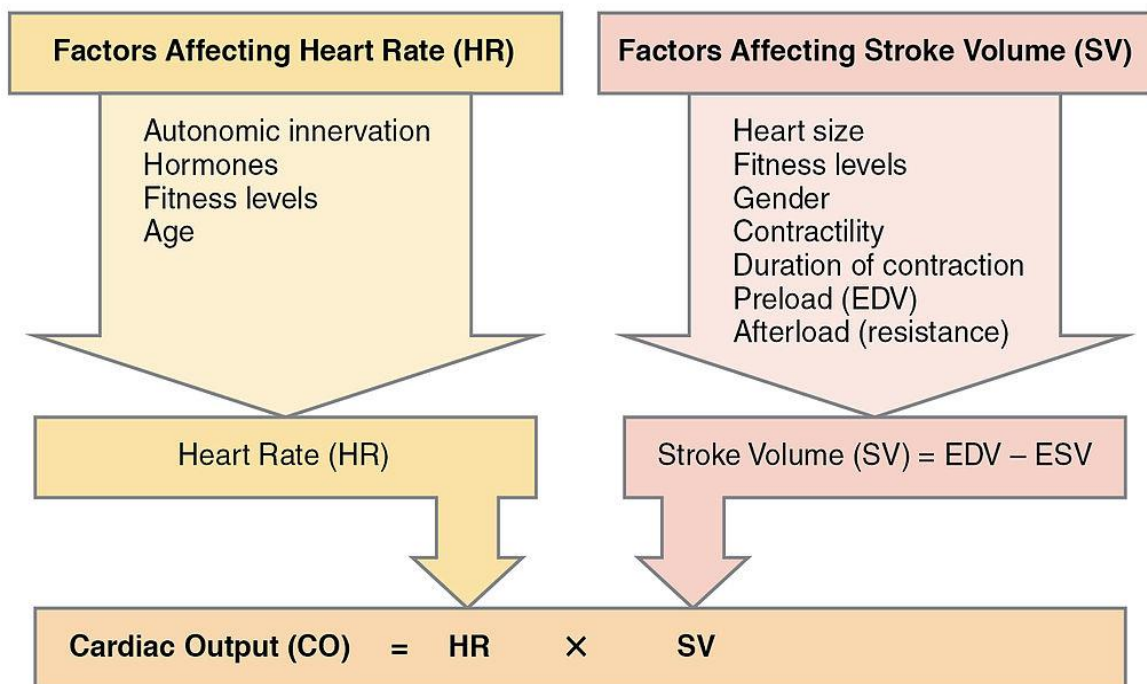


Figure 1: **Factors influencing the cardiac output.** Source:

https://en.wikipedia.org/wiki/Cardiac_output#/media/File:2031_Factors_in%20Cardiac_Output.jpg

Autonomic nervous regulation of the heart and vasculature

The capacity of the heart must adapt to short-term volume- and pressure fluctuations as well as to the requirements of the supplying tissue. The normal blood volume ejected at rest is approximately 5-6 l/minute, but under stress, it can increase up to 25 l/minute.

The heart function can be regulated by the following mechanisms:

1. the Frank-Starling mechanism
2. the autonomic nervous system (parasympathetic and sympathetic nervous system)

The Frank-Starling mechanism is a mechanism which enables the heart to adapt its activity for a short time to an increased end-diastolic filling volume (increased preload) as well as to an increased mean aortic pressure (increased afterload). An increase of the venous return, e.g. by higher muscular activity, increases the amount of blood back flowing to the right ventricle. Therefore, the end-diastolic filling volume in the left ventricle, too, increases. By the higher filling volume, the heart becomes more stretched, which is denoted as the preload. This mechanism leads to an increase in the stroke volume. By the Frank-Starling mechanism, the heart can react to an increased ejection resistance (afterload). If the mean aortic pressure increases (e.g. through hypertonia), primarily, the heart can only eject a decreased stroke volume, and therefore, more of a rest volume stays in the ventricles. The next time the ventricles fill, the preload increases because of the rest volume and, therefore, also the stroke volume increases to its normal value.

Sympathetic and parasympathetic nervous system

The normal heart rate is influenced by several factors. One of the most important factors is the autonomic nervous system which has sympathetic and parasympathetic nerves. The sympathetic nervous system increases the heart rate, and the parasympathetic nervous system decreases it. Apart from the heart rate, the autonomic nervous system regulates body functions such as digestion, vasomotor activity, respiratory rate, pupillary response, urination, and sexual arousal. The sympathetic nervous system of the ANS answers with quick responses; therefore, it is often called a “fight or flight system“, while the parasympathetic system does not react so quickly. The parasympathetic system is often called the “rest and digest system”.

The main functions of the sympathetic nervous system are vasoconstriction, the increase in the blood flow through lungs and skeletal muscles, the increase in heart rate and cardiac cells contractility, the dilatation of the bronchioles in the lung, the vasodilatation of the coronary vessels of the heart, the constriction of the intestinal sphincters, the stimulation of orgasm, the inhibition of peristalsis, and the dilatation of the pupils.

Most of all, noradrenaline acts as a neurotransmitter. Neuropeptide Y is also implicated, but its role is not so important. It works as a positive inotrope (the contractility of the heart increases), as positive chronotropic (the heart frequency increases), as positive dromotropic

(transition time at AV-node increases), and as positive lusitropic (the relaxation time of the working myocardium increases).

On the other hand, the parasympathetic system oversees the dilatation of the blood vessels leading into the gastrointestinal tract, the constriction of the bronchioles in the lung, the constriction of the pupils, the stimulation of salivary glands, and the decrease of the heart rate.

The parasympathetic nervous system innervates through the vagus nerve and its rami cardiac cervicis and thoracis the sinus node, the AV-node, and the atria. Acetylcholine (Ach) acts as a neurotransmitter. A parasympathetic nervous system regulation of the ventricles is also possible, but its role is not of significance. It acts as a negative inotrope, negatively chronotropic, and as a negative dromotrope.

In the atria of the heart, there are mechanoreceptors. A-sensors register the muscle tension, and B-sensors respond to the passive stretching of the heart. The activation of the A- and B-sensors leads to an inactivation of the sympathetic nervous system and an activation of the parasympathetic nervous system via sensoric afferences, which together with the vagus nerve, strain the sympathetic and parasympathetic nuclei of the central nervous system.

Receptors influencing the cardiovascular control

The cardiovascular system has its own receptors that help to regulate and sustain the blood flow. These receptors are the baroreceptors, volume receptors, and chemoreceptors. The baroreceptors are in the aortic sinus, carotid bodies, the venae cava, the pulmonary vessels, and the right side of the heart (**Figure 2**, below).

If there is an increase in the pressure and stretch, the baroreceptors transmit this information through the vagus nerve and the glossopharyngeal nerve to the central nervous system (cardiovascular centre located in the medulla oblongata). Immediately, the activity of the parasympathetic nervous system increases. At the same time, the sympathetic nervous system activity decreases. This leads to a decrease in the heart rate, the tonus of the blood vessels, and the total peripheral resistance. The capacity vessels can take more blood and therefore blood volume, and the stroke volume decrease. Altogether, this mechanism leads to a decrease in the blood pressure.

During the transition from a lying position to a standing one (orthostasis), approximately 500ml of blood shifts into the legs. Primarily the preload and, therefore, the stroke volume and the blood pressure decrease. Within 1-2 seconds, the following reflex starts: The

decreased impulse frequency of the baroreceptors leads to an increase in activity of the sympathetic nervous system and a decrease in the parasympathetic nervous system activity. This leads to an increase in heart rate, contractility of the heart, and total peripheral resistance. By the contraction of the capacity vessel, the preload and, therefore, the stroke volume increases again. All these mechanisms lead to a very rapid increase in the blood pressure, which is very important to ensure the perfusion of the brain and thus avoiding syncope.

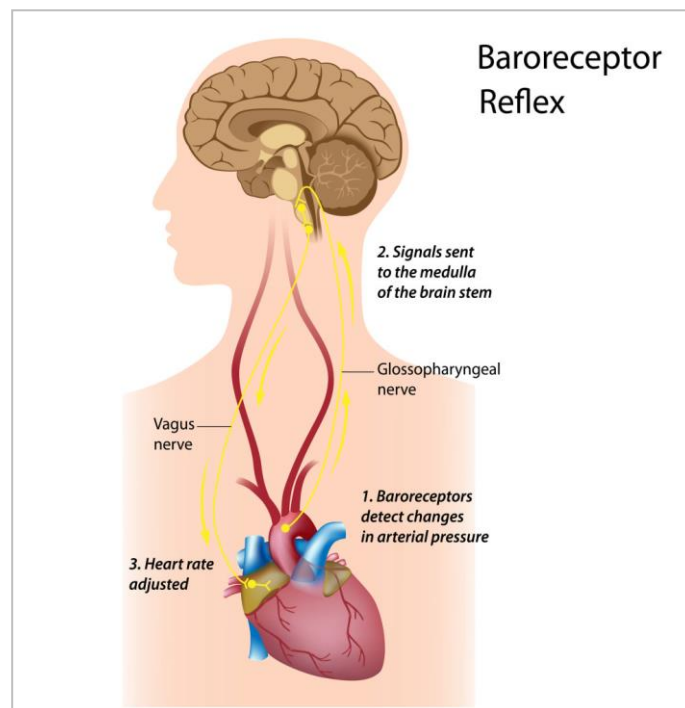


Figure 2: **The Baroreceptor reflex.** Source:
<http://forflyttningsorgan.malenlis.ru/baroreceptors/>

Chemoreceptors

There are two types of chemoreceptors, the peripheral and the central. The central chemoreceptors are located in the medulla oblongata, and their function is to detect changes in the pH of the cerebrospinal fluid. The peripheral receptors are located in the aorta (aortic body) and carotid sinuous (carotid body). The carotid receptors detect changes in the partial pressure of blood oxygen, the partial pressure of carbon dioxide, and the pH, while the aortic receptors only detect changes in the partial pressure of blood oxygen and the partial pressure of carbon dioxide. When they detect such changes, they send the

information to the medulla oblongata to regulate the breathing. Furthermore, they stimulate the sympathetic nervous system to increase the heart rate and the heart minute-volume.

Local metabolic regulation mechanisms for organ circulation

Local mechanisms are mechanisms within the organs for regulating the circulation. The concentration of different metabolism-influencing factors is measured, such as PO₂, Pco₂, K⁺, HPO₄²⁻, ADP, AMP, or adenosine. By adapting perfusion, it is possible to remove or to deliver substances. As a result, the chemical environment of the cells can be ensured.

A vasodilatation and, therefore, an increased perfusion result in:

1. an increase in PCO₂, lactate, K⁺, HPO₄²⁻, ADP, AMP, adenosine, osmolarity, and some hormones such as bradykinin.
2. a decrease in PO₂ and the pH (=increase of H⁺ ions)

Local chemical regulation mechanisms for organ circulation

The endothelium of the blood vessels plays a part in the circulatory regulation by the production of vasoactive substances. Vasoactive substances are nitric oxide (NO), Endothelin 1 (ET-1), endothelium-derived hyperpolarizing factor (EDHF), and prostacyclin (prostaglandin I₂, PGI₂).

1. Nitric oxide (NO)

Nitric oxide is released by the following mechanisms:

1. Mechanical exposure: The higher the blood flow, the higher also the shear stress, and therefore, more nitric oxide is released.
2. Bonds of different substances: bradykinin, some prostaglandins, histamine, and acetylcholine bind to receptors of the endothelium and lead to a release of nitric oxide.

In both cases, nitric oxide results in a vasodilatation.

2. Endothelin 1 (ET-1)

Endothelin 1 is released by the following mechanisms:

1. the pathological increase of perfusion pressure
2. through PGF₂α

Depending on the receptor, endothelin 1 can either lead to a vasoconstriction (ETA-receptors) or a vasodilatation (ETB-receptors). Arteries mostly have ETA-receptors, and vessels of the low-pressure system mostly have ETB-receptors.

3. Endothelium-derived hyperpolarizing factor (EDHF)

If blood flow and shear stress increase, the endothelium-derived hyperpolarizing factor gets released, which leads to a vasodilatation.

4. Prostacyclin

If blood flow and shear stress increase, prostacyclin gets released, which leads to a vasodilatation. There are some vasoactive substances that are not produced from the endothelium but are created by an arachidonic-acid metabolism. These substances are thromboxane and different prostaglandins (PGD, PGE, PGF). Thromboxane leads to vasoconstriction. Prostaglandin D and E lead to vasodilatation, and prostaglandin F causes vasoconstriction.

5. Local mechanical regulation - Bayliss effect

Due to this mechanism, the blood flow becomes adjusted through the muscles of the vessels. An increase in blood pressure would, with the same vessel diameter, induce a higher perfusion of the organ. The vascular muscles inhibit this by a constriction, and therefore, the blood pressure can be held constant. This effect is known as the Bayliss effect (**Figure 3**, below). There is only one exception: The vessels of the lung become dilated when the blood pressure increases.

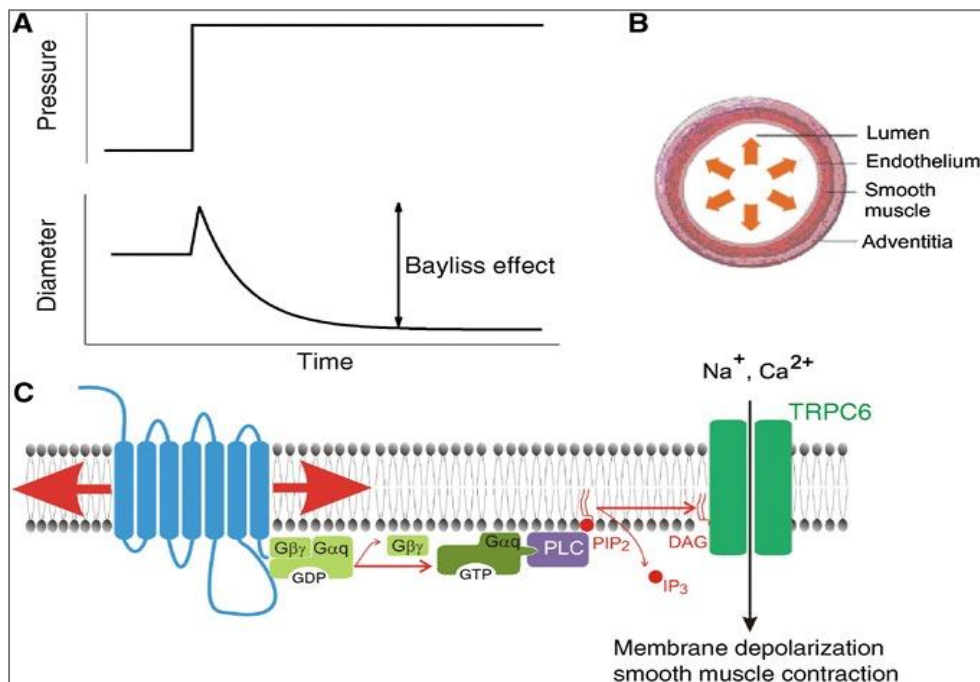


Figure 3: **The Bayliss effect.** Source:

https://www.researchgate.net/figure/23764566_fig1_Figure-1-The-Bayliss-effect-A-Increasing-pressure-in-certain-blood-vessels-causes

1.1.1.2 Long-term regulation

The mechanisms of the long-term blood-pressure regulation change the water and electrolyte balance and thus influence the blood pressure by the blood volume. The sensors for measuring blood pressure are in different parts of the body, but they all influence excretion from the kidneys.

The renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system is a control loop. Its main function is to regulate the plasma sodium concentration and the arterial blood pressure (**Figure 4**). The juxtaglomerular cells in the kidneys measure the plasma sodium and the blood flow. If the plasma sodium or blood flow is reduced, the juxtaglomerular cells transform the prorenin into renin and release it into the blood. The renin itself activates the renin-angiotensin-aldosterone system. First, it cleaves an enzyme called angiotensin (produce by the liver) into angiotensin 1. Then angiotensin 1 is converted to angiotensin 2 to ACE (in the lungs). Angiotensin 2 has many functions which all are for increasing the blood pressure. First, it

is a very potent vasoconstrictor. Furthermore, it leads to an increased secretion of aldosterone and antidiuretic hormone. It also increases the re-uptake of sodium ions in the kidneys and the excretion of the potassium ions. Renin itself works as a vasoconstrictor too. Its main function is to be part of the renin-angiotensin-aldosterone system.

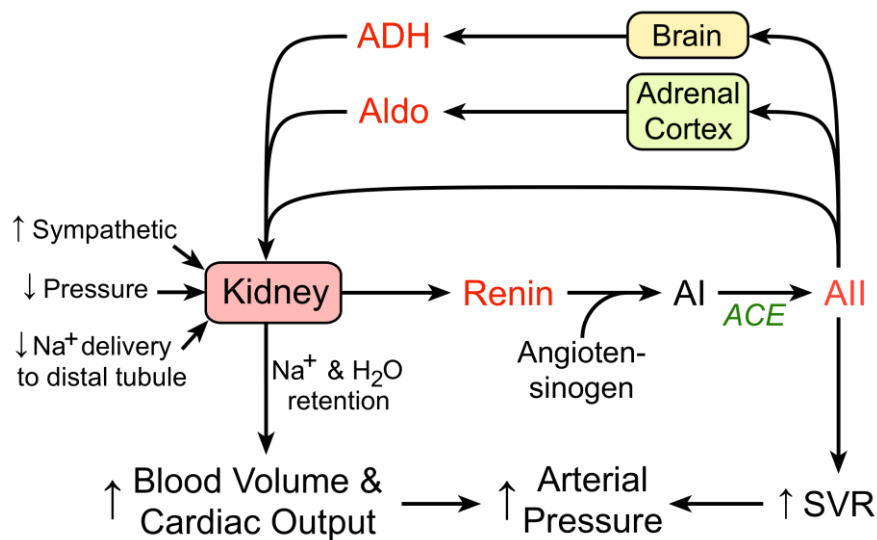


Figure 4: **The renin-angiotensin-aldosterone system.** Source: <http://www.cvphysiology.com/Blood%20Pressure/BP015>

Angiotensin 2

Angiotensin 2 has effects on the cardiovascular, neuronal, adrenal, and renal systems. In the case of the cardiovascular system, it works as a vasoconstrictor. Its neuronal functions are of increasing the thirst, decreasing the response of the baroreceptor reflex, and increasing the desire for salt. Moreover, it causes the adrenal cortex to release aldosterone and induces the proximal tubules of the kidneys to reabsorb more sodium.

Aldosterone

Aldosterone is a mineralocorticoid hormone produced by the adrenal cortex. As explained above, it is part of the renin-angiotensin-aldosterone system. It regulates the plasma sodium, extracellular potassium, and arterial blood pressure. To increase the blood pressure, aldosterone causes the distal tubules and collecting ducts of the nephron to reabsorb sodium and excrete potassium. Through this mechanism, more water is reabsorbed into the blood vessels and the blood pressure increases as a result.

Antidiuretic hormone (vasopressin)

The antidiuretic hormone, also called vasopressin, is a hormone released by the neurohypophysis. Its functions are vasoconstriction and the retention of water by increasing the reabsorption of water in the kidneys' collecting ducts. Furthermore, it increases peripheral vascular resistance. All these mechanisms lead to an increased blood pressure.

Epinephrine and norepinephrine

Epinephrine and norepinephrine act as hormones and neurotransmitters and are also used as a medication. In the case of the cardiovascular system, the hormones increase the central blood volume due to a vasoconstriction in the skin and kidneys (alpha 1 mediated). On the other hand, they cause a vasodilation of central muscle supplying vessels (beta 2 mediated). By activating the beta 1 receptors, they work positively inotropic, chronotropic, as a dromotrope, and bathmotropic. In the case of the smooth muscles, adrenalin and noradrenaline cause a slackening through the beta 2 receptors. This means that the peristaltic in the gastrointestinal tract becomes inhibited and the bronchioles dilatated. Furthermore, the uterus in pregnancy can be relaxed due to this mechanism. Organs that have a lot of alpha 1 receptors, e.g. the urinary bladder and the sphincter muscle, become contracted. Moreover, they cause a beta 3-mediated lipolysis and a beta 2-mediated neogenesis of glucose. This mechanism becomes enhanced by an alpha 2-mediated inhibition of insulin. The higher amount of glucose in the blood leads the muscles to a higher intake of it.

Atrial natriuretic peptide (ANP)

ANP is produced and released by the heart muscle cells in the atria. Its function is the direct opposite to aldosterone. It has effects on the renal, adrenal, and vascular systems. In the case of the renal system, it leads to an increasing glomerular filtration rate, which means that more sodium and water is excreted. Furthermore, it is an antagonist of renin and it reduces aldosterone release. Regarding its vascular function, it leads to a vasodilatation. All these functions are necessary for reducing blood pressure.

1.1.2 The physiology of standing

When changing to an upright posture, the cardiovascular system must react quickly to the effects of gravity. During standing up, approximately 500-1000 ml of blood moves from the thorax to the lower extremities and splanchnic vasculature. [63] Furthermore, the increased hydrostatic pressure leads to a shift in intravascular volume to the stroma. This results in a 10 % shift in the plasma volume. [64] [65] For reaching and maintaining an upright position, the active contraction of abdominal and leg muscles is necessary. A compression of the capacitance vessels, an increased vascular resistance, and blood pressure are the results of these muscular contractions. [66] This mechanism is useful for maintaining blood pressure in the long term, but not in the short term. When standing up, the muscular contraction increases the intra-abdominal pressure and briefly increases the venous return to the heart. [67] Due to the increased intra-abdominal pressure, the low-pressure cardiopulmonary receptors respond by decreasing the sympathetic tone, which leads to a decreased vascular resistance and lower blood pressure. This phenomenon, in addition to the effects of gravity, leads to a decreased stroke volume, venous return, and lower blood pressure. The decrease of blood pressure is immediately detected by the high-pressure (carotid sinus and aortic arch) and low-pressure baroreceptors. These receptors react to a change of pressure. A decrease in blood pressure leads them to increase the sympathetic activity and decrease the parasympathetic activity. This leads to a peripheral vasoconstriction and an increased heart rate, both for sustaining an adequate blood pressure. Clinically, this can be seen by an increase in the heart rate by about 10-20 beats per minute, a 5 mmHg increase in the diastolic blood pressure, and a minimal increase in the systolic blood pressure. After a time, the renin-angiotensin-aldosterone system and vasopressin help to maintain the blood pressure. [68]

The autonomous nervous system is very important for regulating and maintaining the blood pressure. In case of autonomic failure, this capability becomes inadequate, which may lead to orthostatic hypotension, pre-syncope, or syncope. [62]

1.2 Syncope

Syncope is defined as a short loss of consciousness and muscle strength due to a reduced blood flow through the brain. It can be provoked by several causes. Typically, there is a fast onset, a short duration, and a spontaneous recovery. It is very common and are the

cause for 1-3 percent of admission to emergency departments. There are many different causes for syncope. Some are quite benign, and some are life threatening. The routine requirements for diagnosis are the medical history, an electrocardiogram and physical examination. [1] Syncope is often accompanied by prodromal signs. Such symptoms are for example nausea, sweating, weakness, light-headedness and impaired vision. Usually syncope does not last longer than 20 seconds, but some cases have been described in which syncope lasts up to several minutes. Sometimes the post-syncope period is marked by fatigue or retrograde amnesia, but in most cases an immediate recovery of appropriate behaviour and orientation occurs. [3] Orthostatic syncope, vasovagal syncope and cardiac syncope are the most common types of syncope. However, there are also other, less common forms. To distinguish the different forms from each other is very important, as the therapy is different for each form. The different forms will be discussed in more detail later.

Basically, the cause for syncope is a decreased blood pressure, leading to reduced blood flow to the brain. It has been shown that 6-8 seconds without sufficient blood flow to the brain and a systolic blood pressure lower than 60mmHg is enough to cause syncope. [4] The cardiac output (CO) and total peripheral vascular resistance primarily affect the systemic blood pressure. Low peripheral resistance can either be caused by an inappropriate reflex activity, or functional or structural impairments of the autonomous nervous system. These impairments can be drug related or caused by primary and secondary autonomous nervous system failure. In case of an autonomic nervous system failure, it is not possible to increase the blood pressure in an upright position. This leads to venous pooling below the diaphragm and therefore to a decreased venous return and cardiac output. Inappropriate reflex activity leads to bradycardia and vasodilatation, which manifests as vasodepressor, mixed or cardioinhibitory reflex syncope. There are several causes for low cardiac output. First, there is a reflex causing bradycardia. The second cause is a failure in the cardiovascular system, e.g. arrhythmia and pulmonary embolism or hypertension. The last reason for low cardiac output is a low venous return due to venous pooling. [2]

As stated previously, the first response to a patient who experienced syncope is to review the patient's history, physical examination, ECG, and orthostatic blood pressure measurement. The outcomes of the above can detect the cause for syncope in 23-50 percent of patients. [4] [5] If the causes cannot be found with these methods, carotid sinus

massage, orthostatic challenge, tilt-table-testing, electrocardiographic monitoring, electrophysiological study, adenosine triphosphate test, echocardiography and other imaging techniques, exercise stress testing, cardiac catheterization, neurologic evaluation and psychiatric evaluation should be performed. The main aims of the treatment of syncope are to reduce mortality, reduce physical injuries and prevent recurrences. The treatment depends of course on the type of syncope. [2]

1.2.1 Differential Diagnosis of Syncope

1.2.1.1 *Cardiogenic Syncope*

Cardiac syncope appears as the second most common syncope after vasovagal syncope. Causes for cardiac syncope are arrhythmias, mechanical and structural abnormalities. Generally cardiac syncope is more frequent in adults. [6]

Mechanical abnormalities for cardiogenic syncope are pulmonary emboli and pulmonic stenosis. In both illnesses the right ventricle is not able to pump blood into the lungs. As a result, less blood gets back to the left heart, and because the left heart can only pump what it gets, the ejection fraction is reduced, and syncope occurs. [7]

Arrhythmias that can lead to syncope are for example bradyarrhythmia, ventricular tachyarrhythmias, supraventricular tachyarrhythmias, long QT-syndrome and pacemaker dysfunction. The symptoms occur mostly abruptly and unprovoked. Palpitations are also frequent.

Hypertrophic and obstructive cardiomyopathy also leads the left heart to generate a reduced cardiac output. Moreover, obstructive cardiac lesions also lead to a reduced cardiac output. The most common obstructive cardiac lesions are aortic and mitral stenosis. [6] Furthermore, a myocardial infarction and a pericardial tamponade can cause a pump failure, which leads to cerebral hypo perfusion and therefore to syncope. [2] Many types of medication such as beta-blockers can also cause bradycardia and consequently syncope. Rare illnesses that lead to cardiac syncope are the sick sinus syndrome (1), the Adams Stokes syndrome (2), the subclavian steal syndrome (3), and aortic dissection (4).

1. Sick sinus syndrome: The sinus node, the pacemaker of the heart, does not work normally, and the heart rate alternates between bradycardia and tachycardia. [2]

2. Adams Stokes syndrome: The Adams Stokes syndrome is characterised by periodic fainting, often accompanied by seizures (caused by brainstem hypoxia). [2]
3. Subclavian steal syndrome: The subclavian steal syndrome is a hypo perfusion of the vertebral artery caused by a stenosis of the proximal part of the subclavian artery or the brachiocephalic trunk.
4. Aortic dissection: Aortic dissection is a dissection (mostly the tunica intima) of the layers of the aortic wall, which causes blood to flow between the aortic walls. In many cases it indicates dangerous complications such as a cardiac tamponade. [8]

Diagnosis

As stated previously, the medical history and a physical examination are very important for diagnosing syncope. The onset and the activities before fainting help in making the correct diagnosis, e.g. series of syncope that occur in uncomfortable situations lead to suspect a vasovagal syncope. Information on medication (e.g. medication that lowers the blood pressure or changes the electrical conduction of the heart) is also very important for finding the correct diagnosis. Furthermore, it is essential to ask patients about their family medical history, e.g. if there are any cases of sudden death or heart failure amongst relatives. The physical examination should include measuring blood pressure and heart rate, while the patient is standing, lying down and seated. Furthermore, a cardiovascular neurological examination should also be carried out. Moreover, every patient who suffers from syncope should be given an electrocardiogram for diagnosing arrhythmia, an underlying heart disease, or an inherited syndrome of sudden death. Sometimes a long-term electrocardiogram is necessary for the diagnosis, e.g. arrhythmias. If dangerous arrhythmia is suspected, it is possible to do a heart catheterization, termed electrophysiological study, during which it is possible to provoke and determine arrhythmias. By using an ultrasound scan it is possible to diagnose valve abnormalities or a cardiomyopathy. Exercise stress testing and coronary catheterization is indicated if syncope occurs under stress. Differential diagnoses of cardiogenic syncope are vasovagal and orthostatic syncope, which can e.g. be diagnosed with a tilt table test. [2]

Therapy

The therapy of cardiogenic syncope depends on the causes:

1. Sinus node dysfunction: Cardiac pacemaker therapy is very effective in sinus node dysfunction. [48] (Circulation 1997). Furthermore, it is important to eliminate medication that induces bradycardia. [2]
2. Atrioventricular conduction system disease: Cardiac pacing is the therapy of choice with AV-Block. [53] [56]
3. Paroxysmal supraventricular and ventricular tachycardias: Catheter ablation is recommended in patients who suffer from paroxysmal AV nodal reciprocating tachycardia, AV reciprocating tachycardia, or typical atrial flutter associated with syncope. In case of a therapy failure, drug therapy is the treatment of choice. [51]
4. Syncope secondary to structural cardiovascular disease: The treatment depends on the diagnosis. Surgery is recommended for patients suffering from severe aortic stenosis or atrial myxoma. In patients with myocardial infarction, pulmonary embolism or pericardial tamponade, the underlying process should be treated. Patients with hypertrophic cardiomyopathy should undergo antiarrhythmic therapy. In many cases it is necessary to implant an ICD. [2]
5. Syncope in patients with a high risk of cardiac death syndrome: The therapy of choice is to treat the etiological disease that causes the syncope. The mechanism causing syncope in this group of patients has not yet been found. Aim of the treatment is to reduce cases of death. Even in cases with appropriate treatment of the etiological disease, syncope may still occur. [52]
6. Ischaemic and non-ischaemic cardiomyopathies: Ischaemic cardiomyopathies should be treated with revascularization. Nevertheless, antiarrhythmic treatment and the implantation of an ICD may be indicated in ischaemic and non-ischaemic cardiomyopathies. Furthermore, the implantation of an ICD might be indicated in patients with dilated cardiomyopathy and depressed LVED (left ventricular ejection fraction). [53] [51] [55] [56]
7. Hypertrophic cardiomyopathy: In the case of hypertrophic cardiomyopathy, there are several causes leading to syncope. These are supraventricular tachycardia, outflow tract obstruction, bradyarrhythmia, decreased blood pressure and reflex mediated syncope. Studies have shown that high-risk patients benefit the most from an ICD. [55] [51]

8. Arrhythmogenic right ventricular cardiomyopathy: It has been shown that patients with severe arrhythmogenic right ventricular cardiomyopathy should be treated with an ICD. [55] [51]

1.2.1.2 Vasovagal Syncope (Neurally Mediated Syncope)

Neurally mediated syncope or vasovagal syncope is the most common type of syncope in adults. Vasovagal syncope, also called neurocardiac syncope, is a syncope mediated by an overshooting autonomous nervous system. Vasovagal syncope is mediated through a reflex that leads to vasodilatation and bradycardia. The vasodilatation in the legs causes blood pooling in them. Because of blood pooling the blood pressure is reduced, which leads to decreased blood flow to the brain. This may lead to syncope (**Figure 6**, below). Symptoms before vasovagal syncope are nausea, diaphoresis, abdominal discomfort, and blurred vision.

Triggers for vasovagal syncope are stress, fear, pain, cold, fasting, banal bleeding and heat. A sub-group is type of syncopies caused by pressure, e.g. by the vasalver manoeuvre or the micturition syncope and defecation syncope. Furthermore, a hypersensitive carotid sinus can cause syncope due to low pressure at the carotid sinus.

Vasovagal syncope has two forms:

1. Isolated episodes of syncope: This form is more common in persons of adolescent age and is often associated with fasting, exercise, abdominal straining, heat or alcohol. There are no warning symptoms before fainting.
2. Recurrent syncope with complex associated symptoms: This form is associated with sleepiness, visual disturbance, sweating, pale skin, nausea, dizziness, yawning, a cold clammy sweat, feeling warm and light headedness.

There are many background factors that lead to vasovagal syncope. A low blood volume, e.g. from a low salt diet, can be one of these factors. Other reasons, for example heat, can worsen the effect of a low blood volume by causing vasodilatation. Then the adrenergic response occurs, e.g. caused by fear. Subsequently the vasomotor centres try to increase the heart rate, but this is not possible due to the low blood volume and the decreased return. Furthermore, the vagal tone tries to regulate the ineffective sympathetic activity, which decreases the heart rate even more. The blood flow to the brain is reduced, which

leads to dizziness and syncope. Normally recovery after such an episode begins in less than one minute. But care must be taken not to stand up too soon to avoid fainting again. [9] Many psychological factors have also been found which can lead to vasovagal syncope. Such factors are a high prevalence of psychological distress, especially anxiety and depression. Furthermore, some patients develop safety behaviours, such as avoiding crowded or public places, because they feel embarrassed in the case they faint. [10]

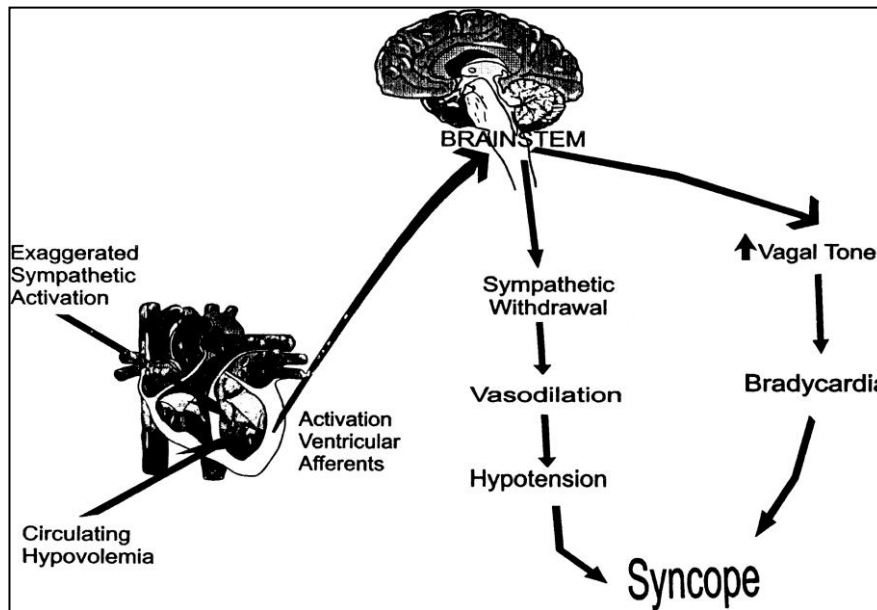


Figure 5: **Pathway of vasovagal syncope.** Source: <http://gazettereview.com/2015/08/vasovagal-syncope-disease-linked-to-fainting-spells/>

Diagnosis

Normally vasovagal syncope is harmless, but there is a risk of injury during an episode. If someone experiences syncope for the first time, it is necessary to carry out some tests to exclude any serious causes of syncope, for example heart or brain disorder. Tilt-table-testing has been shown to be the best way for diagnosing vasovagal syncope. If no cardiac reason for the syncope is found, tilt-table-testing should be performed. [9]

Therapy

Isometric physical counterpressure manoeuvre of the legs (leg crossing) or the arms (hand grips and arm tensing) can increase the blood pressure in patients with vasovagal syncope. [57] There is no sufficient pharmacological therapy yet. [2]

1.2.1.3 Orthostatic Syncope (Orthostatic Hypotension)

Orthostatic syncope is a syncope caused by a malfunction of the orthostatic reaction. The orthostatic reaction ensures in healthy people that the cardiovascular system works correctly in an upright position. When counter regulation does not work as it should while standing up, orthostatic dysregulation occurs. This dysfunction causes symptoms such as dizziness, tachycardia, nausea, and weakness in an upright position. These complaints force those affected to sit or lie down. In some cases, syncope also occurs. The symptoms of orthostatic syncope appear after a fast change of position, especially from lying down to standing up. The symptoms deteriorate during longer periods in a standing position.

The following symptoms can appear during orthostatic dysregulation:

1. General symptoms: uneasiness, breaking into a sweat, paleness, sensation of cold, acrocyanosis, nausea
2. Cardiac symptoms: feeling of constriction, tachycardia, palpitations
3. Neurological symptoms: dizziness, headache, ear noise, unsteadiness in standing and walking, blurred vision, flickering before the eyes, tunnel view

There are several clinical syndromes of orthostatic intolerance:

1. Classical orthostatic hypotension: Classical orthostatic hypotension is defined as a decrease of the systolic blood pressure $>20\text{mmHg}$ and the diastolic blood pressure $>10\text{mmHg}$ within three minutes of standing. It is described in patients with pure autonomous nervous failure, hypovolemia, or other forms of autonomous nervous failure.
2. Initial orthostatic hypotension: Initial orthostatic hypotension is defined as a blood pressure decrease immediately on standing of $>40\text{mmHg}$. The blood pressure becomes fast and spontaneously normal, so the period of hypotension is short.
3. Delayed (progressive) hypotension: Delayed hypotension is very common in older people. It is related to an impairment of compensatory reflexes, a stiffer heart and a decrease of preload as age increases. A slow decrease of the systolic blood pressure in an upright position is typical for this syndrome.
4. Postural orthostatic tachycardia syndrome (POTS): Postural orthostatic tachycardia syndrome is characterized by orthostatic intolerance and an increased heart rate. Syncope does not occur. POTS is often accompanied by chronic fatigue syndrome and is mostly found in younger women. [2]

Diagnosis

For diagnosing orthostatic hypotension, a good anamnesis is very important. Furthermore, a Shellong-test (lying to standing orthostatic test) or a tilt-table-test ensures the diagnosis. In case of a propensity to syncope, a long-term ECG should be carried out.

Blood pressure measurement

Because of its reliability and simplicity, the mercury column sphygmomanometer has shown to be a very popular device for routine clinical testing of blood pressure. [12] [13] Automatic arm-cuff devices could be a disadvantage, because there is a possibility that they are unable to measure the fast dropping blood pressure in orthostatic hypotension. Auscultatory measurement should only be done by professionals. [14] Generally it is important that the arteria brachialis is held at the level of the heart during the measurement. [15] Other possible mistakes are inadequate cuff inflation, too rapid cuff deflation and repeated measurements at intervals more frequent than 15 seconds. [15] [16] In arterial research laboratories, measurement using a Finapres monitor is very common. It uses the Penaz method, which measures waveform indirectly. [17] [18] There are also other blood pressure measurements that monitor radial artery pressure and its waveform (based on arterial tonometry). Studies have shown a very good consistency of non-invasive blood pressure measurements and intra-atrial blood pressure measurements. [19] [20]

Heart rate monitoring

Heart rate monitoring is necessary to diagnose orthostatic intolerance. In clinical practice heart rate and blood pressure are measured together, when standard automatic blood pressure devices are used. Heart rate usually rises by about 5-12 beats per minute when changing from a lying to a standing position. [22] In case of sympathetic autonomic failure the heart rate does not increase concurrently with the drop-in blood pressure. [21] But there are also exceptions, e.g. healthy older people might have a reduced heart rate response because of the down regulation of baroreceptors. [23] Furthermore, many kinds of medication can reduce the heart rate. Contrarily, a paradox increase of the heart rate might be noticed in patients with autonomic failure. [57] Moreover, concentrated intravascular volume can lead to an increased heart rate. [24]

Orthostatic stress tests

The ideal orthostatic test must meet many criteria. It should be like real life situations and simple to perform. Its instruments should be generally available, and it should only demand little patient cooperation. The most used orthostatic stress tests are the lying to standing test, the lying to sitting test and the head up tilt test (HUTT). The lying to standing test is the closest to real life conditions, while the head up tilt table test is the most different from real life conditions. Only a few studies compare the different orthostatic tests. [25] In research the lower negative pressure test is in use as well. [31] There is also a sitting to standing test, but this is very rarely performed because a considerable number of cases are not detected. [27]

a. The lying to standing orthostatic test

The blood pressure is measured after 5-10 minutes in a horizontal position. Then the patient must stand up and the measurement is repeated while he stands motionless for 3-5 minutes. As mentioned before, the cuffed arm needs to be at the same level as the heart during the measurements. The patients are asked to report if they experience any symptoms (dizziness, faintness, blurred vision). In case the blood pressure drops too fast or presyncope occurs the measurement is stopped. Severe autonomic failure can be easily diagnosed with this test, as the blood pressure drops very quickly. [28] [29] [30] However, if someone suffers from delayed orthostatic hypotension, the diagnosis may be missed within this form. [31] [38]

b. The lying to sitting orthostatic test

There is no standardized protocol for the lying to sitting orthostatic test. [33] [34] [38] [36] [37] Often a single blood pressure measurement in a lying position followed by blood pressure measurements after 1, 3 and 5 minutes of sitting is taken. [38] The other methods differ in time and number of blood pressure measurements. The rest of the examination is identical to the method described above.

c. The head up tilt test (HUTT)

The head up tilt test is quite an exact method for diagnosing orthostatic intolerance. Patients are exposed to a controlled passive postural stress to challenge the cardiovascular responses. These are measured as heart rate and blood pressure. The HUTT consists of two

phases, the supine pre-tilt phase and the passive head-up tilt. There are many protocols used for performing this test. The European Society of Cardiology recommends a pre-tilt phase that does not exceed 5 minutes. If venous blood sampling is part of the study it should not last longer than 20 minutes. The passive head up tilt phase should last around 20 to 45 minutes. The tilt angle should be about 60°-70°. [30] [37] The repeated measurements are taken at 30-second intervals after the patients experience symptoms (faintness or dizziness). After experiencing syncope, the test should be ended. Blood pressure measurement can be done with a mercury column sphygmomanometer and the heart rate can be recorded on an electrocardiographic monitor. Finger plethysmography can be utilized for continuous heart-rate and blood-pressure monitoring. [39]

2 Aims and Objectives

Orthostatic intolerance is very common, especially in older people and young women. In some cases, it can lead to syncope. Moreover, there are several other causes for syncope, like vasovagal and cardiogenic syncope, which must be distinguished between (**Figure 6**). [2]

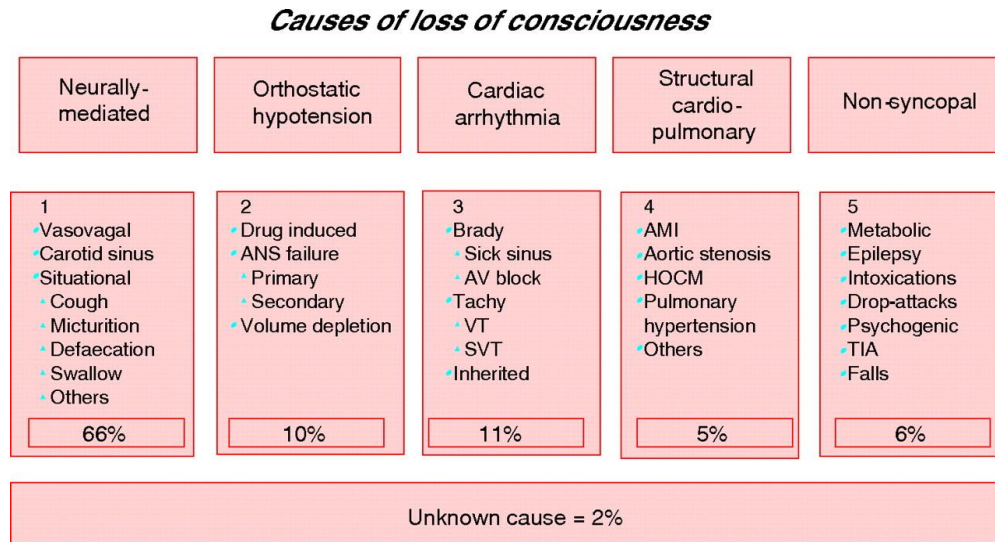


Figure 6: **Causes of loss of consciousness**. Source: <http://heart.bmj.com/content/93/1/130>

Tilt table testing is routinely used in clinical practice to assess the aetiology of orthostatic intolerance, especially in patients with histories of regular syncope. The head up tilt test is a quite exact method for diagnosing orthostatic intolerance. Patients are exposed to a controlled passive postural stress to challenge the cardiovascular responses. These are measured as heart rate and blood pressure. The HUTT consists of two phases, the supine pre-tilt phase and the passive head-up tilt.

The aim of this diploma thesis is to **explore the physiology of orthostatic intolerance**. Therefore, data was collected from LKH Knittelfeld, where tilt table testing was being performed to diagnose orthostatic intolerance. Furthermore, this diploma thesis gives a short insight into the most common differential diagnoses of orthostatic dysregulation.

The study of LKH Knittelfeld will provide important results for a better understanding of cardiovascular regulation in people suffering from orthostatic intolerance and thus help to achieve better treatment for orthostatic intolerance.

3 Methodology

This thesis is written within the framework of the LKH Knittelfeld project, which is currently being carried out to provide missing data on a few hundred people who have experienced syncope. Due to the Data Protection Act and patient confidentiality, only two patients were included in the framework of this thesis, one with orthostatic intolerance and one without.

3.1 Subjects

Inclusion criteria: the doctor on duty decides whether a patient meets the indication criteria for tilt-table-testing or not. Nevertheless, syncope with unknown aetiology in the past is one of the requirements.

Exclusion criteria: the exclusion criteria for tilt-table-testing are a pathological murmur over the carotids, a stroke, TIA or an infarct within the last three months.

3.2 Protocol

On the day of the test the patients had to fast. If they had to take medication, they could take it with a glass of water.

Simultaneously, a questionnaire related to the symptoms of syncope was handed to the patients. Specific questions posed were aspects related to complaints, first syncope, frequency of syncopes in the past, number of incidents of dizziness in the past, injuries, symptoms, underlying diseases, diseases in the family, results of the investigation (syncope, complaints, the same as at home). Appendix A shows a typical questionnaire.

The Ethical Committee of the Medical University of Graz approved the study protocol.

Room: The examination room was moderately warm and quiet.

Head up Tilt Table Test (HUTT): The head up tilt test is quite an exact method for diagnosing orthostatic intolerance. The patients were exposed to controlled passive postural stress to challenge the cardiovascular responses, measured as heart rate and blood pressure. The HUTT consisted of two phases, the supine pre-tilt phase and the passive head-up tilt. The tilt angle was about 60 degrees (**Figure 7**). The test commenced with a rest period of 30 minutes, in which patients had to be in a horizontal position.

Subsequently they were tilted to an upright position of 60 degrees for a duration of 20 minutes, followed by a carotid pressure test.

The classical orthostatic hypotension was defined as a decrease of the systolic blood pressure >20 mmHg and the diastolic blood pressure >10 mmHg within 3 minutes of HUTT. The late orthostatic hypotension was defined as a similar decrease of the systolic blood pressure within minute 4 and 5, associated with a decrease of the heart rate not over 10 percent.

For the purposes of this study, development of syncope was identified using the following signs and symptoms. The symptoms patients experience may be grey out, light-headedness, dizziness, headache, ear noise, tunnel view, flickering before the eyes, blurred vision, omnidirectional vertigo, sudden sensation of heat, palpitations, sensation of cold, paleness, nausea, or sweating. The signs are a systolic blood pressure decrease over more than 15 mmHg, and/or a sudden decrease of the heart rate over more than 15 bpm, or a prolonged tachycardia over 1 min. [91]



Figure 7: **Tilt Table Testing.** Source: <http://www.cnsystems.com/products/task-force-monitor#stateofheart>

Included in this DA are data from only two males, with histories of syncope. They both underwent tilt table testing for diagnosis: one was diagnosed with orthostatic intolerance, and the other not. The haemodynamic data was measured with a Task Force Monitor.

3.3 Data Collection

Electrodes: The investigation was recorded on a Task Force Monitor (**Figure 8**). The Task Force Monitor is a tool for continuous non-invasive haemodynamic measurement. It is the state-of-the-art tool for syncope assessment. Its use is also very common in experimental settings. It measures heart rate, continuous blood pressure, heart-time-volume, and peripheral resistance. Furthermore, it provides a high resolution 6-channel ECG. Blood pressure is measured as continuous non-invasive arterial pressure (CNAP). A finger sensor is applied which measures beat-to-beat on the finger artery. The finger blood-pressure values are automatically calibrated to the brachial artery with an integrated upper arm measurement and absolute blood pressure values are given. The cardiac output is measured based on the CNAP waveform. Preload, afterload, compliance of the vessels and contractility determine the cardiac output, which can all be derived from an accurate pulse waveform. The cardiac output can be measured with the same sensor used for the beat-to-beat-blood-pressure measurement. [63]

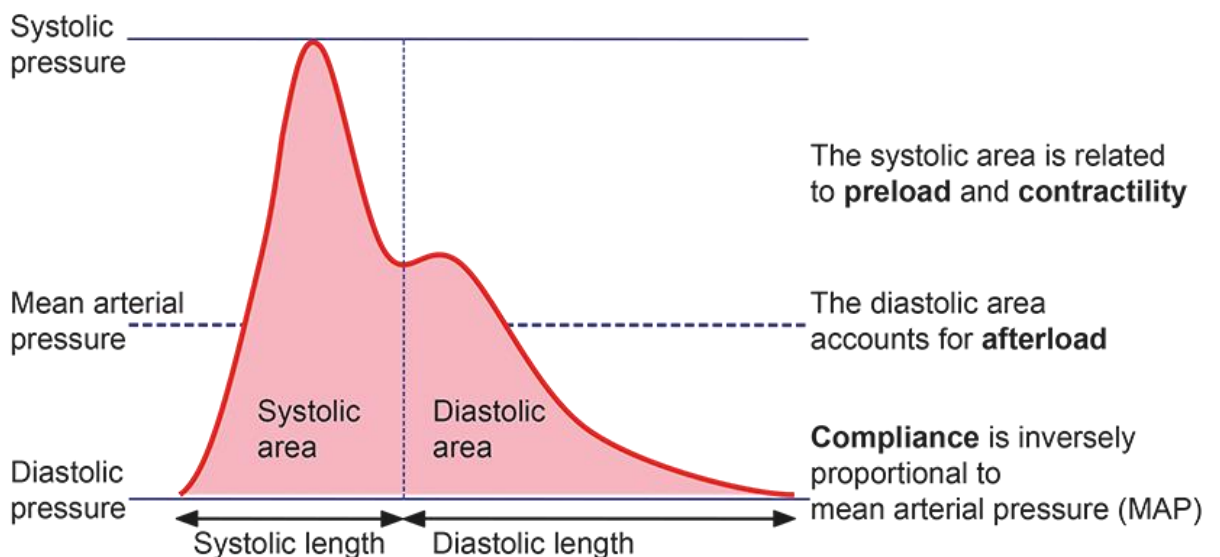


Figure 8: **Physiological markers related to cardiac output.** Source:

<http://www.cnsystems.com/innovation/hemodynamic-optimization/co-cardiac-output-pca>

3.4 Measurements

Data collected were cardiovascular response, time to syncope and the questionnaire related to causes of syncope.

3.5 Analyses

Two examples of patients who had experienced syncope in the past are given in this thesis. Both are male, and about 80 years old. One patient experienced syncope during tilt table testing and was therefore diagnosed with orthostatic intolerance/syncope. The other patient showed a quite constant blood pressure throughout the measurement and therefore orthostatic intolerance was not diagnosed.

4 Results

Two cases of male patients with syncope in their histories are discussed in this thesis. One patient is suffering from orthostatic intolerance, the other not. Both patients underwent head up tilt table testing (HUTT). HUTT is a quite exact method for diagnosing orthostatic intolerance. Patients are exposed to a controlled passive postural stress to challenge the cardiovascular responses. These are measured as heart rate and blood pressure. The test commenced with a rest period of 30 minutes, in which the patients were in a horizontal position. Subsequently they were tilted to an upright position of 60 degrees for duration of 20 minutes. In the event of syncope, the test was stopped immediately. Afterwards, a carotids pressure test was performed. If the patient experiences syncope during the investigation, orthostatic intolerance is proven.

Measurements were performed at LKH Knittelfeld, and the data was recorded on a Task Force Monitor. The Task Force Monitor is a tool for continuous non-invasive haemodynamic measurement. [63]

Data collected were cardiovascular response (blood pressure, heart rate), time to syncope and the questionnaire (**Appendix A**) related to causes of syncope.

4.1 Case 1

Patient 2 is an 85-year old man, who had experienced syncope on two occasions.

Figure 9 shows the diastolic, the systolic and the mean arterial blood pressure throughout the duration of the test. The first red line marks the point when the test was recorded, the second when the passive head up tilt was started, and the third when the tilt table was returned to a supine position. Throughout the test the blood pressure remained quite constant, so the tilt table testing was negative in that patient and orthostatic syncope could not be diagnosed.

Figure 10 shows on the left side the heart rate and on the right side the continuous-non-invasive blood-pressure of the patient throughout the duration of the test. The first red line marks the point when the test was recorded, the second when the passive head up tilt was started, and the third when the tilt table was returned to a supine position. Throughout the test the blood pressure and heart rate were quite constant, so the tilt table testing was negative in that patient and orthostatic syncope could not be diagnosed.

Figure 11 shows the heart rate, continuous blood pressure, stroke index, total peripheral resistance, and cardiac index of the patient throughout the duration of the test.

The first red line marks the point when the test was recorded, the second when the passive head up tilt was started, and the third when the tilt table was returned to a supine position. Throughout the test the blood pressure and heart rate were quite constant, so the tilt table testing was negative in that patient and orthostatic syncope could not be diagnosed.

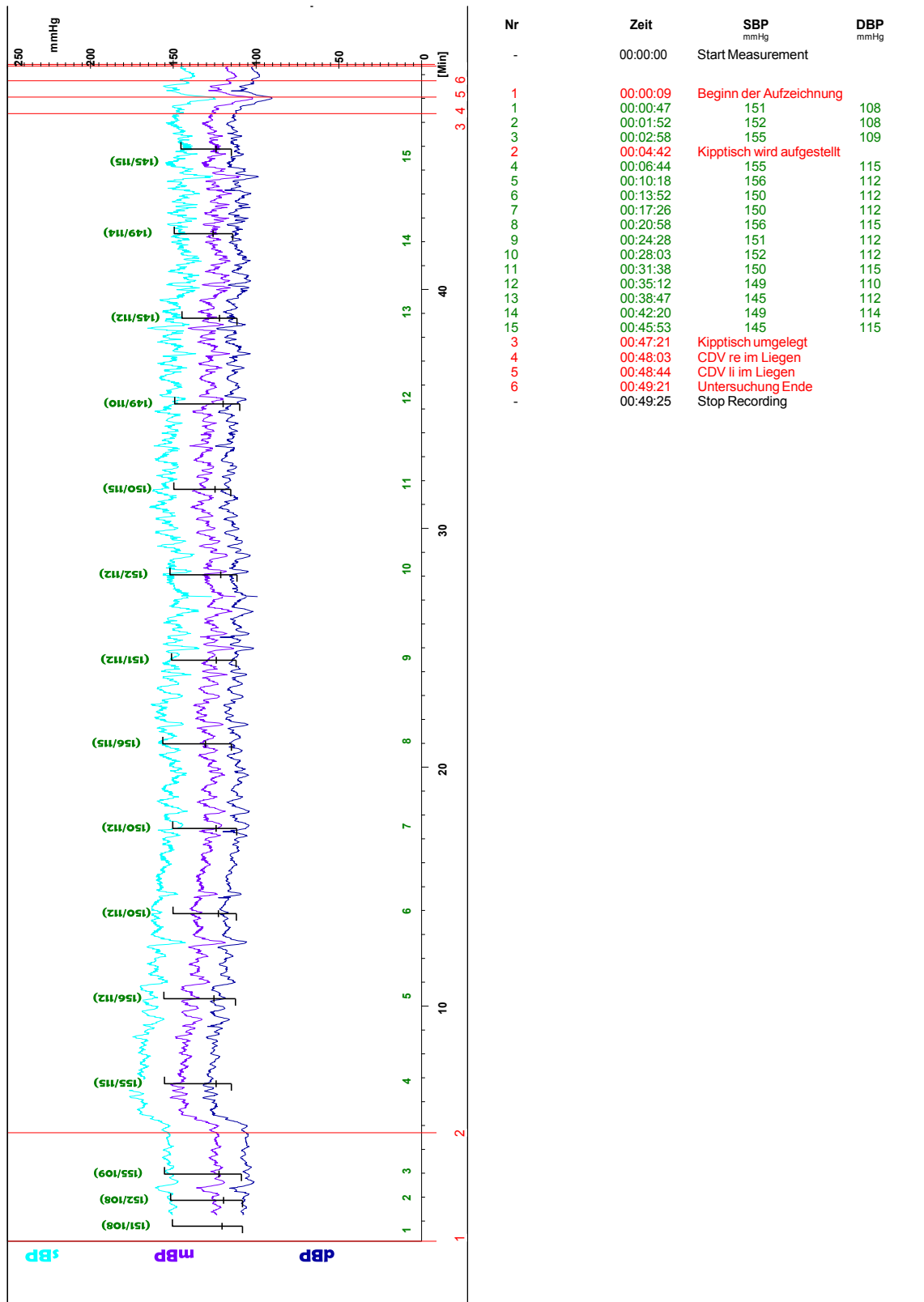


Figure 9: Blood pressure measurement during tilt table testing; case 1

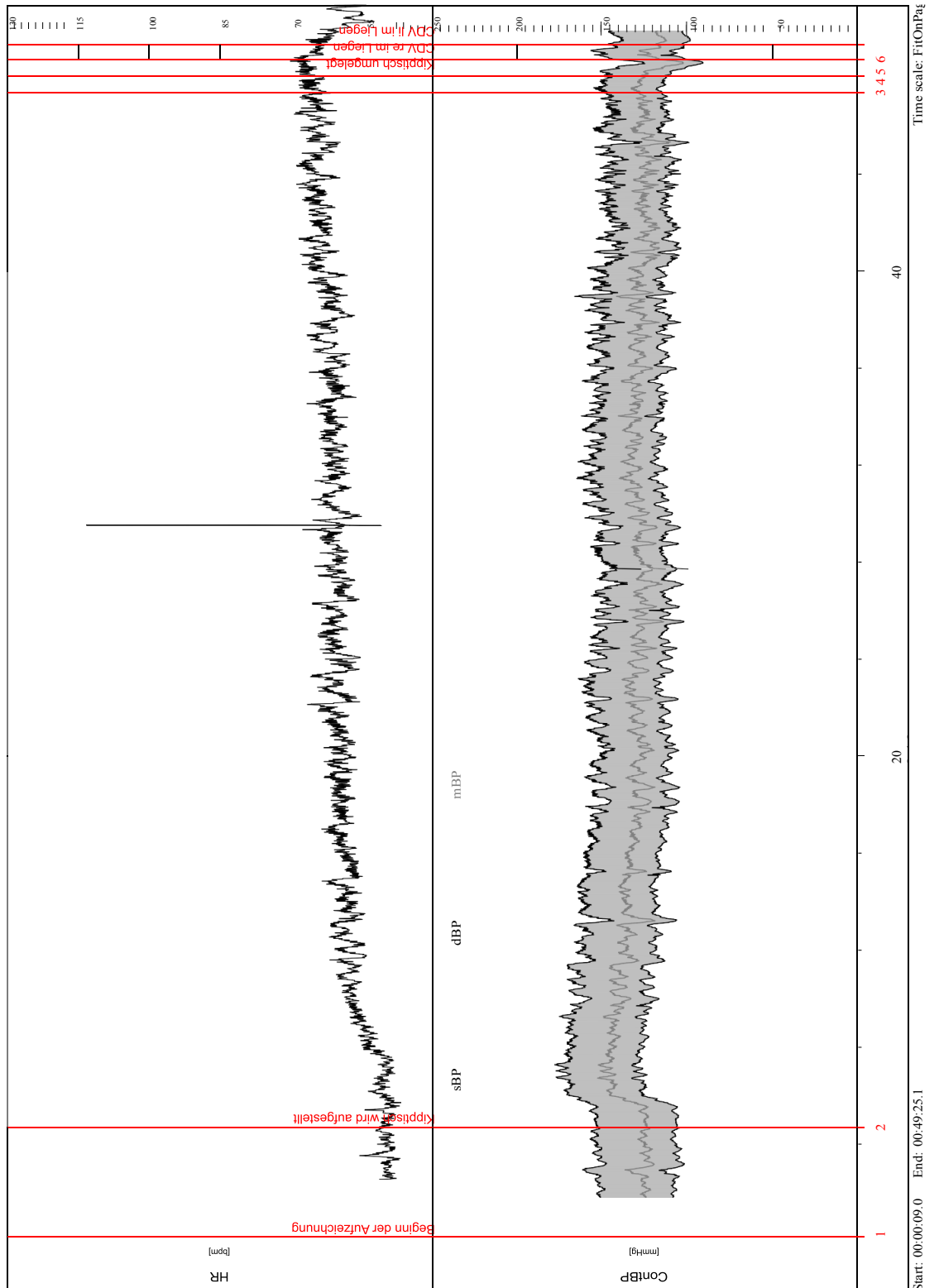
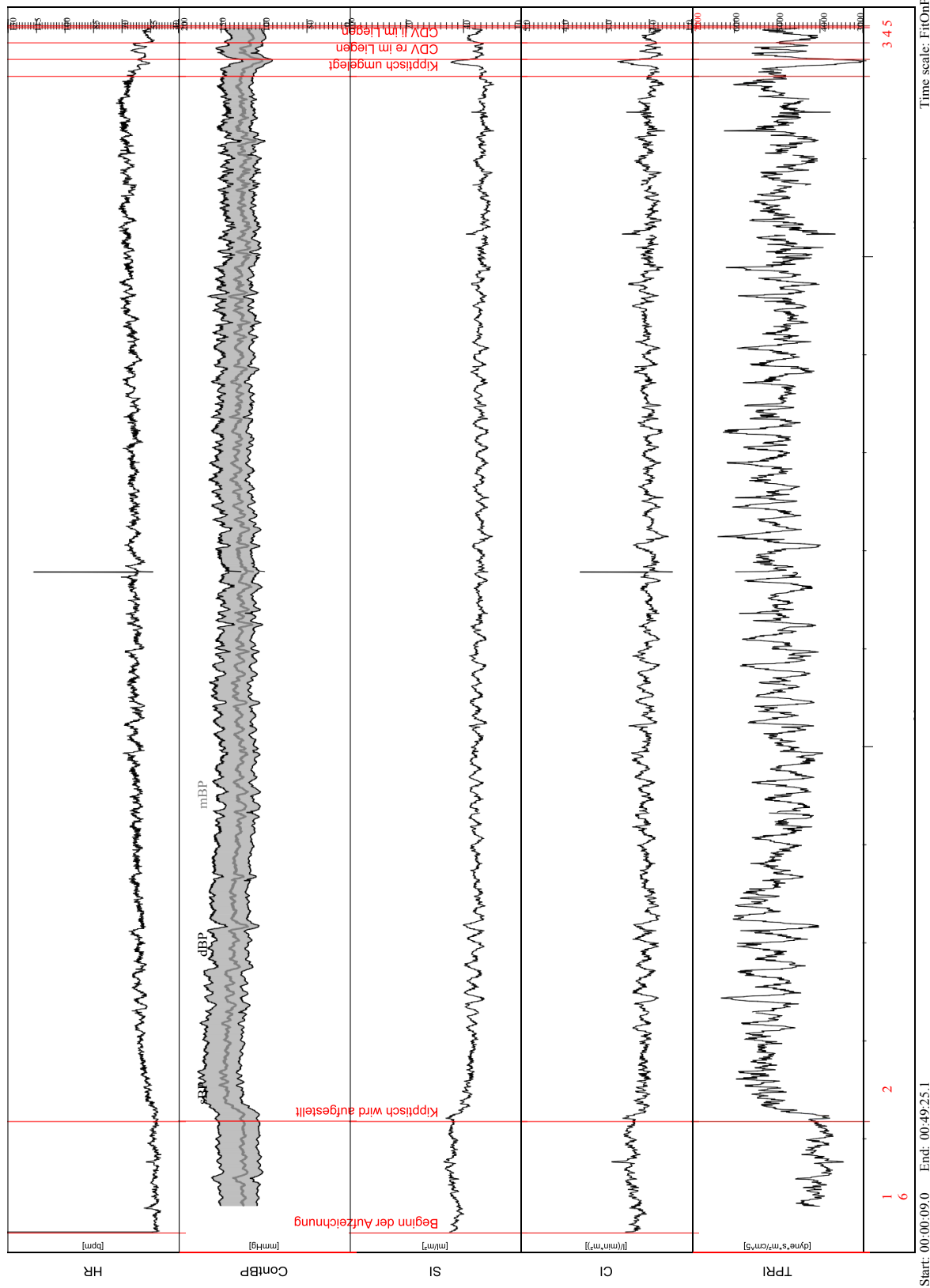


Figure 10: Heart rate and continuous blood pressure measurement during tilt table testing; case 1



Start: 00:00:09.0 End: 00:49:25.1 Time scale: FitOnPag

Figure 11: Heart rate, continuous blood pressure, stroke index, total peripheral resistance, and cardiac index during tilt table testing; case 1

4.2 Case 2

Patient 1 is an 82-year old man, who experienced syncope after a skiing tour.

Figure 12 shows the diastolic, the systolic and the mean arterial blood pressure throughout the duration of the test. The first red line marks the point when the test was recorded, the second when the passive head up tilt was started, and the third when the tilt table was returned to a supine position. After the head up tilt was started the systolic blood pressure decreased continuously (from about 152 mmHg to 110 mmHg). Furthermore, the diagram shows a sudden decrease of the systolic blood pressure (75mmHg) approximately 18 minutes after the passive head up tilt was started. At that point the patient experienced syncope (marked with the orange line) so the tilt table was brought back to a supine position and the systolic blood pressure of the patient increased.

Figure 13 shows on the left side the heart rate and on the right side the continuous-non-invasive blood-pressure of the patient throughout the duration of the test. The first red line marks the point when the test was recorded, the second when the passive head up tilt was started, and the third when the tilt table was returned to a supine position. After the head up tilt was started the continuous-non-invasive blood pressure decreased continuously. Simultaneously the heart rate increased slightly. Furthermore, the diagram shows a sudden decrease of the continuous blood pressure and heart rate approximately 18 minutes after the passive head up tilt was started. At that point the patient experienced syncope (marked with the orange line) so the tilt table was brought back to a supine position and the blood pressure of the patient increased.

Figure 14 shows the heart rate, continuous blood pressure, stroke index (stroke volume/body surface area), total peripheral resistance (systemic vascular resistance), and cardiac index ((stroke volume x heart rate)/body surface area) of the patient throughout the duration of the test. The first red line marks the point when the test was recorded, the second when the passive head up tilt was started, and the third when the tilt table was returned to a supine position. After the head up tilt was started the systolic blood pressure and the total peripheral resistance decreased continuously (from about 152 mmHg to 110 mmHg). Simultaneously heart rate and cardiac index increased slightly. The stroke index did not change at the beginning. Furthermore, the diagram shows a sudden decrease of the

blood pressure approximately 18 minutes after the passive head up tilt was started. The heart rate, stroke index, total peripheral resistance, and cardiac index decreased too. At that point the patient experienced syncope (marked with the orange line) so the tilt table was brought back to a supine position and the systolic blood pressure of the patient increased.

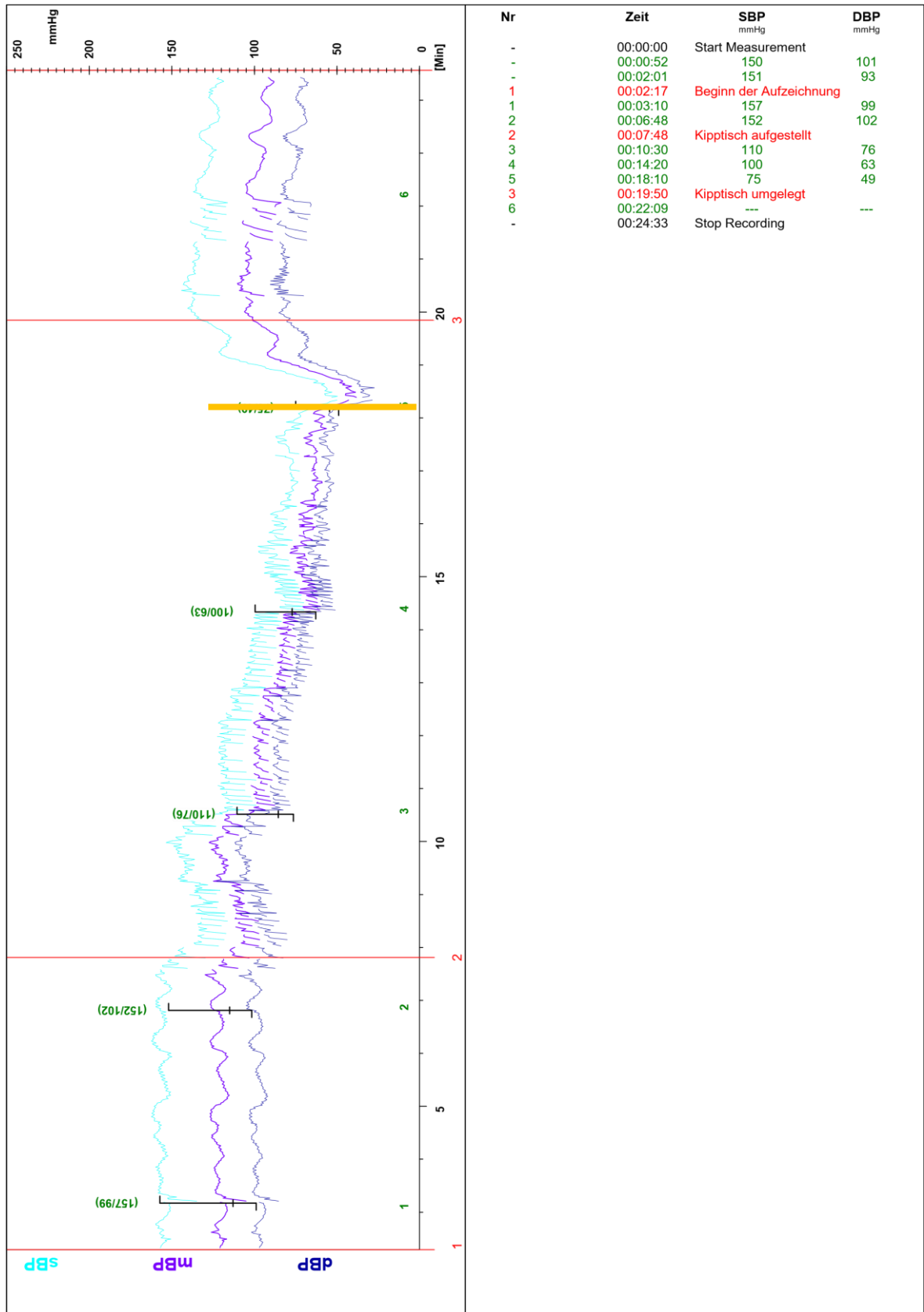


Figure 12: Blood pressure measurement during tilt table testing; orange line marking presyncope; case 2

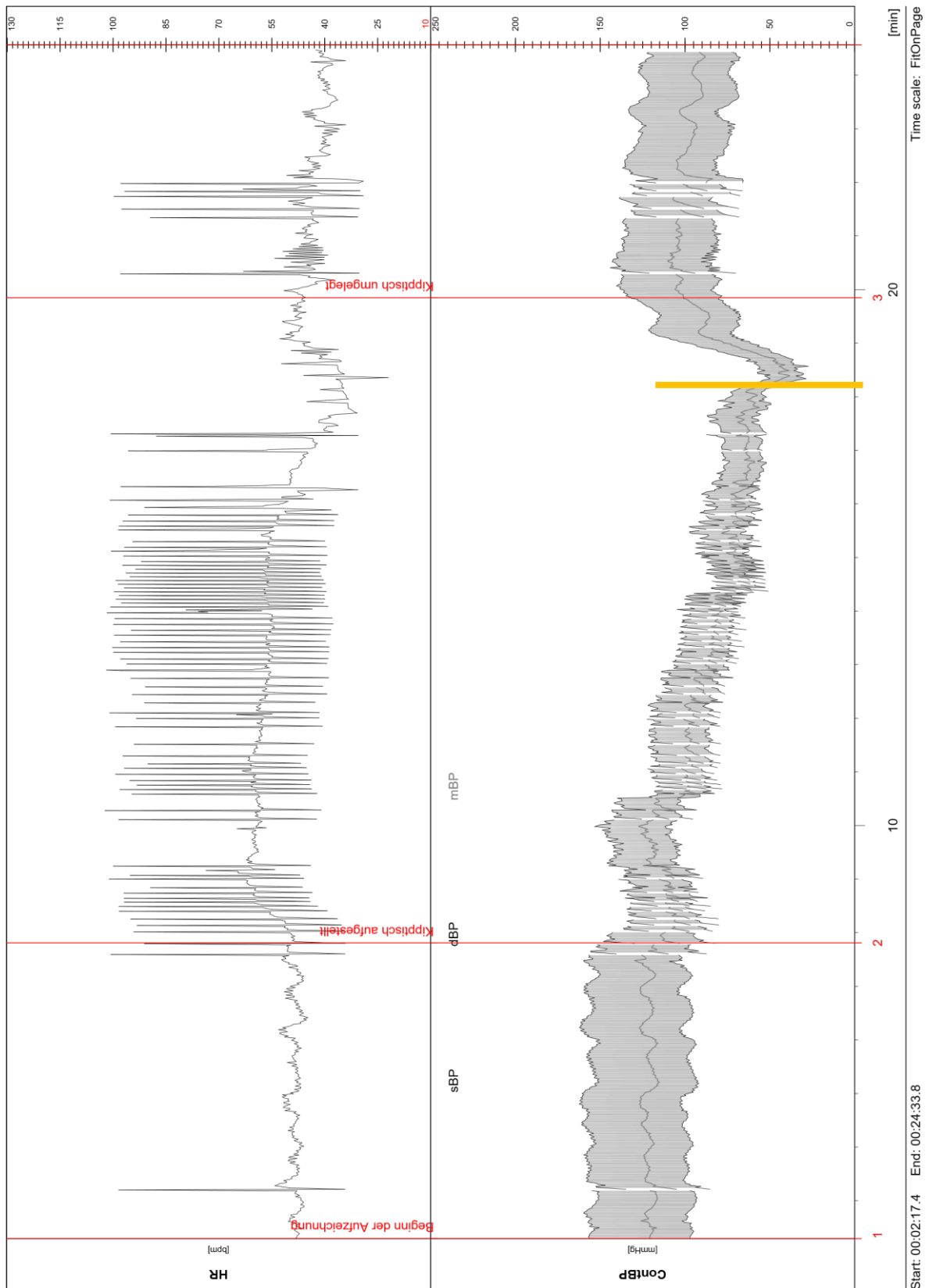


Figure 13: Heart rate and continuous blood pressure measurement during tilt table testing; orange line marking presyncope; case 2

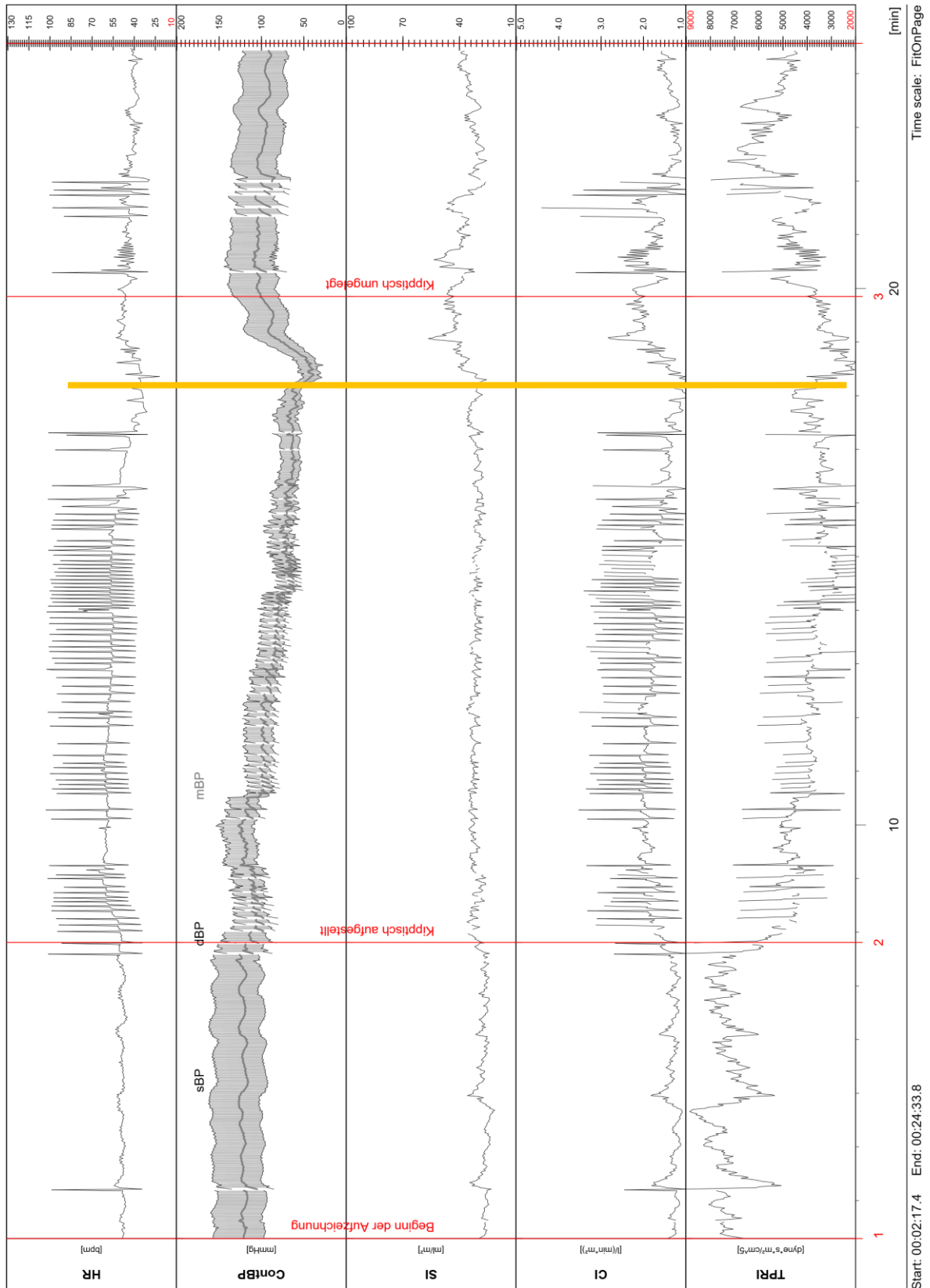


Figure 14: Heart rate, continuous blood pressure, stroke index, total peripheral resistance, and cardiac index during tilt table testing; orange line marking presyncope; case 2

5 Discussion

The data presented here show the differences in cardiovascular response in one patient who experienced syncope during tilt-table-testing compared to another patient who did not. It was shown that the patient without orthostatic intolerance had a quite constant blood pressure and heart rate throughout the test. In comparison, the patient suffering from orthostatic intolerance experienced a decrease of the systolic blood pressure (from about 152 mmHg to 110 mmHg). Simultaneously the heart rate increased slightly. Furthermore, the systolic blood pressure decreased to 75 mmHg approximately 18 minutes after the passive head up tilt was started. At this point the heart rate decreased too and the patient experienced syncope.

It can be assumed that the patient who did not experience syncope has better compensatory mechanisms (**Figure 15**, below). When getting to an upright posture, the cardiovascular system must react quickly to the effects of gravity. As said previously, when standing up the muscular contraction increases the intra-abdominal pressure and briefly increases the venous return to the heart. [67] Due to the increased intra-abdominal pressure the low-pressure-cardiopulmonary receptors respond by decreasing the sympathetic tone, which leads to a decreased vascular resistance and blood pressure. This phenomenon, in addition to the effects of gravity, leads to a decreased stroke volume, venous return and blood pressure. The decrease of blood pressure is immediately detected by the high-pressure (carotid sinus and aortic arch) and low-pressure baroreceptors. These receptors react to a change of pressure. A decrease in blood pressure leads them to increase the sympathetic activity and decrease the parasympathetic activity. This leads to a peripheral vasoconstriction and an increased heart rate, both for sustaining an adequate blood pressure. Clinically, this can be seen by an increase of the heart rate by about 10-20 beats per minute, a 5 mmHg increase of the diastolic blood pressure, and a minimal increase of the systolic blood pressure. After a time, the renin-angiotensin-aldosterone-system and vasopressin help to maintain the blood pressure. [68]

control loop of the blood pressure under orthostatic stress

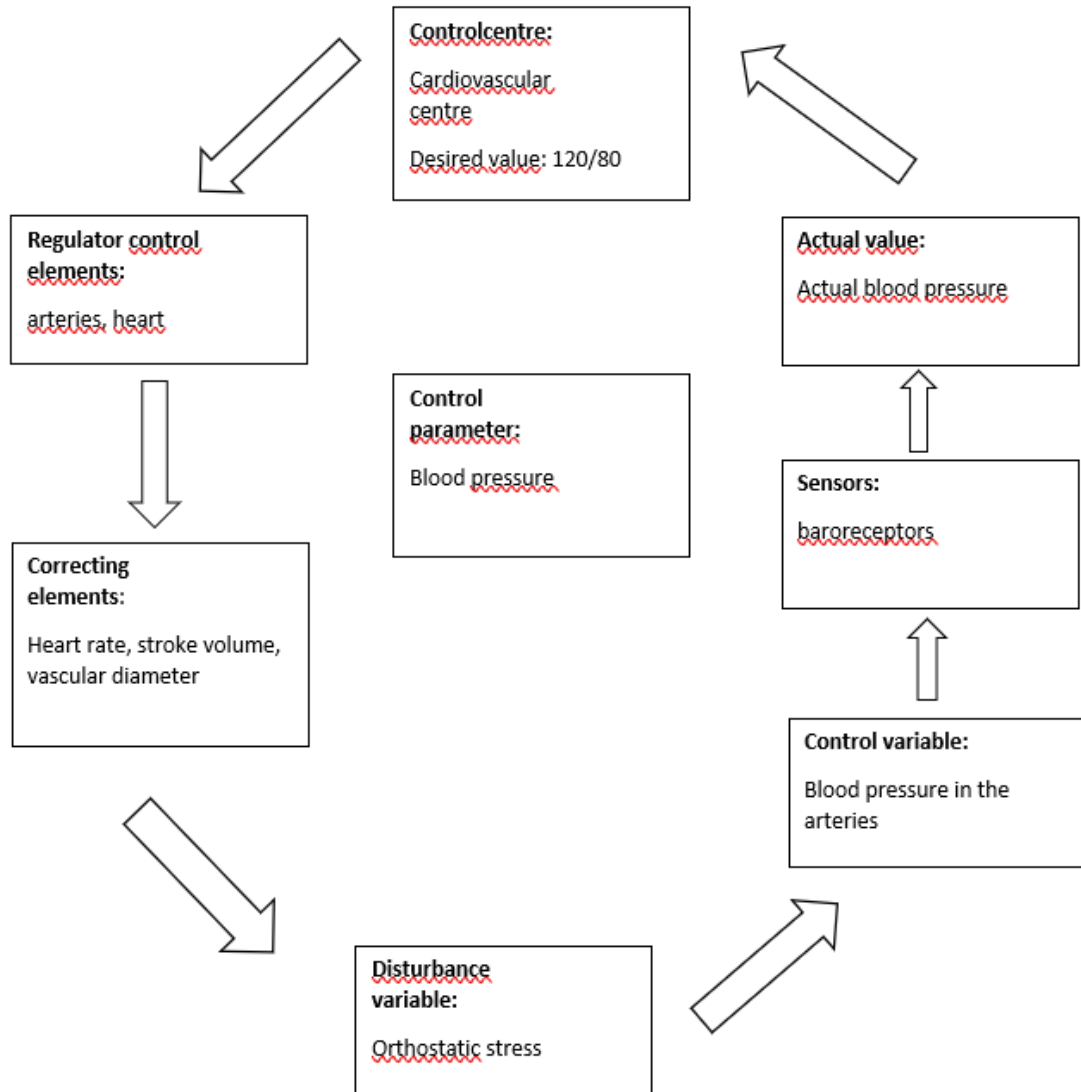


Figure 15: **Control loop of blood pressure**

In the case of the patient who experienced syncope during tilt-table-testing, the compensatory mechanisms did not work as they should have. After the head-up tilt was started the systolic blood pressure and the total peripheral resistance decreased continuously (from about 152 mmHg to 110 mmHg). However, cerebral blood flow must remain stable to provide enough oxygen and glucose for the brain. Therefore, a mechanism called cerebral autoregulation is very important to sustain the blood flow (**Figure 16**,

below). As the mean arterial pressure changes and cerebral perfusion pressure remains the same, the only variable left to control is the cerebral vascular resistance. In adults with normal blood pressure values, cerebral blood flow is maintained at ~50 mL per 100 g of brain tissue per minute. The autoregulation of the cerebral blood flow can work flawlessly with a mean arterial blood pressure between 60-160 mmHg in the brain. Above and below this pressure, autoregulation cannot work as it should, and cerebral blood flow increases or decreases linearly. To avoid ischaemia if the cerebral blood flow drops below the normal values, the brain increases the oxygen extraction from the blood. Therefore, it is possible for the cerebral blood flow to drop below the normal range without any physiological consequences. If the perfusion decreases too much, the increased extraction may not be able to get enough oxygen to the tissue. Then the patients experience symptoms of hypoperfusion. These symptoms are dizziness, altered mental status, and eventually irreversible tissue damage (infarction). Local factors that influence cerebral vessel diameter seem to be mainly metabolic by-products, or the deficit of metabolic substrates such as carbon dioxide concentration in the brain parenchyma, pH of the blood, lactate, potassium and low oxygen. Acute hypoxia causes an increase in cerebral blood flow due to vasodilatation of the arteries. In addition, hypoxia quickly increases nitric oxide and adenosine production, also leading to vasodilation. Carbon dioxide (CO₂) has reversible effects on the cerebral blood flow. Hypercapnia causes vasodilation of cerebral arteries and increases the blood flow. Hypocapnia causes vasoconstriction and a decreased blood flow. The blood pressure changes are immediately noticed by the vascular smooth muscles in the arteries, which then change their calibres to sustain an adequate blood flow. The vascular smooth muscles become innervated through autonomous nervous innervation. [92] In this case, autonomous cerebral regulation failing can be assumed at the point the patient experiences syncope.

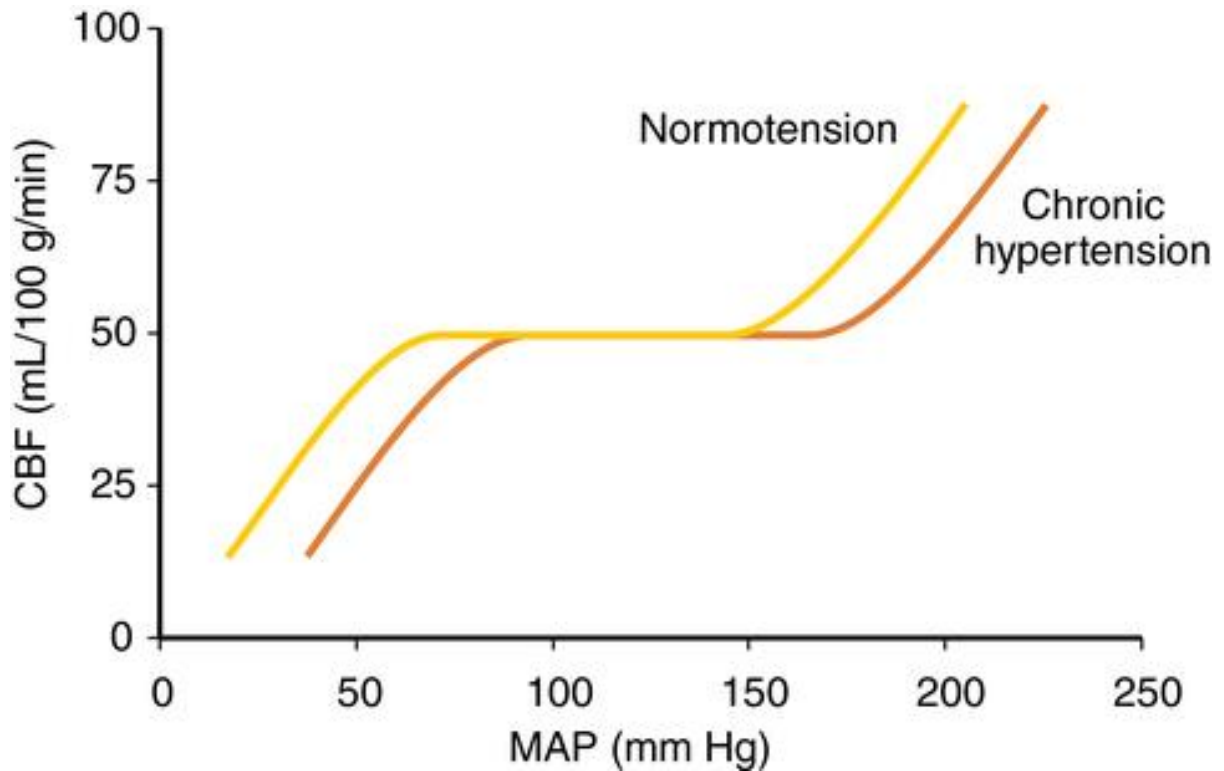


Figure 16: **Autoregulation of blood flow.** Source: <https://clinicalgate.com/factors-affecting-cerebral-blood-flow/>

As stated previously, mean arterial pressure is dependent on cardiac output, systemic vascular resistance and central venous pressure. We could see in our patient that at the beginning, the increase of the heart rate was able to sustain an adequate cardiac index and stroke index. Blood flow to the brain was ensured. After the heart rate dropped, the cardiac index and stroke volume also dropped. As a further consequence this led to a decrease in the blood pressure. Blood flow to the brain could not be sustained anymore and the cerebral autoregulation also failed, which is why the patient experienced syncope.

5.1 Challenges of this study

In this study, the HUTT consisted of two phases, the supine pre-tilt phase and the passive head-up tilt. The tilt angle was about 60°-70°. The test commenced with a rest period of 30 minutes, in which patients had to be in a horizontal position. Subsequently they were tilted to an upright position of 60 degrees for a duration of 20 minutes. Afterwards, a carotid pressure test was performed.

Nevertheless, there are no clear guidelines for the necessary supine resting time to achieve a stable blood pressure. A study using Finapres says that a resting time of 5 minutes

ensures a stable blood pressure in elderly people. For elderly people with reduced cardiac compliance, a resting time of about 12 minutes is recommended. [40] Other studies recommend a supine resting time before measuring the blood pressure of 5 minutes, [41] 5-10 minutes, [30] more than 10 minutes [42] [40] or measuring when getting up in the morning. [43]

Furthermore, there are no clear guidelines for the duration of postural stress to detect orthostatic hypotension. In a recent study, 88 percent of the participating patients developed orthostatic hypotension after 1 minute, another 11 percent developed orthostatic hypotension after 2 minutes and the remaining 1 percent after 3 minutes. [44] Another study evaluated the data of 400 patients who were undergoing HUTT due to syncope or non-specific dizziness. The classical orthostatic hypotension was defined as a decrease of the systolic blood pressure >20 mmHg and the diastolic blood pressure >10 mmHg within 3 minutes of HUTT. The late orthostatic hypotension was defined as a similar decrease of the systolic blood pressure within minute 4 and 5, with a decrease of the heart rate not over 10 percent. In this study 17.2 percent of the participating patients showed orthostatic hypotension within 1 minute of HUTT, 9.5 percent within 2 minutes, and 4.7 percent within more than 3 minutes. Late orthostatic hypotension was diagnosed in 7.2 percent of the examined patients. Both classical and late orthostatic hypotension showed similar symptoms. Systolic orthostatic hypotension, diastolic orthostatic hypotension, and mixed orthostatic hypotension occurred with a similar frequency, furthermore they had similar heart-rate changes. After the patients had experienced orthostatic hypotension, on continuation of HUTT, the blood pressure was similar in both groups. So, it was concluded that patients who experience orthostatic hypotension in the first 3 minutes and patients with orthostatic hypotension within the 4 or 5 minutes of HUTT can be compared. Moreover, this study shows that more cases of orthostatic hypotension may be detected with continuing postural stress for 5 minutes. [38]

A recent study describes late orthostatic hypotension to be as frequent as classical orthostatic hypotension. This study found that from 108 patients, 46% developed orthostatic hypotension in the first 3 minutes of HUTT, 3% after 3-5 minutes, 12% after 5-10 minutes, and 39% after 10 minutes. [45] [46]

Another study that describes the temporal progress of the systolic blood pressure during the first 5 minutes of HUTT divides the orthostatic hypotension into a stable orthostatic hypotension, a transient orthostatic hypotension with either an early or a late improvement

of the blood pressure, and a prolonged orthostatic hypotension with a continual decrease of the blood pressure. Patients who suffer from progressive orthostatic hypotension are assumed to have severe adrenal failure.

Gender differences in cardiovascular regulation in older persons?

As the case studies involve two males, it would be interesting to examine female patients in future as well. Cardiovascular and hormonal regulation differ significantly between men and women, and many studies have failed in the past in attempting to understand these different mechanisms. One of the reasons for this is that the hormone status of females changes over the 28-day cycle. In view of this changing background it is quite difficult to plan experiments. In the case of men, it has been shown that the hormone testosterone is quite constant. Therefore, they are “easier” candidates for cardiovascular-control studies. [72] Nevertheless, a considerable number of studies have been conducted in the recent past to investigate these differences.

Low blood pressure has been shown to appear more often in premenopausal women than in men of the same age. Furthermore, it has been found that premenopausal women tend to have a higher risk of orthostatic hypotension/dysregulation than men. [87] [88] It is possible that the many anatomical differences between men and women have an impact on these findings. First, women have smaller hearts than men. Moreover, they have decreased elasticity of the heart muscle and increased blood pooling in the pelvic region as compared to men. All these differences mean that women have a smaller cardiac preload than men. Because of the smaller cardiac preload, the stroke volume in women is also decreased. This might be one of the reasons why women tend to have a higher incidence of orthostatic hypotension/dysregulation. [88] [89] [90]

It has been shown that women have higher heart rates than men. [74] The sexes have been found to respond differently to cardiovascular stress. While women challenge cardiovascular stress by increasing their heart rate, men tend to respond more by increasing the vascular resistance. Furthermore, recent studies have shown that men have higher sympathetic activity than women, whereas women have enhanced parasympathetic activity in comparison to men. [75] The consequence of this is that during a change of body position, females tend to be more vulnerable to developing orthostatic hypotension. [76] It has been found that the sympathetic tone dominates in post-menopausal women. [86] If cardiovascular stress continues, the cardiovascular system adapts and remodels. The long-

term-consequence of this stress is that the vessels remodel, and this results in a sustained hypertension. [77]

Furthermore, no change of the cardiovascular response in males and females after a meal was found, although women have a lower mean arterial pressure than men. [78]

The composition of the blood cells circulating in the body also differs between the sexes.

Women have less red cells circulating in the body and therefore a lower haematocrit. [81]

Both lipid and plasma protein concentration show differences in females and males. Pre-menopausal women have a higher high-density lipoprotein (HDL) and lower triglyceride concentration than men, which is one of the reasons why premenopausal women have a decreased risk of cardiovascular diseases in comparison to men of the same age. This blood lipid profile is seen as “anti-atherogenic” and is associated with a lower risk of cardiovascular disease. Cardiovascular diseases increase the risk of developing orthostatic intolerance, which will be discussed below in more detail. [70] [71] After the menopause the lipid profile of females’ changes, and becomes more similar to that of men. [82]

Furthermore, men tend to have a higher blood pressure than pre-menopausal women of the same age. [79] After the menopause this difference is lost. [80] There is significant evidence that oestrogen protects against developing high blood pressure, whereas the opposite is true for testosterone. Many laboratories have seen evidence of oestrogen protecting against high blood pressure and thus coronary vascular disease. Furthermore, it has been seen that oestrogen replacement decreases the amount of low-density-lipoprotein (LDL) and increases the amount of high-density-lipoprotein levels. [83] However, this effect could not be observed in all studies. [84] [85] Lower blood pressure in premenopausal women could be one of the reasons why pre-menopausal women develop orthostatic dysregulation more often than men.

Orthostatic hypotension in older versus younger persons

Moreover, orthostatic hypotension is more prevalent in people above 65 years of age.

There are several risk factors for orthostatic hypotension in older people. One of these is impaired baroreceptor sensitivity. [70] This means that normally when someone stands up blood goes to the legs and then it must be redistributed, so that enough blood is available for the brain. The nervous system transmits signals to the heart and blood vessels to do this. In older people these responses are not as fast as they should be, and therefore they tend to faint more often. [71] Furthermore, cardiovascular diseases such as aortic stenosis,

pericarditis/myocarditis or arrhythmias, dehydration (decrease of preload) and some medication (blood pressure medication, surgical medication, anti-anxiety medication, diuretics, heart medication, antidepressants, narcotic painkillers) also increase the risk of orthostatic hypotension. These risk factors are also more common in older people. [70] [71] Moreover older people more often have stiffer hearts, which makes the heart unable to pump as well. [2] However, orthostatic hypotension can also occur in younger people. In this group it is caused by volume depletion or chronic autonomous nervous failure. [70]

Therapies for countering orthostatic hypotension

There are several strategies to increase the blood pressure in orthostatic hypotension without pharmacological intervention. Primarily important for the treatment of orthostatic hypotension is an increased intake of fluids (up to 2-3 litres per day) and salt. The goal of this is to increase the intravascular blood volume and thus the blood pressure. [58] In addition to increasing the blood volume throughout the day, the rapid ingestion of water also increases the blood pressure. A study from the Vanderbilt University found that a rapid intake of approximately 500 ml of water increases the systolic blood pressure >40 mmHg. The increase of blood pressure takes about 5-10 minutes to start, at 20-40 minutes it is at its highest level, and 60 minutes after ingestion it starts to decrease. Furthermore, the blood pressure increase was greater with 500 ml of water taken orally than with 500 ml of 5% dextrose in water given intravenously. [59] [60] Moreover, it has been found that abdominal binders and compression stockings can be used to decrease blood pooling in the lower extremities. With abdominal binders the systolic blood pressure can be increased by about 11 mmHg. However, their effectiveness is limited to the extent to which patients agree to use them. In these cases, family members can assist the patients. [61] There are several kinds of medication for patients who suffer from orthostatic hypotension. Normally they are used when non-pharmacological treatment fails, or the symptoms are very severe. Medication in use for treating orthostatic hypotension is Midodrine, an alpha1 adrenergic-agonist, fludrocortisone, a mineral corticoid, pyridostigmine, acetylcholinesterase inhibitor and droxidopa, a synthetic precursor of norepinephrine. Furthermore, there are several off-label agents, such as atomoxetine, octreotide, yohimbine, pseudoephedrine, ergotamine, and recombinant erythropoietin in use. [62]

5.2 Limitations

Nevertheless, there are some limitations of the case studies presented in this thesis. Due to the limited number of samples, it is difficult to generalize these data for patients of a different age and gender.

Despite the limitations of this work, it should be mentioned that this thesis is written within the framework of a more extensive study at LKH Knittelfeld, involving a few hundred patients. All these patients have experienced syncope and underwent tilt-table-testing for diagnosis. The outcome of this study will lead to a better understanding of the physiology of orthostatic intolerance. Such knowledge might be important for a better treatment of orthostatic intolerance, and can also serve a basis for further studies involving a higher number of patients.

5.3 Conclusions

The data presented here show the differences in cardiovascular responses in one patient who experienced syncope during tilt-table-testing, compared to one patient who did not. It has been shown that the patient without orthostatic intolerance had a quite constant blood pressure throughout the test, whereas the patient suffering from orthostatic intolerance experienced a drop of blood pressure and heart rate. The strength of this study lies in the fact that differences in cardiovascular response between patients suffering from, and those not suffering from, orthostatic intolerance during tilt-table-testing can be seen, even when only examining two patients.

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Appendix A

Name / ID		
Alter		
Geschlecht		
Geburtsdatum		
Größe		
Gewicht		
INDIKATION(EN)		
BESCHWERDEN	ja	nein
Erste Synkope (Ohnmachtsanfall)...1,2-5,>6		
Anzahl der Ohnmachtsanfälle		
Anzahl der Schwindelanfälle		
VERLETZUNGEN		
Keine		
Gering		
Schwere		
SYMPTOME		
Orthostatisch	ja	nein
Im Stehen/beim Aufstehen	ja	nein
Im Liegen/Sitzen	ja	nein
<i>Vasovagale Symptome</i>		
Symptome im Stehen	ja	nein
Schweißausbruch	ja	nein
Erblassen	ja	nein
Eintrübung oder Verengung des Gesichtsfeldes	Ja	nein
Wärmegefühl	ja	nein
Übelkeit/Erbrechen	ja	nein
Schwindelgefühle	ja	nein
während des Urinierens oder Lachens	ja	nein
Bei einer Blutabnahme	ja	nein
Nach dem Niederliegen	ja	nein
Prodromalsymptome	ja	nein
Nach einem heißen Bad		

atypische Anamnese	ja	nein
GRUNDERKRANKUNGEN		
Bluthochdruck	ja	nein
Hyperlipidämie	ja	nein
Diabetes mellitus	ja	nein
Hyperthyreose	ja	nein
Bereits erlittener Schlaganfall	ja	nein
Benigne Prostatahyperplasie	ja	nein
KRANKHEITEN IN DER VERWANDTSCHAFT	ja	nein
ERGEBNISSE		
Beschwerden während der Untersuchung	ja	nein
KOLLAPS		
Genauso wie zu Hause	ja	nein

