Thesis

Effects of Meditation on cardiovascular responses in patients undergoing cardiac rehabilitation: a pilot study

submitted by

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STATUTORY DECLARATION

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Guidelines of the Medical University of Graz on Good Scientific Practice ".

Graz, 06.09.2022 *Maximilian Elliot Rudlof eh.*

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List of abbreviations

ACE	angiotensin converting enzyme
ACS	acute coronary syndrome
ANS	autonomic nervous system
ARB	angiotensin receptor blocker
CABG	coronary artery bypass grafting
CCB	calcium channel blockers
CCD	chronic coronary disease
CCS	chronic coronary syndrome
CI	cardiac index
CO	cardiac output
CVD	cardiovascular disease
ECG	electrocardiography
EEG	electroencephalography
HDL	high density lipoprotein
HR	heart rate
HRV	heart rate variability
HRR	heart rate recovery
IHD	ischemic heart disease
LDL	low density lipoprotein
MAP	mean arterial pressure
MBP	mean blood pressure
MFR	myocardial flow reserve
MI	myocardium infarction
PAR	population attributable risks
PET	positron emission tomography
PCI	percutaneous coronary intervention
PNS	parasympathetic nervous system
RCT	randomized controlled trials
RRI	RR-intervals
SBP	systolic blood pressure
SNS	sympathetic nervous system

S(V)I	stroke (volume) index
SV	stroke volume
TM	Transcendental Meditation
TPR	total peripheral resistance
TPRI	total peripheral resistance index

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Abstract

Background: Cardiovascular diseases (CVD) are the leading death cause worldwide and despite continuous progress of medical care the prevalence of CVD increases. A growing body of evidence indicates that the practice of Transcendental Meditation (TM) positively affects the long-term outcome of CVD. While most of the studies address the issue of cardiovascular prevention or therapy, barely any research exists about the effects of TM in cardiac rehabilitation.

Objectives: The aim of this diploma thesis is to find out if the additional practice of TM during a cardiac rehabilitation program of patients that suffered a cardiac event, positively affects the rehabilitation outcome. Hence, the hypothesis that performing TM by patients undergoing a 4-week cardiac rehabilitation program augments the recovery of cardiovascular parameters during and after the rehabilitation was tested.

Methods: 20 volunteers attending a 4-week in-patient cardiac rehabilitation program were randomly assigned to group control (control) or group TM (TM). Cardiovascular parameters such as heart rate (HR), RR-interval (RRI), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), stroke volume (SV), stroke volume index (SI), cardiac output (CO), cardiac index (CI), total peripheral resistance (TP) and total peripheral resistance index (TPRI) were assessed with the Task Force Monitor®. Measurements were performed at the beginning (Pre) and at the end (Post) of the rehabilitation and 4 weeks later (Follow-up).

Results: Pre-Post: in both groups (n=18, males 89%, mean age 59.17 years, mean weight 87.50 kg, mean height 175.33 cm) the parameters RRI (p=0.05) and SBP (p=0.012) changed significantly. However, the magnitude of parameter changes was almost equal in both groups.

Pre-Post-Follow-up: due to the low number of participants and several missing values no group comparison was performed. The total follow-up population (n=11, males 100%, mean age 61.27 years, mean weight 86.91 kg, mean height 176.18 cm) showed significant changes in HR (p=0.017), RRI (p=0.002), CO (p=0.003) and CI (p=0.003).

Conclusion: Within one month of cardiac rehabilitation no additional positive effect could be achieved through the addition of TM to the rehabilitation program. However, cardiac parameters kept improving even one month after the rehabilitation in the whole follow-up population. As literature suggests that effects on the cardiovascular system through the practice of TM unfold in the longer term, future studies should comprise a longer follow-up.

Zusammenfassung

Hintergrund: Kardiovaskuläre Erkrankungen sind die weltweit häufigste Todesursache und trotz eines kontinuierlichen Fortschritts medizinischer Versorgung nimmt deren Prävalenz zu. Wissenschaftliche Untersuchungen zeigen zunehmend, dass sich die Ausübung von Transzendentaler Meditation (TM) positiv auf den Langzeitverlauf von Herzkreislauferkrankungen auswirken kann. Während sich die meisten Studien mit dem Thema kardiovaskuläre Prävention oder Therapie befassen, existieren kaum Untersuchungen zur Wirksamkeit von TM bei der kardialen Rehabilitation.

Ziele: Im Rahmen dieser Diplomarbeit soll untersucht werden, ob tägliches TM-Praktizieren von Patient*innen, die ein kardiales Ereignis hatten und deshalb an einer Herzrehabilitation teilnehmen, das Rehabilitationsergebnis verbessern kann. Folglich wurde die Hypothese überprüft, ob TM-Ausübung die Regeneration der kardiovaskulären Parameter während und nach einer 4-wöchigen kardialen Rehabilitation verbessert.

Methodologie: 20 Probanden, die an einem 4-wöchigen stationären Kardio-Rehabilitationsprogramm teilnahmen, wurden zufällig der Gruppe „control“ oder der Gruppe „TM“ zugeteilt. Kardiovaskuläre Parameter wie Herzfrequenz (HR), RR-Intervall (RRI), systolischer Blutdruck (SBP), diastolischer Blutdruck (DBP), mittlerer arterieller Druck (MAP), Schlagvolumen (SV), Schlagvolumsindex (SI), Herzminutenvolumen (CO), Herzindex (CI), totaler peripherer Widerstand (TPR), und totaler peripherer Widerstands Index (TPRI) wurden mit dem Task Force Monitor® gemessen. Die Messungen wurden zu Beginn (Pre) und am Ende (Post) der Rehabilitation und weitere 4 Wochen später (Follow-up) durchgeführt.

Ergebnisse: Pre-Post: in beiden Gruppen (n=18, männlich 89%, Durchschnittsalter 59,17 Jahre, Durchschnittsgewicht 87.50 kg, Durchschnittskörpergröße 175.33 cm) veränderten sich die Parameter RRI (p=0,05), SBP (p=0,012) signifikant. Die Größe der Veränderung war in beiden Gruppen jedoch annähernd gleich.

Pre-Post-Follow-up: Aufgrund der geringen Probandenzahl und einiger fehlender Werte wurde kein Gruppenvergleich durchgeführt. Die gesamte Follow-up-Population (n=11, männlich 100%, Durchschnittsalter 61.27 Jahre, Durchschnittsgewicht 86.91 kg, Durchschnittskörpergröße 176.18 cm) zeigte wiederum signifikante Veränderungen in HR (p=0,017), RRI (p=0,002), CO (p=0,003), CI (p=0,003).

Schlussfolgerung: Innerhalb eines Monats konnte kein zusätzlich positiver Effekt durch die Ergänzung von TM im Rehabilitationsprogramm festgestellt werden. Allerdings verbesserten sich

die kardialen Parameter auch noch einen Monat nach der Rehabilitation in der gesamten Nachbeobachtungspopulation. Da die Literatur darauf hindeutet, dass sich Effekte auf das kardiovaskuläre System durch TM erst längerfristig zeigen, sollten zukünftige Studien eine längere Nachbeobachtungsperiode umfassen.

1. Introduction

1.1 The chronic coronary syndrome

The term “chronic coronary syndrome” (CCS) describes a condition of insufficient supply by oxygenated blood of the heart muscle, the so-called myocardium. It is mostly affected by a diameter decrease (stenosis) of the blood vessels, that supply the myocardium (coronary arteries), in consequence of an atherosclerosis disease, which is by far the most frequent cause of the CCS (1,2). When searching the literature synonyms describing the same pathology as “cardiovascular disease” (CVD), “Ischemic heart disease”, “Coronary heart disease”, and “Coronary artery disease” can be found (3,4).

Atherosclerosis is an immunoinflammatory process of the artery endothelial layer (the inside lining of all vessels) affecting primarily large and medium-sized arteries. While at the beginning of the disease the lesions of the endothelium are minimal and appear as so called “fatty streaks”, through reactive changes the pathogenesis goes on and a “plaque” is developing in the underlying vessel wall. With further progression this leads to a blood vessel stenosis. A big plaque can rupture which leads to a platelet activation and consequently a vessel occlusion by a thrombus. The described process of disease progression with the outcome of a thrombosis is responsible for the majority (76%) of all fatal heart attacks (2,5).

The CCS causes typically a symptom complex that is called “stable coronary syndrome”. Patients describe it as chest discomfort, squeezing pain or pressure. It is usually precipitated by exercising or emotional stress, when the oxygen demand of the myocardium exceeds the oxygen maximum that can be delivered by the narrowed coronary vessels. If the discomfort vanishes after a short period of resting or through the intake of nitroglycerine, it is called “stable angina pectoris”. However, there can also occur atypical symptoms, affecting especially women, like atypical chest pain, dyspnea and silent ischemia (without chest pain) (1,6).

With further progression of the disease the probability of an “acute coronary syndrome” (ACS) increases. This is a potentially life-threatening situation if the ACS is caused by myocardium Infarction (MI). As describes above, it comes to an acute occlusion (thrombosis) due to a rupture of an unstable arteriosclerosis plaque, of one or more coronary branches. The lack of oxygen leads to an irreversible damage of myocardial cells. The scope of the heart muscle damage depends on

the grade and localization of the occlusion as well as on the duration until it comes to a revascularization (5–7).

The WHO estimates that in 2016 17.9 million people died in the consequence of CCD. Claiming 31% of all global deaths this disease is the number one death cause worldwide (8).

1.2 Cardiovascular risks

The inflammatory process that leads to atherosclerosis seems to be highly affected by humans´ behavior. A study published in 2000 by the New England Journal shows that just via a healthy lifestyle up to 80% of the CCS cases could potentially be avoided (9). Moreover, between 1985 and 2000 there was a significant decrease in deaths due to CCS in Ireland. A conducted study suggests that more than the half of this death-rate-decline has been attributed to lifestyle intervention that lead particularly to a reduction of cholesterol, blood pressure and nicotine abuse (10). The "ECS Guidelines on cardiovascular disease prevention in clinical practice" points out that the prevention of cardiovascular diseases is more cost effective and sustainable than its treatment (11). However, for a successful primary and secondary prevention, modifiable risk factors first have to be detected and defined. In this context the findings of the INTERHEART study, that was published in 2004 in the Lancet, might be the most important reference. About 30.000 people all over the world were included. Salim Yusuf and his team found nine parameters that should represent about 90% of all modifiable risk factors associated with MI, so-called "population attributable risks" (PAR). These nine defined PARs are: smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial stressors, unhealthy nutrition, alcohol consumption and physical inactivity (12). These are almost identical to the modifiable risk factors listed in the UpToDate guidelines (April 2020) for CCS (11).

1.2.1 Risk factor: stress

Further on, the cardiovascular risk factors shall be explained more precisely. The findings of the INTERHEART study show that current smoking and dyslipidemia are the major risk factors, followed by diabetes, hypertension and psychosocial factors (12). Although the psychosocial parameter increasingly proves to play an important part in the pathogenesis of CCS, this parameter is quite difficult to define and to measure objectively. The initiators of INTERHEART study claim to have found a convenient way to assess stressors and suggest that this aspect, despite its increasing recognition, still might be highly underestimated (13). The importance of these findings is

highlighted by another study which found that about three-fourths of cardiac patients are burdened with high level of psychological distress (14).

Stress has to be separated into acute and chronic stress as each affects the cardiovascular system in a different way. The experience of acute mental stress is associated with the appearance of ACS and MI. One example is the phenomenon that after natural catastrophes (e.g. an earthquake) the incidence of heart attacks considerably increases (15) or another, that after an outburst of anger, the likeliness of an acute cardiovascular event is fivefold heightened (16). Just like physical stressors, psychic stressors activate the sympathetic nervous system (SNS) and lead to a withdraw of the parasympathetic nervous system, which effects an immediate increase of the arterial pressure and the heart rate, including a higher oxygen demand of the cardiac muscle. Further negative effects are a transient dysfunction of the endothelium and an increased atherothrombotic activity (17).

The effects of a persisting stress burden are quite complex and not yet entirely discovered. However, through the SNS and the hypothalamic-pituitary-adrenal axis, several molecular cascades are generated that modify the organism´s immune state, metabolism and nervous system. Especially the persisting cortisol elevation leads to salt retention (hypertension), insulin resistance (diabetes mellitus), visceral fat syndrome (obesity) and increase of LDL cholesterol (dyslipidemia) (17). All these factors contribute to the progression of atherosclerosis and CCS, as described in the chapters above. The term “chronic stress” includes conditions like work-stress, home-stress, social isolation, low income, financial stress and chronic emotional disorders like anxiety and depression (13,17).

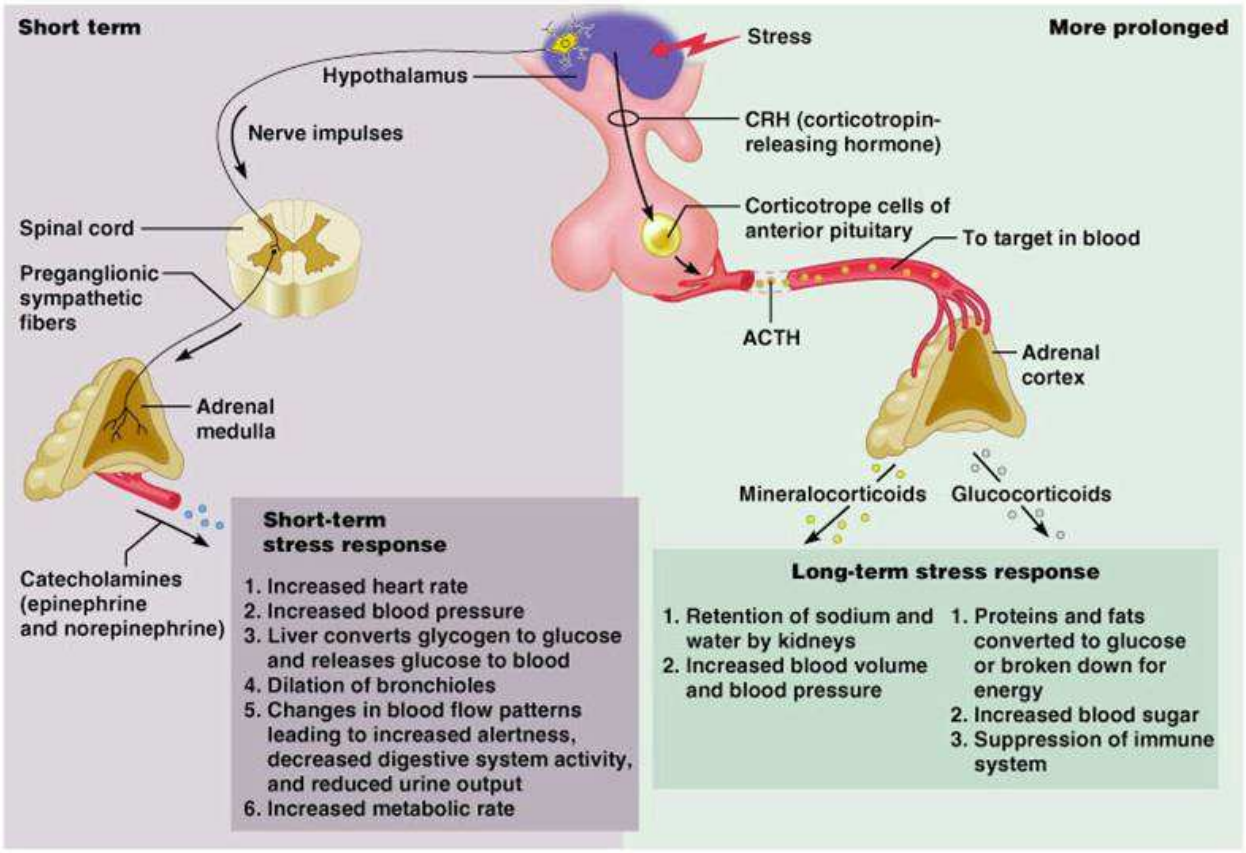

Figure 1: Schema of the HPA-axis (hypothalamic-pituitary-adrenal-axis). The response to short and long-term stress is shown. Acute stress signaled by the hypothalamus leads to catecholamine release of the adrenal medulla which leads to the typical "fight or flight"-reaction (temporary increase of heart rate, blood pressure, blood glucose, etc.). Prolonged stress however leads to an augmented stimulation of the adrenal cortex through the hormones CRH (corticotropin releasing hormone) and ACTH (adrenocorticotropic hormone). Consequently, Mineralocorticoids and Glucocorticoids are secreted into the blood and cause a prolonged increase of blood pressure, blood glucose and immune suppression.
(taken from: austincc.edu/apreview/PhysText/Endocrine.html)

1.2.2 Regulation of the autonomic nervous system (ANS)

Charles Darwin already noticed that there is a strong correlation between emotions and the heartbeat. He observed that certain emotional states can effect an instant change of the heart´s activity (18). Today it is known that the autonomic nervous system (ANS) regulates the homeostasis and adapts the organism to external stimuli and internal needs. Therefore, the ANS is separated into two subsystems, the parasympathetic and the sympathetic nervous system. The parasympathetic nervous system (PNS) also referred to as "vagus" (which is accurately the tenth cranial nerve and represents the main branch of the PNS) promotes functions like growth and recovery. With a predominant PNS activity the organism mainly deals with the restoration and conservation of energy resources ("rest and digest"), the gastrointestinal tract is well supplied by blood and the vital organs come to rest. An increased activation of the sympathetic nervous system

(SNS) however mobilizes energy resources (catabolic metabolism), increases the heart lung activity and shifts the blood from the gastrointestinal tract to the skeletal muscles to enable the physical performance that is required to coupe with external challenges ("fight or flight") (19). The two branches of the ANS and its effects are illustrated in the figure below.

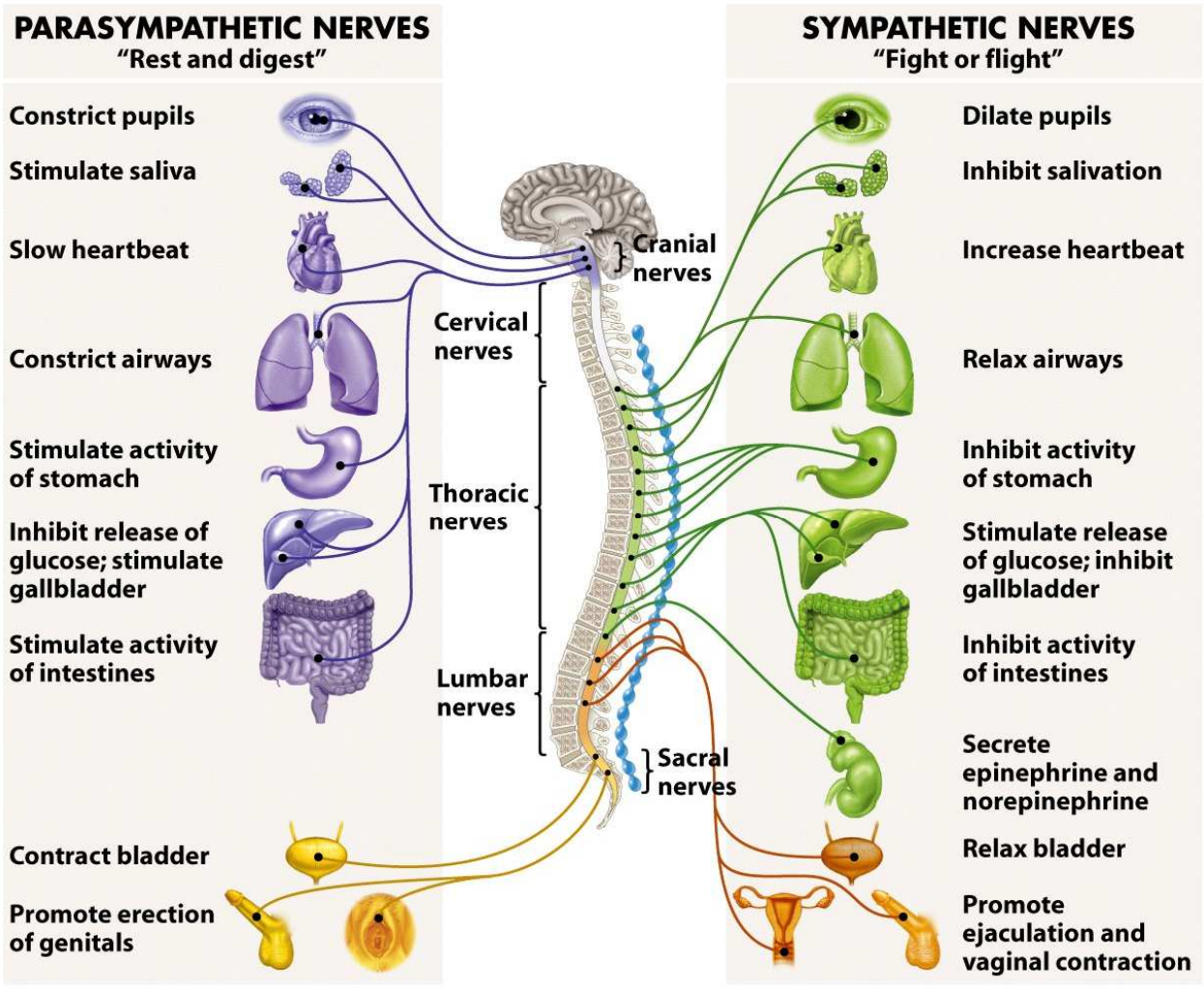

Figure 45-20 Biological Science, 2/e
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Figure 2: Schema of the autonomic nervous system (ANS). On the left side the parasympathetic nerve branches are shown (violet and yellow) and on the right sight the sympathetic nerve branches are shown (green and orange). Beside the illustrated organ(systems) the certain effects are described that are evocated whether by the parasympathetic ("rest and digest") or by the sympathetic ("fight or flight") system. (taken from: scienceforsport.com/heart-rate-variability-hrv/)

While both the PNS and the SNS are differently structured, they also mediate their activity through different neurotransmitters. The sedative effect by the PNS, which lowers the heart rate and the system velocity, is regulated by a synaptic release of the neurotransmitter acetylcholine. The mediation through acetylcholine has extremely low latency and allows the vagus to regulate the

cardiac activity within milliseconds beat by beat. This enables the heart to work with maximum economic efficiency while resting. In contrast, an increase of the SNS activity is mediated through the neurotransmitter noradrenalin and this happens comparatively slowly, since it takes some time to reabsorb and metabolize this certain transmitter (20).

Since the early 1960s, the different latency time of the SNS and PSN found utilization in clinical practice. It was known that a reduced beat to beat (R-R interval) variation is associated with an increased morbidity and mortality. Scientists soon discovered that lower heart rate variability (HRV) is caused by a PNS withdraw and an augmentation of the SNS. By recording the HRV, it was possible to do a real time non-invasive analysis of the organism´s sympatho-vagal balance (20). Through being able to monitor the parasympathetic state, a new method of stress assessment was developed (19).

Going more into detail of HRV, there are high and low frequent changes in the variability of R-R intervals. While high frequent (HF) changes between 0.15 and 0.40 hertz are associated to the PNS adapting the cardiac activity to the breathing, which causes periodic changes of the intrathoracic pressure, low frequent (LF) changes between 0.04 and 0.15 hertz are associated to sympathetic activity (20).

There is a long list of diseases that cause autonomic dysfunction leading to a HRV decline. Among these are diabetes mellitus (type one and two), cardiac diseases, renal diseases, chronic liver diseases, chronic respiratory diseases and severe autonomic dysfunctions (e.g. HIV) as well as psychological diseases (e.g. depression) (20,21).

The assessment of HRV provides a valuable prognostic factor: to identify patients at high risk, to track the disease´s progression, to find an appropriate treatment and as follow-up after therapeutic interventions (20).

To come back to Charles Darwin´s findings, stressors do not compulsory have to be physical, also mental stress and emotional disorders affect the ANS. Even here HRV has proven as a valid, objective and simple method when it comes to assess psychical stress (22).

A study that analyzed the data of over 90.000 postmenopausal women found that patients with depression had a significantly higher likeliness to suffer on a cardiovascular disease and had a higher overall mortality (23). Moreover, the HRV decreases with the growing severity of depression (24). As a meta-analysis found, depression might even be a more important risk factor

for the genesis of cardiovascular diseases than smoking or diabetes (25). In general, a close link between physical and mental illness can be seen.

1.3 Standard Therapy

The therapy of the CCS implicates a wide range of interventions with the aim of reducing the anginal symptomatic and preventing cardiovascular events. Beyond pharmacological management, lifestyle changes (e.g. weight reduction, smoking cession, exercise), education and revascularization procedures play an important role.

Pharmacological management (3,26)

Usually, CCS patients´ first line medication consist of a short acting nitrate for immediate relief of angina pectoris symptoms, one or two anti-ischemic drugs like beta-blockers or calcium channel blockers to improve the cardiac muscle´s blood supply and working efficiency plus drugs to prevent further cardiac events. The medication should be individually adapted depending on the patient´s health condition, comorbidities, preexisting medication and personal preferences.

Anti-ischemic medication

Nitrates - Patients with stable angina pectoris should have short-acting nitrates. Those are taken at the onset of acute angina symptoms sublingual or as oral spray. These so-called NO-donors (NO = nitric oxide) are rapidly delivering NO which leads to an immediate relaxation of the smooth muscle cells in the vascular walls of bigger arteries (including the coronary arteries) and veins which thereby improves the myocardial perfusion. A further beneficial effect of NO is a platelet aggregation inhibition.

As long-time medication first line therapy are beta-blockers or calcium channel blockers (CCB). In severe cases both might by prescribed.

Beta-blockers - By blocking the beta-receptors, it comes to a partial inhibition of the sympathetic nervous system especially in vessels and the heart. The sympathetic nervous system usually prepares the organism for fight or flight through forcing up heart rate and blood pressure. Beta-blockers lead to a decline of the cardiac output by reducing the cardiac chronotropy (heart rate) and inotropy (force of cardiac muscle contraction). This also drops the oxygen consumption of the myocardium effecting a reduction of cardiac events and thereby the cardiac mortality.

Calcium channel blockers - CCB unfold their effects in inhibiting L-type calcium channels (L stands for long-lasting). Three groups of calcium channel blockers are described. The dihydropyridine, the phenylalkylamine and the benzodiazepine. While the first group has higher affinition to calcium channels of the blood vessel´s smooth muscle cells, phenylalkylamine and the benzodiazepine tend to block the calcium channels of the myocardial cells and thereby they have different effects. The vessel dilation caused by Dihydropyridine leads to a significant blood pressure reduction. Phenylalkylamine and benzodiazepine however affect the heart conduction system and the cardiac muscle activity by negative chronotropy (heart rate), negative inotropy (inotropy (force of cardiac muscle contraction) and negative dromotropy (deceleration of the cardiac nervous conduction).

Event prevention medication:

Antiplatelet drugs also make up an important part of morbidity and mortality reduction in patients with high cardiovascular risk. Either low-dose aspirin or if contraindicated or not tolerated, the P2Y12 inhibitor Clopidogrel can be used alternatively. Through different mechanisms these substances inhibit the platelet activation, which is the main player in forming a thrombus. As described in chapter "1.2 Chronic coronary syndrome" this might lead to an acute occlusion of a coronary artery by thrombosis.

Further medication:

CCS is mostly associated with several other morbidities such as dyslipidemia, hypertension, diabetes and others. Therefore, it is indispensable to treat these comorbidities as well as to reduce disease progression and the risk of cardiovascular events.

Dyslipidemia should be managed with lipid-lowering drugs together with a lifestyle modification. According to the ESC Guidelines of 2019, every patient with CCS is recommended to receive statins, irrespective of the serum cholesterol levels. Statins inhibit the synthesis of cholesterol by blocking the enzyme HMG-CoA reductase in the liver.

Moreover, for CCS patients with hypertension a blood pressure regulating therapy should be considered strongly. It is recommended to use ACE-Inhibitors (ACE = Angiotensin converting enzyme) or if not tolerated ARBs (Angiotensin receptor blockers). This substance group inhibits the renin-angiotensin-aldosterone-system, which is an important regulator for the blood pressure. This happens either by disrupting the synthesis of angiotensin II (ACE Inhibitors) or by blocking

its receptors (ARBs). Angiotensin is a very potent vasoconstrictor and increases the renal sodium and water retention, both contributes to a blood pressure elevation.

A coexisting diabetes mellitus also has a massively negative impact on the progression and prognosis of the disease, which is why an appropriate therapy should immediately be initiated.

To achieve the best possible outcome for the patient, it is important to diagnose and treat all other comorbidities that might negatively affect the CCS.

Revascularization (3,27,28)

Cardiovascular revascularization intervention aims to improve the myocardial perfusion by either eliminating or circumventing the stenose with a bypass graft. Its noteworthy that a such an intervention does not replace the medical therapy and brings some risks. Therefore, it is important to evaluate the individual risk-benefit ratio. Nevertheless, revascularization might relieve angina symptoms and even allow a medication dose reduction in many cases. When considering an interventional reperfusion strategy, the shared decision-making aspect is very important.

With the percutaneous coronary intervention (PCI) and the coronary artery bypass grafting (CABG) there are two different types of revascularization therapy.

The PCI is a minimal invasive procedure. Access to the vascular system is typically gained through the radial or femoral artery. Then a wire is passed through the arterial vessels up to the coronary arteries and further trough the stenose. Along this wire a catheter carrying a deflated balloon is placed in the narrowed area, which gets eliminated when the balloon expands. Through this procedure it is also possible to place a stent that covers the balloon and remains in the vessel once expanded.

However, the CABG is a surgical intervention and requires a sternotomy (a cut through the breastbone) or at least a mini-thoracotomy in certain cases. This form of intervention seeks to bypass the stenotic area by creating an extra vessel that is sewn distal of the stenosis and is thereby enabling a sufficient blood supply of the myocardium. The left or right internal thoracic artery is usually used as bypass craft or alternatively a radial artery. Venous bypass grafts, like the great or small saphenous vein, are no longer used preferentially, since arterial bypass grafts have proven to last longer.

PCI is the preferred therapy intervention for ACS. It allows a quick revascularization which is crucial to improve the prognosis of a MI. For the treatment of stable angina pectoris both PCI and CABG can be performed, but in case of a severe three vessel disease (meaning that all three coronary arteries are affected by arteriosclerotic stenoses) the CABG has shown a significant survival benefit according to the SYNTAX-study conducted by Thuijs et al. (2019) that has examined the survival of patients with either PCI or CABG over ten years.

1.4 Cardiac Rehabilitation

The American Heart Association strongly recommends that after any cardiovascular event (myocardium infarct, acute coronary syndrome, heart failure or revascularization therapy) patients should participate in a cardiac rehabilitation program to accelerate recovery, reduce symptoms and increase quality of life (29,30). According to the European Society of Cardiology all patients with established coronary artery disease, would benefit from rehabilitation (31).

Cardiac rehabilitation therapies are usually prescribed by cardiology health professionals. To enable maximum benefits form the rehabilitation, it is recommended to attend the rehabilitation as soon as possible after the event or diagnosis (32). Rehabilitation is commonly conducted in a rehabilitation facility and supervised by a dedicated team of doctors, nurses, various trainers, nutritionists and counselors. The American Heart Association Guidelines states that the program should be multidisciplinary and comprise the following core components: baseline health assessment, physical exercise, specific risk factor management, psychological assistance and education (33).

The intensity of the exercise should be adapted individually. Hence, patients should get classified in different performance groups based on their physical condition (34). By following the classification standards, the beneficial effect of supervised exercise-based rehabilitation outweighs the risk to of further cardiovascular events by far (35). Aerobic low impact activities, that particularly require the big muscle groups, such as walking, jogging, cycling or the like, at least thrice a week are recommended. The intensity and target heart rate during the training depends on the performance group and the baseline assessment (34).

For the management of hypertension, dyslipidemia and diabetes, it is essential that next to a pharmacological therapy, patients get encouraged to lifestyle modifications through education and counseling especially on diet and weight management (33).

To improve the long-term outcome it is crucial to eliminate nicotine abuse as a major risk factor. Due to the combination of physical and psychical dependence, smoking cession is hart to achieve. Strategies like individual counseling or group therapy, pharmacological support (nicotine replacement therapy or bupropion) or even interventions like acupuncture or hypnosis might be helpful (33).

Physiological issues, especially depression, anxiety and denial, are quite frequent among patients that suffered major cardiac events (36). The mortality is told to be four-fold higher after a cardiac event in patients with depression (37). Hence, the engagement of psychological professionals is indispensable during rehabilitation. Moreover, it has been proven that the medical outcome of cardiac rehabilitation programs further increases by adding stress management training (38).

While the combination of all the listed core components contributes to the beneficial long-time outcome of cardiac rehabilitation, especially the physical exercise training seems to play a major role. Through exercise an improvement of functional cardiac capacity, a delayed onset of ischemia, a reduction of anginal symptoms (39–41), a reduction of abnormal heart rate and an increase of the ejection fraction (42) can be achieved. Beyond heart associated improvements, especially overweight patients, that make out the majority of persons attending the cardiac rehabilitation, benefit from high-calorie expenditure exercises, by weight reduction and a decrease of body fat, blood pressure, insulin resistance and dyslipidemia (43). Moreover, a decline of the inflammation marker CPR can be observed (44). Through all these mechanisms a lower long-time incidence of hospital admission, recurrent MI and mortality can be achieved (45–49). This might enable patients to return to work and leisure activities. Particularly for elder patients this might contribute to an independent life (39).

1.5 Meditation therapy

Meditation can be seen as a calm exercise that is routinely performed to seek recovery and to sustain health. There are various forms of meditations originating from various ancient traditions. Some are linked to religious or spiritual ideologies. As the practice of meditation becomes increasingly popular in the west some techniques have been studied since the 70s and revealed numerous possible positive effects on human health. Hence, mediation is by now classified as integrative approach to improve general heath and therapeutic success (50).

1.5.1 American Heart Association Statement 2017

In 2017, the American Heart Association (AHA) made a statement about meditation as therapy. Considering the results of numerous studies about meditation therapy, the association suggests that there seems to be a beneficial, though not definitely established, effect on cardiovascular diseases and its risk factors. Since meditation therapy is low in costs and associated with low risks, in this statement it is recommended as optional adjunction to guideline-based therapy and risk reduction, especially for those that are interested in this certain kind of lifestyle modification. Further, it is stated that about half of the cardiovascular patients seem to be interested in complementary therapy approaches (51).

1.5.2 Transcendental meditation (TM)

The technique of the transcendental meditation (TM) derives from an ancient Vedic tradition of India. It was brought to the West in the 50s by the so-called Maharishi Mahesh Yogi. Since then, more than five million people have been instructed to this certain technique of meditation. It is systematically taught by trained professionals in a standardized procedure. This ensures that the practice of TM is always performed in the same way and that the research globally done on this topic can be compared. Up to 2012 more than 600 studies about TM were conducted. The technique is told not to be tied to any type of spirituality or religion and can be learned by anyone regardless of age, education level, cultural background and socioeconomic status. It is practiced twice a day about 20 minutes in a comfortable sitting position with closed eyes. During the meditation, the ordinary thinking process is “transcended” and a state of pure consciousness achieved, which is described as the experience of inner stillness, rest and absence of mental burdens. Although this old technique was not primarily developed with the intention to treat diseases, a frequent practice seems to relieve stress and its deleterious effects on the organism (52–54).

There are a few strengths that the TM has compared to other relaxation techniques. First, it is taught and practiced in the same way all over the world, which makes it easier and more attractive to put effort in research. Hence, the TM program obviously is the most extensively investigated method of its kind. Second, compared to other relaxation techniques like autogenic training, biofeedback methods, progressive muscle relaxation and a variety of further stress management techniques, the TM seems to be the most effective strategy, in context of stress and cardiovascular risk reduction. A systematic review of over 100 studies about elevated blood pressure revealed that only the TM

program was capable to achieve a significant blood pressure reduction. Third, the technique is easily learned and effortlessly practiced and because of that in clinical trials participants show a very high compliance, which might also be responsible for its effectiveness (52–55).

1.5.2.2. Evidence based benefits of TM

There is growing body of evidence revealing the sustainable effects of TM on the organism's well-being. However, this chapter will be restricted to those trials addressing the cardiovascular system.

A number of studies, including independent randomized clinical trials (RCT), showed that through the practice of TM blood pressure could be decreased by up to 13 mmHg systolic and 8 mmHg diastolic (55–60). A pilot RCT of participants with CVD showed a significant increased heart performance after 8 month of practicing TM. Compared to the control group, they had a delayed onset of myocardial ischemia (ST segment depression), a higher exercise tolerance and a higher work load of the heart during exercise (61). Further, the Left ventricular mass (LVM), which is an important progression indicator of heart diseases, was stable in patients that practiced TM, compared to controls that received health education. Moreover, the LVM even reduced in younger people that learned the TM technique (52,62,63). A study that was published in the *Stroke* journal found remarkable changes in the intima-media thickness (vessel wall) of the TM practicing group, suggesting that stress reduction through TM is associated with reduction of atherosclerosis (64). Also a significant decline of hypercholesterolemia could be observed after a time of three months or more in the TM groups (65,66).

A meta-analysis of 31 studies and several other trials found consistent evidence of sympathetic activity reduction during and after the practice of TM. Using various research procedures, a decline of acute and chronic stress hormone baseline levels and turnover rates, a normalizing of the hypothalamic–pituitary–adrenal axis (HPA axis) function and a decrease of heart rate baseline, respiratory rate, plasma lactate and spontaneous skin resistance, could be found. All these parameters represent a lower chronic stress load (52,67–70).

Further, the TM technique has proven as a highly effective treatment in respect of psychological disorders. A meta-analysis that compared various relaxation techniques found out that TM was significantly more efficient in reducing anxiety compared to the other techniques (like Progressive Relaxation, EMG Biofeedback, other forms of meditation) (71). Even as treatment of posttraumatic stress disorders (PTSD) in veterans the TM technique seems to has been quite effective (72). The

practice of TM also showed a significant reduction of psychosocial distress, burnout and depression prevalence (73,74).

The major risk factor smoking also seems to be positively affected by the practice of TM, according to a meta-analysis of 19 studies with collectives from all social classes. The review focused on substance abuse overall and concluded that the TM program had the biggest effect on the cession of harmful substance abuse, especially for cigarettes, and was more sustainable than other techniques (75). Another trial observed, that although the TM program does not particularly advice to quit smoking, half of the high compliant participants in the TM group stopped smoking within two years. This is believed to be achieved through an increased sensitivity for harmful effects and a reduced urge for stimulation (76).

Overall morbidity and mortality seem to decline drastically among patients participating in clinical TM trials. An investigation on medical insurance claims showed, that a number of 2.000 TM practitioners had a 53% lower in-patient and 44% lower out-patient hospital admission compared to 60.000 other insurance members by using the chi-square statistic. In the category of heart and blood vessel diseases the admission reduction was even higher with 87% (77). Further studies have shown an all-cause mortality decline of 43% (over a period of 5 years) and a cardiovascular mortality decline of 44% (over a period of 15 years) for the participants of the TM groups (78,79). A related study with hypertensive patients older than 54 years found that the all-cause mortality after three years was lower by 23% and the cardiovascular mortality by 30% with TM, which is comparable to the efficiency of pharmacological antihypertensive therapies (80).

In a trial of Herron et al. that was conducted in Quebec with 1.418 matched TM subjects, the TM group showed an average payment decline to physicians of 13% annually over a period of six years (81). Thereby, the TM technique is found to be very cost-effective lifestyle intervention with sustainable health benefits (54).

Considering all the beneficial effects listed above that could possibly be achieved through the practice of TM, this certain kind of intervention can not only ease symptoms and reduce disease progression, but also be very effective as disease prevention and health promotion, since it is relatively cost effective compared to pharmacological, surgical and rehabilitative interventions. No to be forgotten that it can be learned by practically everyone (53).

However, a few issues should be mentioned that might affect some of the cited studies of this chapter. First, research on this topic has been done soon after the TM technique was established in the west. This means that some of the studies are quite old and hence may contain information or methods that are no longer state of the art. Second, some clinical trials investigated on a relatively small number of participants and others were not RCT, thus not all findings might be generally representative. Third, many of the studies are carried out by the same groups of investigators or by the same organizations. More independent verification is needed to objectify the result. And last, many of the researchers seem to have a strong believe in the technique by their own, which could lead to unintended bias (51,52).

1.6. Cardiovascular assessment

In this chapter some relevant cardiac parameters will be explained, that will be used later to assess individual cardiac conditions of the participants.

HR – Heart Rate: (82)

The count of heart beats per minute (bpm). The reference range in adults is between 60 to 80 bpm. It raises during physical activity to guarantee a sufficed blood supply of the organism and declines while resting. Further the heart rate depends on factors like age, sex and fitness level.

RRI – RR-Intervals: (82)

The R-peak is usually the highest spike of the QRS-complex in the ECG. The duration in between two heart beats is measured from one R-spike to the next and is called the RR-interval. It is commonly given in milliseconds (ms). When the heart rate increases the RR-interval gets shorter and the other way round.

HR = 60 -> RR-interval = 1000 ms

HR = 85 -> RR-interval = 705,9 ms

SBP – Systolic Blood Pressure: (83)

With the contraction and blood ejection of the heart (systole) the pressure in the vessels reaches a peak. This peak is the so-called systolic blood pressure and is given in millimetre of mercury (mmHg). The normal systolic blood pressure should be at 120 mmHg or less in healthy adults.

DBP – Diastolic Blood Pressure: (83)

During heart relaxation and blood filling (diastole) the blood pressure reaches its minimal mmHg value which is called the diastolic blood pressure and should be down to approximately 80 mmHg in healthy adults.

MAP – Mean Arterial Pressure: (84)

The mean arterial pressure depends on the cardiac output (CO) and the peripheral resistance (TPR). It represents the organism´s perfusion. It can be invasively measured or approximately calculated form the SBP and the DBP with the following formulas:

$$central\ MAP = 1/2 * (SBP + DBP)$$

$$peripheral\ MAP = DBP + 1/3 * (SBP - DBP)$$

SV – Stroke Volume: (85)

The stroke volume is the amount of ejected blood during the systole by the left ventricle measured in milliliter (ml). It is the difference between the left ventricular end-diastolic volume (maximal filling) and the left ventricular end-systolic volume (minimal filling). The stroke volume in an untrained healthy adult count between 70 and 100 ml.

$$SV = LVEDV - LVESV = ml$$

SVI – Stroke Volume Index: (86)

The stroke volume (SV) divided by the body surface generates the stroke volume index, which is a cardiac performance. It physiologically should amount 30 to 65 ml/m^2.

$$SVI = SV / Body\ surface = ml/m^2$$

CO – Cardiac Output: (87)

Cardiac output is the amount of blood that is ejected by the heart within one minute. It is calculated from the stroke volume (SV) and the heart rate (HR) and given in liters per minute (l/min). During rest the CO accounts about 5 l/min and can increase to 30 l/min during exercise.

$$CO = SV * HR = \ l/min$$

CI – Cardiac Index: (88)

The cardiac index represents the cardiac output related to the body surface. It can be used for hemodynamic monitoring of the heart performance and accounts between 2,5 and 4 l/min/m^2.

$$CI = CO / Body\ surface = l/min/m^2$$

TPR – Total Peripheral Resistance: (89)

The total peripheral resistance is the vascular resistance of the body circulation that must be overcome to keep the blood flowing. It is mainly affected by precapillary vessels and is high if these vessels are constricted and low if they are dilated. For its calculation a further parameter that has not yet been described needs to be assessed, which is the central venous pressure (CVP). The CVP is usually invasive assessed with a central venous catheter sonde in the right antrum. It normally ranges from 2 to 8 mmHg. The value for the TPR however is calculated form the quotient of arteriovenous blood pressure difference (MAP - CVP) and the cardiac output (CO).

$$TPR = (MAP - CVP) / CO = mmHg*min/l$$

However, the unit that is commonly used for peripheral resistance instead of *mmHg * min/l* is *dyne * seconds/cm^5*:

$$1\ mmHg * min/l = 80\ dyne*s/cm^5$$

$$TPR = [(MAP - CVP) / CO] * 80 = dyne*s/cm^5$$

The TPR ranges physiologically from 700–1600 *dyne*s/cm^5* or 8,75 to 20 *mmHg*min/l*.

TPRI – Total Peripheral Resistance Index: (89)

The TPR-Index is once more related to the body surface and as the TPR usually given in *dyne*s*m^2/cm^5*. It ranges from 1500 to 2500 *dyne*s*m^2/cm^5*.

2. Aims and Objectives

Despite continuous medical advances, the prevalence of cardiovascular diseases is rising and represents with over 30% the worldwide leading cause for deaths (8). Meditation as one of many integrative therapy approaches, particularly the TM technique, has proven of several beneficial effects on the cardiovascular system. While most of the trials investigate the effectiveness of TM in cardiovascular prevention or in cardiovascular therapy, it remains unclear if TM could also be useful in cardiac rehabilitation.

The aim of this diploma thesis is to find out if the additional practice of Transcendental Meditation during a 4-week cardiac rehabilitation of patients that suffered a cardiac event, positively affects the rehabilitation outcome.

The hypothesis that providing TM to patients undergoing a cardiac rehabilitation program leads to additional improvement of the cardiovascular parameters during and after the rehabilitation shall be tested.

The primary endpoints are changes in cardiovascular characteristics such as the HR, RRI, SBP, DBP, MAP, SV, SI, CO, CI, TPR and TPRI in between the study groups. Moreover, the outcome of this pilot study might help to answer questions of feasibility and reasonability to conduct further investigations on this topic and if so, enable the calculation of accurate sample sizes for future investigations.

3. Methodology

3.1 Setting and Location

The “Transcendental Meditation and Yoga in Rehabilitation Study” (TMY-Study) was carried out in October and November 2019 primarily in the Cardiac Rehabilitation Clinic in St. Radegund. The follow-up measurements were performed in the facility of the Physiology Institute of the Medical University of Graz.

3.1.1 Cardiac Rehabilitation Clinic PVA St. Radegund (90,91)

The rehabilitation clinic St. Radegund is a facility of the “Pensionsversicherungsanstalt – PVA”, the biggest retirement pension insurance in Austria, and focuses on the rehabilitation of patients after cardio-vascular events. To participate in the rehabilitation program, the doctor in charge has to submit an application for the patient first. Then the insurance decides whether the patient meets the requirements and indications for a rehabilitation therapy. The standard period of rehabilitation in St. Radegund is four weeks.

The rehabilitation program is multidisciplinary and consists of the core components ‘exercise therapy’ (strength, endurance, mobility, coordination and physiotherapeutic trainings, but also passive intervention like massage and electro-therapy), ‘healthy nutrition’ (mixed healthy diet and education by dieticians), ‘psychological counseling’ (psychosocial assistance and relaxations techniques) and ‘rehabilitation nursing’ (support and instructions to regain commonplace skills). The relaxation sessions that patients can attend to comprise progressive muscle relaxation after Jacobson, autogenic training, acupuncture massage, and dry water massage. The schedule is individually adapted, depending on the patient´s condition and preferences.

For the health assessment the facility provides the following medical examinations: echocardiography, cardiac ultrasound, ergometry, spirometry, long time blood pressure measurements, sleep laboratory, vascular examinations, blood laboratory and X-ray. The provided therapeutic and diagnostic procedures aim to restore and strengthen the capability to work and participate on everyday familial and social life.

Figure 3: Screenshot of the "PV rehabilitation clinic St. Radegund"-Homepage (taken from: ska-st-radegund.at/de/home/)

3.2 Recruiting process

Over a period of two weeks all patients arriving at the clinic to start their 4-week rehabilitation program which met the including criteria were asked to participate in the study. In a personal interview they got educated about the aim and the procedure of the trial. All participants gave verbal and written informed consent. Since there was only capacity to measure a maximum of five participants per day, on each admission day (Tuesday, Wednesday, Thursday) the first five patients willing to participate were included in the study Within two weeks 20 persons were included and randomly assigned to study group control or TM, each counting ten participants.

3.2.1 Including criteria

Participants had to meet the following criteria to get included in the study:

- Patients after myocardial infarction (MI)
- after ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI)
- after acute coronary syndrome (ACS)
- coronary artery disease (CAD) with percutaneous coronary intervention (PCI)
- after coronary artery bypass graft (CABG)
- age from 40 to 80 years
- admitted to the cardiac rehabilitation center St. Radegund

3.2.2. Excluding criteria

When participants met one of the following criteria they were excluded from the study:

- Patients who must be monitored because of severe disease
- Patients with NYHA III or more
  (*note: the NYHA functional classification is used to grade the extent of heart failure*)
- mini mental score less than 26
  (*note: the mini mental score is a questionnaire to measure cognitive impairment*)
- Patients who are not sufficiently mobilized
- Patients who regularly perform any kind of meditation techniques

3.3 Groups and interventions

The participants that were included in the study were randomly assigned into two groups of ten.

Group control:

This group formed the control group that received the standard rehabilitation therapy program. During the first days at the rehab center all patients get several health checks, such as: echocardiography, cycle ergometer, a chest X-ray and a standard blood laboratory analysis. Afterwards an individual rehabilitation schedule is created for each patient, depending on the patient's health condition and fitness level (performance at the ergometer).

Moreover, the patients receive physical therapy sessions (such as physiotherapy, massages, lymph drainages, electrotherapy, etc.), psychological assistance, educational seminars and further medical tests if necessary (blood analysis, X-rays, ergometer, sonography, 24-hour ECG and 24-hour blood pressure).

The physical exercises may include bicycle, treadmill, nordic walking, hiking (in groups), gymnastics, strength endurance workouts, weightlifting and swimming.

Group TM:

This was the meditation group. In addition to the standard rehabilitation therapy, two meditation sessions of 20 minutes per day were added to the schedule. The first weekend was used to introduce the participants to the technique of the transcendental meditation (TM). Therefore, two TM-professionals of the "Austrian society of Maharishi Vedic sciences" (Österreichische Gesellschaft für Maharishi Vedische Wissenschaft) held an introduction seminar in which the participants learned the technique. The seminar was held within four days in a row and took 1,5 hours per day. After the introduction seminar all participants were able to practice the meditation by their own. The morning meditation was performed at 7am before breakfast and the second session at 5pm in

the afternoon. To provide a quiet place to meditate each morning and evening the vestry and the library of the clinic was reserved for the participants only. Further, every week a supervision meeting with the meditation teachers took place to resolve questions or issues concerning the meditation.

3.4 Study design

The "TMY-Study" was a prospective pilot study designed as a randomized controlled trial, with a control and an intervention group. The participants were randomly assigned to the groups to achieve possibly homogenous collectives. The main measurements (baseline, post-rehab and follow-up) were performed at fixed times (9:00, 10:30, 13:00, 14:30 and 16:00) and individually repeated at the same time.

3.5 Ethics and approval

The ethic proposition was admitted on 07.06.2019 to the Ethic committee of the Medical University of Graz (EK 31-443 et 18/19) and was approved by 16.07.2019. All research was performed in accordance with the Declaration of Helsinki (1989) of the WMA (the World Medical Association). Every participant gave verbal and written informed consent and had the right to withdraw at any point from the study without giving a reason. Participants did not get paid for taking part in the study (except 30 euros for attending to the follow-up measurement as travel expenses)

3.6 General overview of the study

The entire "Transcendental Meditation and Yoga in Cardiac Rehabilitation Study" (TMY-Study) comprised three groups. The group control (standard rehabilitation), the intervention group TM (that additionally performed Transcendental Meditation) and the intervention group Yoga (that additionally performed Yoga). Beyond cardiovascular-measurements, several further tests were conducted (myotensiography, body impedance, pulse wave velocity, retinal image, electroencephalography, hair cortisol sample, psychological questionaries, 24-hour electrocardiography, stool samples and blood samples). As this diploma thesis only deals with the cardiovascular effects of group control and group TM only the therefore relevant aspects will be analyzed, explained and discussed in detail.

3.7 Measurements and Data Assessment

One day after admission to the rehabilitation clinic the first measurement (*baseline measurement*) was conducted. Four weeks later at the end of the rehabilitation program the second (*post-rehab measurement*) and once again four weeks after the rehabilitation program, the third measurement was conducted (*follow-up measurement*) (see figure below). The participants´ names were pseudonymized so that the assessed data could not be generally tracked.

The measurements were conducted within 60 up to maximum 90 minutes. While the cardiovascular assessment with the *Task Force Monitor*® only took approximately 25 minutes, in the remaining time other tests were performed that are not relevant to this thesis. Each of the three main measurements were performed at fixed times (9:00, 10:30, 13:00, 14:30 and 16:00) and the following measurements were individually repeated as far as possible at the same time to avoid interindividual physiological variabilities.

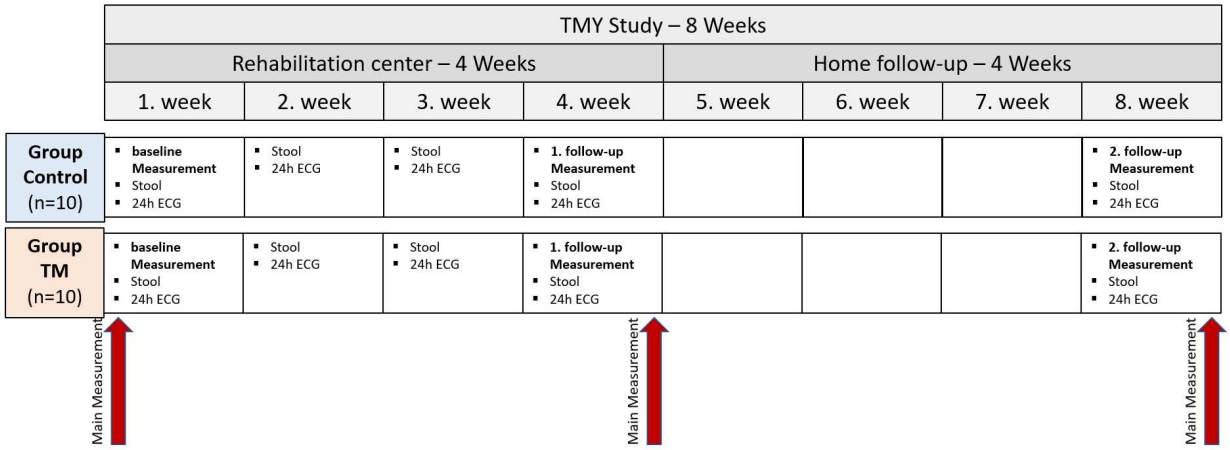

Figure 4: Study overview. This graphic gives an overview of the study duration and the dates when the measurements were conducted. Three "main measurements" were performed, The first at the beginning of the rehabilitation, the second at the end of the rehabilitation and the third one month after the rehabilitation.

3.7.1 Cardiovascular assessment with the Task Force Monitor®

3.7.1.1. The Task Force Monitor®

The Task Force Monitor® (TFM) is an instrument that was developed by the company CNSystems (Graz, Austria) to assess cardiovascular hemodynamics and the autonomic nervous system activity. The hemodynamic monitoring includes the measurement of blood pressure (upper arm oscillometry and finger plethysmography), heart rate (3-lead ECG) and thoracic impedance (impedance electrodes). Autonomic system activity is assessed with a power spectrum analysis of

heart rate (HR) variability and the baroreceptor sensitivity is calculated from continuous monitoring of HR and systolic blood pressure SBP). Assessing these basic parameters allows the calculation of several further cardiac values such as the RRI, MAP, SV, SI, CO, CI, TPR and TPRI. A detailed description of these values can be found in chapter "1.6. Cardiovascular assessment".

3.7.1.2 The Measurement

Before starting the test, all devices to assess the described parameters need to be installed. The participants are monitored for approximately 15 minutes in total. The first five minutes in a relaxed supine position (baseline assessment), then participants are instructed to stand up quickly and remain in a standing position (standing assessment) for the next five minutes and finally they have to lay down aging for five more minutes (recovery assessment). During the whole measurement, participants are required to stand or lie still, trying not to move or speak and be relaxed. Further, a calm and quiet environment is essential for this test to be able to collect valid data, as the autonomic nervous system is highly sensitive to any kind of disruption.

The TFM analyses specific time periods (so called "epochs" of 10 seconds) representatively for the five minutes of baseline, standing and recovery:

Baseline period (5 minutes = 300 seconds):
Baseline (Epoch 1): second 290 - 300

Standing period (5 minutes = 300 seconds):
Stand 1 (Epoch 2): second 0 – 10
Stand 2 (Epoch 3): second 10 – 20
Stand 3 (Epoch 4): second 20 – 30
Stand 4 (Epoch 5): second 170 – 180
Stand 5 (Epoch 6): second 290 – 300

Recovery period (5 minutes = 300 seconds):
Recovery 1 (Epoch 7): second 0 – 10
Recovery 2 (Epoch 8): second 10 – 20
Recovery 3 (Epoch 9): second 20 – 30
Recovery 4 (Epoch 10): second 290 – 300

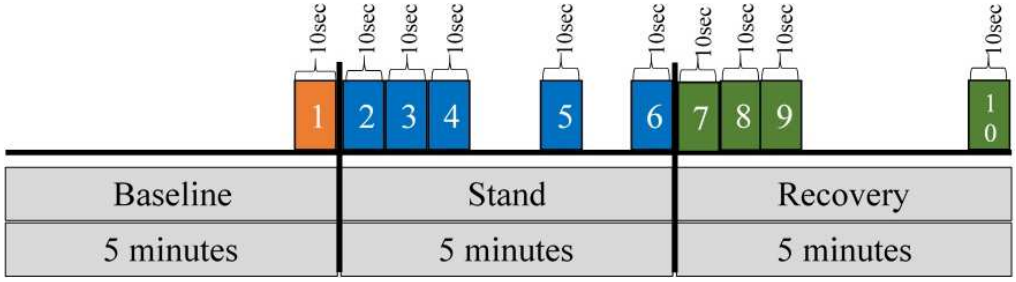

Figure 5: Schematic illustration of the "Epochs" that are used for the analyzation. (taken from: Brix et al. (92)**)**

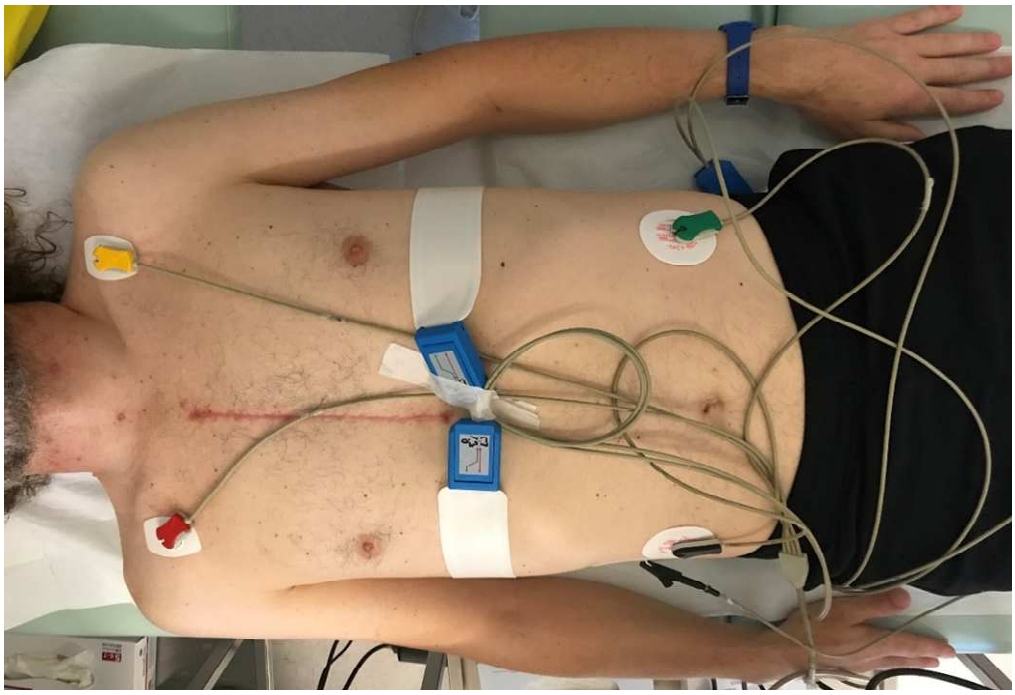

Figure 6: Device installation step 1. Installation of the 3-lead ECG electrodes (red, yellow, green and black electrode) and the impedance electrodes (blue electrode) on the chest before testing. A further impedance electrode will be placed in the neck.

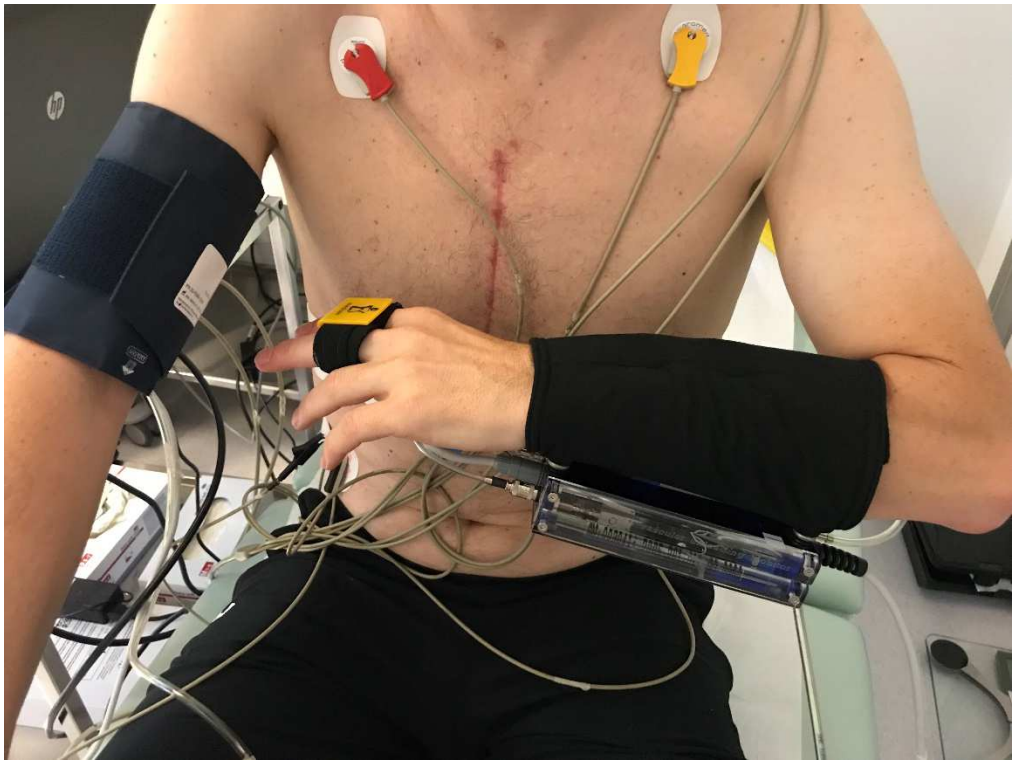

Figure 7: Device installation step 2. Installation of the upper arm oscillometer (right upper arm) and the finger plethysmograph (left lower arm and fingers)

Figure 8: supine position with all measurement devices installed, on the left side stands the Task Force Monitor and the appendant laptop.

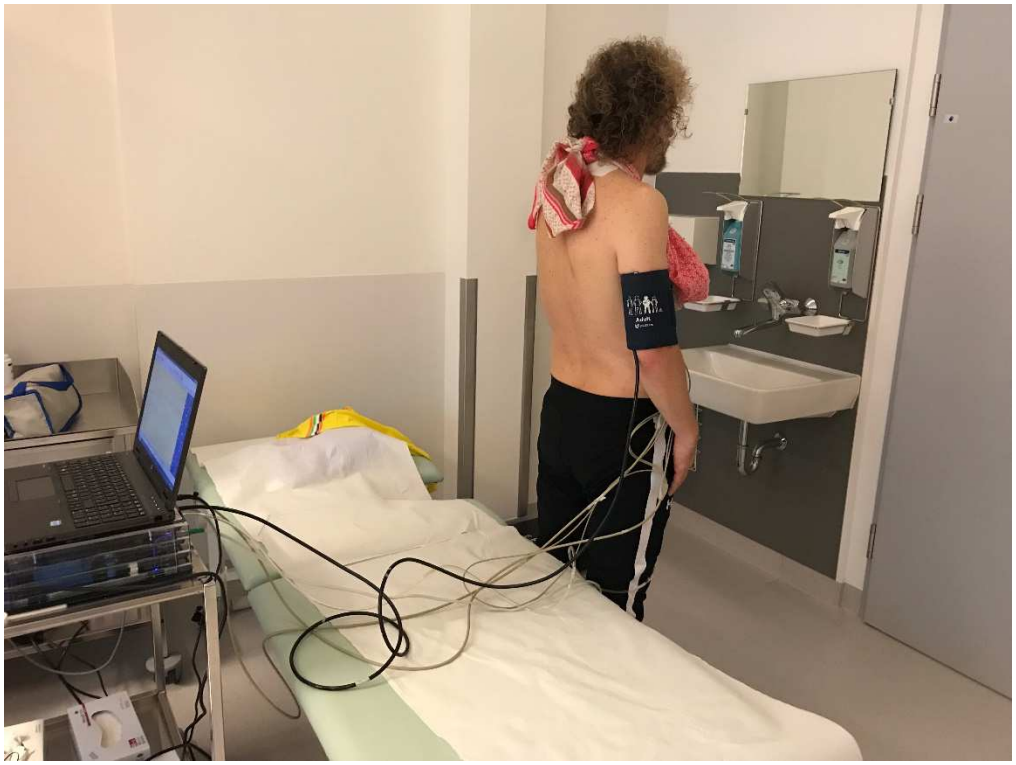

Figure 9: standing position. the finger plethysmograph has been fixed with a sling in order to stay on the same level as the heart.

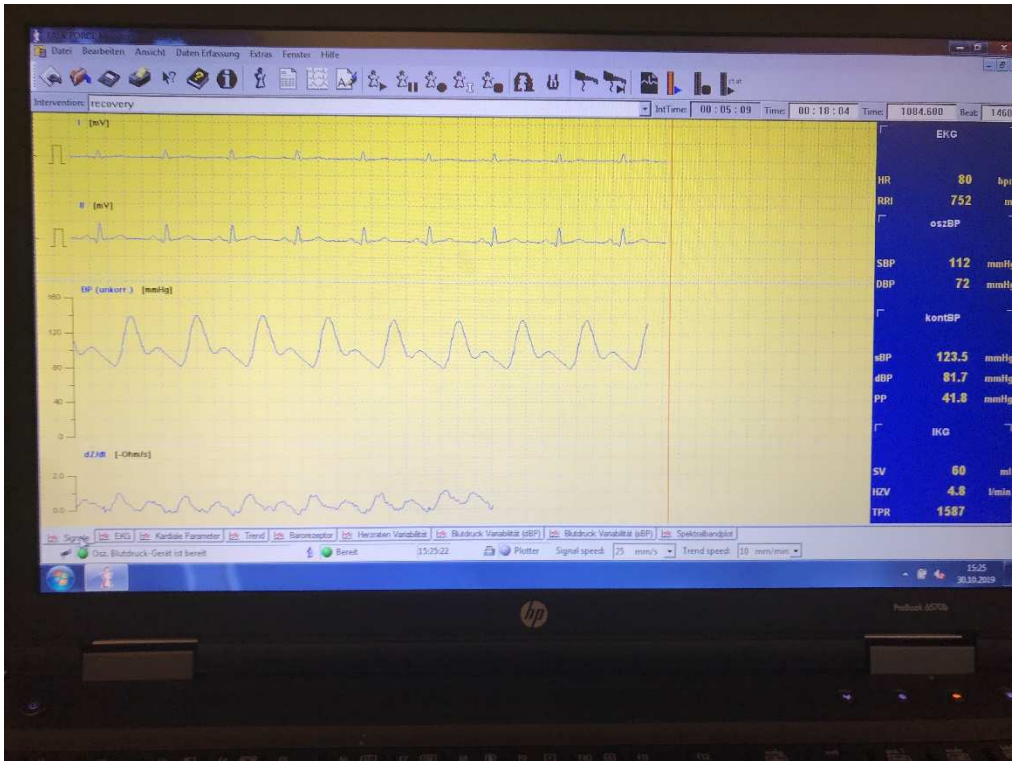

Figure 10: the "Signale"-screen of the TFM during a measurement. Showing from top to bottom the first and the second ECG derivation, the blood pressure curve of the arm oscillometer and the blood pressure curve of the finger plethysmograph below. In the blue box on the right the current values of HR, RRI, sBP, dBP, SV, CO and TPR are shown.

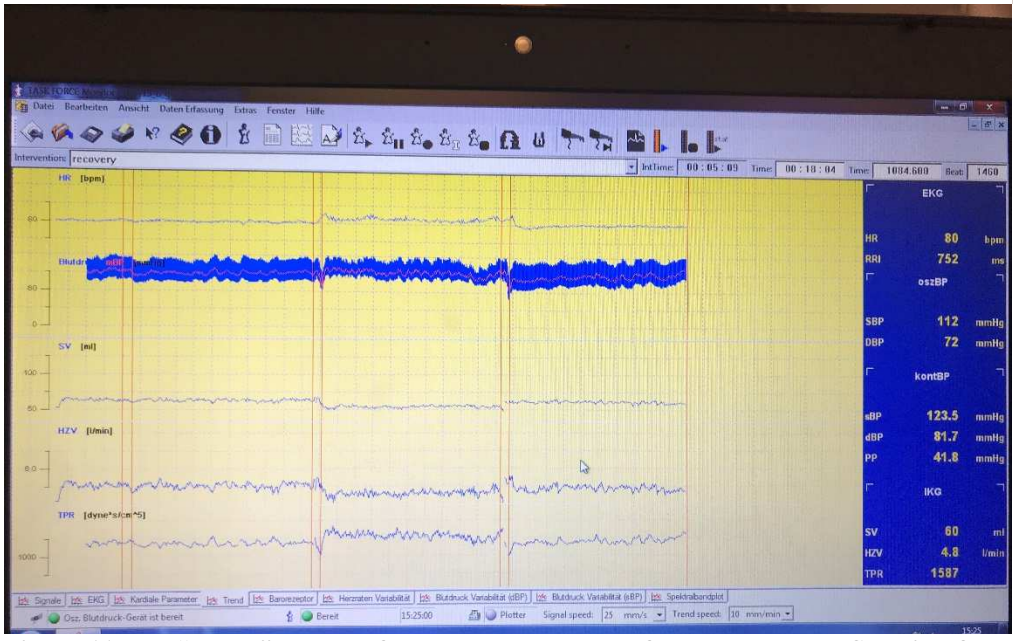

Figure 11: the "Trend"-screen of the TFM at the end of a measurement. Showing from top to bottom the long-time trend of the HR, the blood pressure, the SV, the CO and the TPR. The first two red vertical lines mark the beginning of the measurement, the second two the uprise from supine to standing position and the last two the return to supine position.

3.7.1.3 Statistical analysis:

The analysis of the collected data was performed by a trained grader of the Physiology Institute of the Medical University of Graz that was blinded to participant´s characteristics, groups and identification, as all data were pseudonymized.

The analysis of the data and graphic generation were performed with the programs SPSS (version 26), MATLAB (version 2016A) and Microsoft Excel. All parameters were log-transformed prior to analysis in order to keep a normal distribution, which was checked for with the Shapiro-Wilk and Kolmogorov-Smirnov normality tests. Some of the remaining outliers were removed, though not all to keep the number of participants as high as possible. Any remaining outliers were taken into account when reporting an observed significant effect. The covariates of age, weight, and height were not observed to have a significant effect on the different intervention groups and were therefore excluded from the analysis due to the low number of participants.

The following cardiac parameters were analyzed:

HR – Heart Rate (*bpm*)
RRI – RR-Intervals (*ms*)
sBP – Systolic Blood Pressure (*mmHg*)
dBP – Diastolic Blood Pressure (*mmHg*)
MAP – Mean Arterial Pressure (*mmHg*)
SV – Stroke Volume (*ml/min*)
SVI – Stroke Volume Index ($ml/min/m^2$)
CO – Cardiac Output (*ml*)
CI – Cardiac Index (ml/m^2)
TPR – Total Peripheral Resistance ($dyne*s/cm^5$)
TPRI – Total Peripheral Resistance Index ($dyne*s*m^2/cm^5$)

4. Results

4.1 Results of Baseline (Pre) and Post-Rehabilitation (Post)

In both groups (group control and group TM) nine of ten participants completed the baseline (pre) and the post-reha-measurement (post). Hence, the measurement results of 18 participants could be enrolled. The mean age of this population was 59.17 years, the mean weight 87.5 kg and the mean height 175,33 cm. 16 were males and two females. The covariates of age, weight, and height were not observed to have a significant effect on the different groups and were therefore excluded from the analysis due to the low number of participants. Further, the participant's sex was also not considered in the analysis, since there was only one woman in group control and another in group TM.

Table 1: Study population characteristics mean values: pre - post

characteristics	Group control	Group TM	Group control/TM
Male (n)	8 (89%)	8 (89%)	16 (89%)
Female (n)	1 (11%)	1 (11%)	2 (11%)
Age (years)	58.56 (±7.86)	59.78 (±7.84)	59.17 (±7.45)
Heigh (cm)	177.22 (±6.92)	173.44 (±7.73)	175.33 (±7.53)
Weight (kg)	95.44 (±11.03)	79.56 (±19.22)	87.50(±17.08)
Vaues are mean (± SD)			

Table 2 and Table 3: The following table shows the mean values of the cardiac parameters for each epoch of group control (blue) and TM (red). For each parameter the baseline (pre) and below the post-reha (post) values are given. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). This kind of data presentation allows a better illustration and interpretation of the parameters trend. The standard deviation is put in parenthesis next to the means. The right columns show two p-values. The first (p-value: pre-post) indicates whether the changes of the means (between pre and post) were significant within one group. The second (p-value: pre-post x group) examinates if the change of any cardiac parameter between pre and post was significantly higher in one group compared to the other. A p-value of 0.05 or less means that there has been a significant change.

Table 2: Results Group Control & Group TM: pre - post

		Epochs										p-value:	p-value:
Parameter	Group	Baseline	Stand 1	Stand 2	Stand 3	Stand 4	Stand 5	Recovery 1	Recovery 2	Recovery 3	Recovery 4	pre-post	pre-post x Group
Heart rate [bpm]	Control pre (n=9)	71 (±5)	84 (±8)	79 (±7)	80 (±7)	80 (±11)	81 (±12)	74 (±8)	73 (±9)	71 (±9)	70 (±8)	p=.058	p=.900
	Control post (n=9)	72 (±10)	81 (±16)	78 (±13)	79 (±14)	77 (±13)	77 (±15)	72 (±8)	65 (±6)	65 (±6)	65 (±5)		
	TM pre (n=9)	69 (±14)	75 (±14)	74 (±14)	78 (±15)	73 (±13)	79 (±18)	77 (±23)	67 (±12)	65 (±11)	65 (±12)		
	TM post (n=9)	61 (±10)	74 (±8)	71 (±9)	71 (±9)	70 (±11)	70 (±10)	69 (±11)	61 (±10)	60 (±10)	60 (±11)		
RR-interval [ms]	Control pre (n=9)	855 (±48)	727 (±55)	765 (±67)	768 (±67)	762 (±98)	758 (±108)	832 (±77)	843 (±96)	868 (±100)	874 (±79)	p=.050	p=.836
	Control post (n=9)	891 (±91)	773 (±143)	791 (±129)	781 (±122)	804 (±122)	821 (±132)	863 (±102)	937 (±85)	938 (±75)	946 (±69)		
	TM pre (n=9)	930 (±171)	823 (±147)	839 (±149)	805 (±140)	850 (±152)	805 (±139)	856 (±203)	929 (±165)	955 (±155)	958 (±176)		
	TM post (n=9)	1009 (±146)	836 (±89)	870 (±116)	867 (±102)	887 (±122)	886 (±118)	904 (±156)	1010 (±179)	1032 (±177)	1023 (±171)		
Systolic blood pressure [mmHg]	Control pre (n=9)	127 (±15)	129 (±17)	129 (±17)	129 (±20)	140 (±16)	139 (±18)	132 (±15)	131 (±12)	130 (±13)	125 (±16)	p=.012	p=.854
	Control post (n=9)	116 (±13)	118 (±20)	118 (±19)	117 (±20)	129 (±13)	129 (±17)	126 (±26)	121 (±19)	118 (±15)	114 (±14)		
	TM pre (n=9)	124 (±22)	123 (±21)	127 (±15)	126 (±19)	134 (±24)	136 (±23)	122 (±24)	122 (±21)	123 (±21)	126 (±22)		
	TM post (n=9)	121 (±16)	106 (±20)	114 (±15)	116 (±14)	126 (±12)	126 (±17)	117 (±22)	120 (±18)	118 (±18)	124 (±19)		
Diastolic blood pressure [mmHg]	Control pre (n=9)	81 (±12)	90 (±13)	91 (±13)	91 (±16)	94 (±8)	95 (±10)	75 (±6)	77 (±8)	76 (±7)	80 (±11)	p=.433	p=.928
	Control post (n=9)	76 (±15)	89 (±15)	91 (±19)	93 (±19)	93 (±23)	91 (±30)	76 (±27)	72 (±20)	73 (±19)	75 (±16)		
	TM pre (n=9)	82 (±15)	90 (±19)	93 (±15)	93 (±18)	93 (±21)	95 (±20)	70 (±11)	75 (±17)	76 (±18)	81 (±18)		
	TM post (n=9)	80 (±8)	76 (±9)	83 (±4)	85 (±6)	89 (±7)	89 (±13)	73 (±14)	73 (±10)	74 (±11)	79 (±12)		
Mean arterial pressure [mmHg]	Control pre (n=9)	100 (±13)	105 (±14)	105 (±14)	105 (±17)	112 (±11)	111 (±13)	96 (±8)	97 (±8)	97 (±9)	98 (±13)	p=.088	p=.754
	Control post (n=9)	92 (±15)	95 (±23)	102 (±18)	104 (±17)	107 (±19)	105 (±25)	94 (±27)	91 (±20)	90 (±18)	91 (±14)		
	TM pre (n=9)	99 (±19)	103 (±19)	106 (±15)	105 (±19)	109 (±22)	111 (±21)	95 (±23)	93 (±18)	94 (±19)	99 (±18)		
	TM post (n=9)	97 (±11)	87 (±12)	94 (±7)	97 (±8)	104 (±8)	103 (±13)	89 (±16)	92 (±12)	91 (±13)	97 (±14)		

Vaues are mean (± SD)

Table 3: Results Group Control & Group TM: pre - post

		Epochs										p-value:	p-value:
Parameter	Group	Baseline	Stand 1	Stand 2	Stand 3	Stand 4	Stand 5	Recovery 1	Recovery 2	Recovery 3	Recovery 4	pre-post	pre-post x Group
Stroke volume [ml]	Control pre (n=9)	66 (±14)	59 (±8)	58 (±7)	58 (±4)	56 (±8)	55 (±7)	78 (±14)	81 (±13)	80 (±15)	67 (±16)	p=.926	p=.799
	Control post (n=9)	68 (±20)	60 (±9)	56 (±9)	56 (±7)	57 (±12)	55 (±11)	75 (±14)	78 (±18)	81 (±20)	71 (±18)		
	TM pre (n=9)	63 (±10)	59 (±12)	61 (±11)	61 (±10)	60 (±10)	59 (±12)	66 (±10)	72 (±13)	75 (±15)	61 (±9)		
	TM post (n=9)	66 (±16)	62 (±10)	59 (±9)	58 (±8)	59 (±12)	58 (±11)	69 (±18)	74 (±19)	75 (±19)	67 (±17)		
Stroke index [ml/m^2]	Control pre (n=9)	31 (±7)	28 (±4)	27 (±4)	27 (±2)	26 (±4)	26 (±4)	37 (±7)	38 (±7)	38 (±7)	32 (±8)	p=.797	p=.839
	Control post (n=9)	32 (±7)	29 (±4)	27 (±4)	26 (±2)	27 (±4)	26 (±4)	35 (±7)	37 (±7)	39 (±7)	34 (±8)		
	TM pre (n=9)	33 (±4)	30 (±5)	32 (±5)	31 (±4)	31 (±5)	31 (±6)	34 (±4)	38 (±6)	39 (±8)	32 (±6)		
	TM post (n=9)	35 (±7)	32 (±4)	30 (±5)	30 (±5)	31 (±5)	30 (±5)	36 (±7)	38 (±8)	39 (±8)	35 (±8)		
Cardiac output [l/min]	Control pre (n=9)	4.7 (±0.8)	5.0 (±0.8)	4.6 (±0.5)	4.7 (±0.5)	4.5 (±0.7)	4.4 (±0.4)	5.8 (±1.1)	5.9 (±1.1)	5.6 (±1.0)	4.7 (±0.9)	p=.290	p=.630
	Control post (n=9)	4.8 (±1.9)	4.8 (±1.0)	4.3 (±0.7)	4.3 (±0.4)	4.3 (±0.6)	4.2 (±0.5)	5.3 (±1.1)	5.1 (±1.3)	5.4 (±1.5)	4.7 (±1.3)		
	TM pre (n=9)	4.3 (±1.0)	4.4 (±1.6)	4.1 (±0.4)	4.4 (±0.6)	4.0 (±0.4)	4.4 (±.07)	4.9 (±1.3)	4.8 (±1.0)	4.8 (±1.3)	3.9 (±0.8)		
	TM post (n=9)	4.0 (±1.0)	4.6 (±1.0)	4.1 (±0.8)	4.1 (±0.7)	4.1 (±0.8)	4.0 (±0.7)	4.7 (±1.1)	4.4 (±1.1)	4.4 (±1.0)	4.0 (±1.0)		
Cardiac index [l/(±min*m2)]	Control pre (n=9)	2.2 (±0.4)	2.3 (±0.4)	2.1 (±0.3)	2.2 (±0.3)	2.1 (±0.4)	2.1 (±0.3)	2.7 (±0.2)	2.8 (±0.6)	2.7 (±0.5)	2.2 (±0.4)	p=.217	p=.822
	Control post (n=9)	2.3 (±0.9)	2.3 (±0.5)	2.1 (±0.3)	2.1 (±0.2)	2.0 (±0.3)	2.0 (±0.3)	2.6 (±0.6)	2.4 (±0.6)	2.6 (±0.8)	2.2 (±0.7)		
	TM pre (n=9)	2.3 (±0.6)	2.3 (±0.8)	2.4 (±0.7)	2.5 (±0.7)	2.3 (±0.6)	2.4 (±0.6)	2.6 (±0.8)	2.5 (±0.6)	2.6 (±0.8)	2.1 (±0.6)		
	TM post (n=9)	2.1 (±0.5)	2.4 (±0.5)	2.1 (±0.4)	2.1 (±0.3)	2.1 (±0.4)	2.1 (±0.4)	2.5 (±0.6)	2.3 (±0.6)	2.3 (±0.5)	2.1 (±0.5)		
Total peripheral resistance [dyne*s/cm^5]	Control pre (n=9)	1733 (±298)	1695 (±412)	1808 (±369)	1812 (±460)	2008 (±388)	2029 (±314)	1374 (±277)	1345 (±278)	1404 (±305)	1736 (±374)	p=.627	p=.769
	Control post (n=9)	1714 (±567)	1586 (±394)	1768 (±416)	1887 (±305)	2002 (±417)	2064 (±481)	1441 (±427)	1459 (±431)	1399 (±448)	1645 (±490)		
	TM pre (n=9)	1969 (±565)	1902 (±598)	1947 (±588)	1820 (±524)	2055 (±623)	2065 (±605)	1595 (±466)	1518 (±334)	1547 (±377)	2029 (±525)		
	TM post (n=9)	2000 (±598)	1526 (±406)	1837 (±341)	1910 (±302)	2139 (±430)	2059 (±418)	1559 (±400)	1683 (±421)	1683 (±410)	1983 (±535)		
Total peripheral resistance index [dyne*s*m^2/cm^5]	Control pre (n=9)	3670 (±597)	3595 (±813)	3832 (±712)	3838 (±930)	4269 (±851)	4311 (±710)	2920 (±617)	2855 (±609)	2977 (±646)	3682 (±799)	p=.308	p=.769
	Control post (n=9)	3602 (±1183	3323 (±767)	3707 (±808)	3938 (±591)	4209 (±821)	4328 (±903)	3042 (±914)	3074 (±910)	2952 (±969)	3465 (±1029		
	TM pre (n=9)	3833 (±1350	3751 (±1585	3806 (±1424	3568 (±1330	4028 (±1622	4033 (±1524	2955 (±826)	2971 (±955)	3037 (±1053	3982 (±1500		
	TM post (n=9)	3850 (±1328	3037 (±850)	3634 (±602)	3788 (±605)	4129 (±851)	3952 (±901)	3019 (±995)	3238 (±918)	3223 (±826)	3832 (±1328		

Vaues are mean (± SD)

The diagrams of parameters with significant changes or that are otherwise relevant to this diploma thesis are below. The diagrams of all other parameters can be found in the appendix.

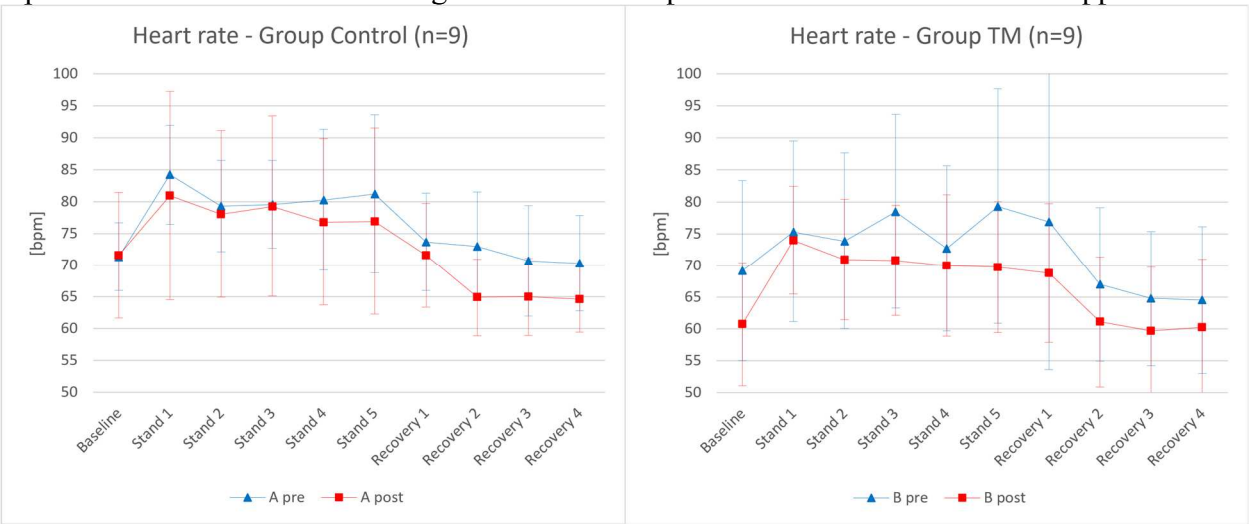

Figure 12: Heart rate (pre-post). This figure shows the change of the heart rate parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter between pre and post was almost significant (p=0.058) in both groups and far from significant (p= 0.9) in between the groups.

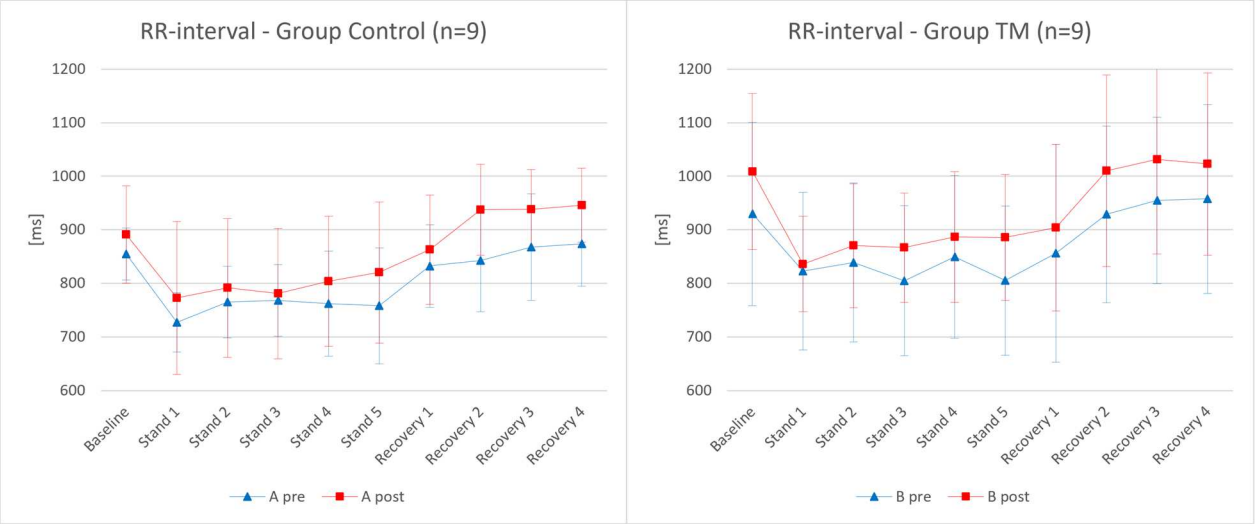

Figure 13: RR-interval (pre-post). This figure shows the change of the RR-interval parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). A significant (p=0.05) change of this parameter between pre and post could be found in both groups, however there was no significance (p=0.836) in between the groups.

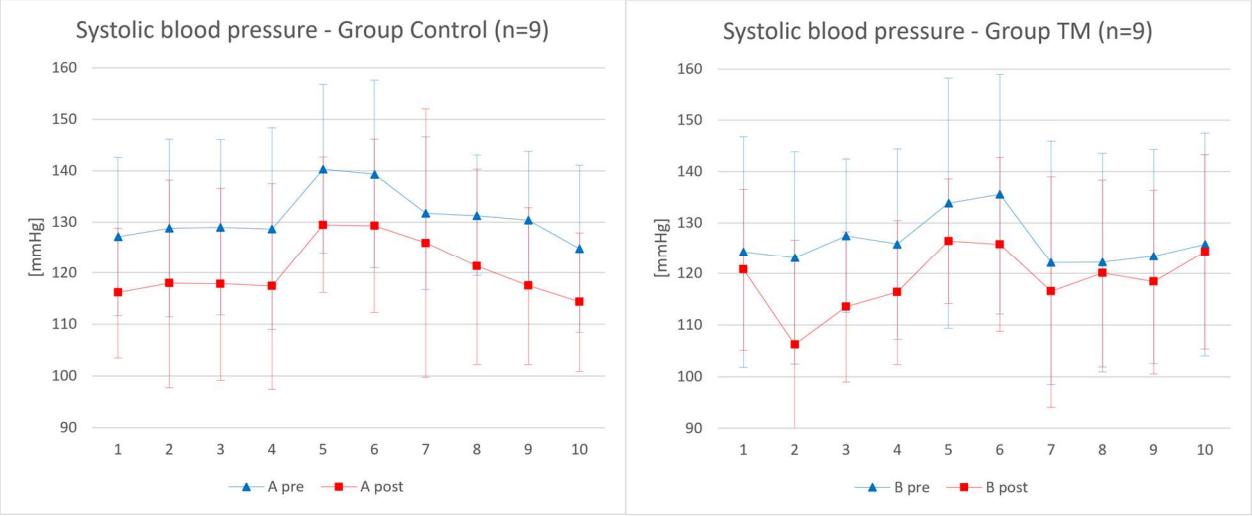

Figure 14: Systolic blood pressure (pre-post). This figure shows the change of the systolic blood pressure parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). A significant (p=0.012) change of this parameter between pre and post could be found in both groups, however there was no significance (p=0.854) in between the groups.

To summarize the results, there has been a significant change of the parameters RR-Interval ($p = 0.05$), Systolic Blood Pressure ($p = 0.018$) and a change close to significance of the Heart Rate ($p = 0.058$) in each group control and group TM between the pre and the post measurement. However, no significant differences in between the groups could be found.

4.2 Results of Baseline (Pre), Post-Rehabilitation (Post) and Follow-Up (Follow-up)

Although follow-up measurements were primarily planned for all study participants, it turned out quite difficult to conduct since the rehab patients came from federal states all over Austria and the rehabilitation center did not provide follow-up examinations of their patients. Therefore, the follow-up measurements were optional. However, two thirds of the study participants were willing to come to Graz for a follow-up measurement at the Institute of Physiology of the Medical University of Graz four weeks after the rehabilitation program. Participants from the group TM were asked to continue with the daily practice of TM**.**

In group control five of ten completed all three measurements (pre, post, follow-up) and in group TM six of ten. The mean age of this population was 61.27 years, the mean weight 86.91 kg and the mean height 176.18 cm. All participants were males. Due to the low number of participants left and several missing values no group comparison was performed. Instead, all participants were put together, forming a group of 11 participants. It was only examined whether any changes in the cardiac parameters could be seen one month after the rehabilitation.

Table 4: Study population characteristics mean values: pre - post - follow-up

characteristics	Group control	Group TM	Group control/TM
Male (n)	5 (100%)	6 (100%)	11 (100%)
Female (n)	0 (0%)	0 (0%)	0 (0%)
Age (years)	61.00 (±9.25)	61.50 (±9.18)	61.27 (±8.74)
Heigh (cm)	179.60 (±6.23)	173.33 (±7.06)	176.18 (±7.15)
Weight (kg)	92.00 (±12.61)	82.67 (±18.57)	86.91 (±16.11)
Vaues are mean (± SD)			

Table 5 and 6: The following table shows the **mean baseline values** of the cardiac parameters for each. As no reasonable inter-group-comparison could be performed, all participants that completed all three measurements (pre, post, follow-up) were put together in one group (CTM). The mean values of each parameter are stacked one below the other of the pre, post and follow-up measurements. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). Next to the means the standard deviation is put in parenthesis. The column on the right shows the p-values (p-value: pre – post – follow-up).

Table 5: Results group control/TM: pre – post – follow-up (part 1)

Table 5: Results Group Control/TM (CTM): pre - post - follow-up												
		Epochs										p-value:
Parameter	Group	Baseline	Stand 1	Stand 2	Stand 3	Stand 4	Stand 5	Recovery 1	Recovery 2	Recovery 3	Recovery 4	pre - post - follow-up
Heart rate [bpm]	CTM pre (n=11)	71 (±8)	78 (±12)	77 (±12)	80 (±10)	77 (±14)	79 (±14)	76 (±11)	72 (±9)	70 (±9)	70 (±10)	0.017
	CTM post (n=11)	67 (±11)	79 (±15)	77 (±13)	77 (±14)	77 (±13)	76 (±15)	74 (±6)	65 (±7)	64 (±8)	64 (±9)	
	CTM follow-up (n=11)	62 (±8)	73 (±10)	75 (±13)	75 (±11)	72 (±9)	74 (±13)	65 (±7)	63 (±9)	62 (±7)	61 (±7)	
RR-interval [ms]	CTM pre (n=11)	853 (±89)	789 (±127)	799 (±129)	777 (±99)	801 (±145)	790 (±140)	822 (±100)	855 (±105)	879 (±114)	886 (±143)	0.002
	CTM post (n=11)	931 (±129)	794 (±128)	808 (±133)	804 (±128)	812 (±126)	842 (±143)	835 (±74)	940 (±96)	952 (±106)	961 (±124)	
	CTM follow-up (n=11)	987 (±129)	849 (±118)	834 (±131)	822 (±121)	857 (±94)	850 (±133)	938 (±101)	970 (±112)	980 (±102)	990 (±111)	
Systolic blood pressure [mmHg]	CTM pre (n=11)	125 (±21)	125 (±21)	125 (±18)	124 (±20)	136 (±21)	136 (±20)	121 (±16)	128 (±19)	127 (±19)	123 (±20)	0.418
	CTM post (n=11)	121 (±16)	114 (±18)	118 (±16)	124 (±11)	129 (±13)	128 (±15)	128 (±26)	127 (±18)	124 (±17)	122 (±17)	
	CTM follow-up (n=11)	119 (±25)	117 (±35)	114 (±34)	111 (±26)	126 (±18)	125 (±17)	126 (±22)	121 (±16)	124 (±18)	122 (±15)	
Diastolic blood pressure [mmHg]	CTM pre (n=11)	80 (±15)	88 (±17)	89 (±15)	89 (±18)	91 (±14)	92 (±14)	70 (±5)	76 (±15)	76 (±16)	79 (±16)	0.227
	CTM post (n=11)	80 (±13)	86 (±12)	87 (±7)	89 (±7)	92 (±22)	89 (±26)	78 (±25)	75 (±17)	76 (±18)	79 (±15)	
	CTM follow-up (n=11)	71 (±13)	75 (±14)	75 (±16)	76 (±16)	81 (±8)	81 (±10)	68 (±14)	68 (±15)	68 (±12)	76 (±12)	
Mean arterial pressure [mmHg]	CTM pre (n=11)	98 (±18)	102 (±18)	102 (±16)	102 (±18)	109 (±17)	109 (±16)	88 (±7)	94 (±16)	95 (±17)	97 (±17)	0.296
	CTM post (n=11)	96 (±14)	97 (±12)	98 (±7)	105 (±11)	106 (±18)	103 (±21)	96 (±25)	94 (±18)	94 (±17)	96 (±14)	
	CTM follow-up (n=11)	89 (±15)	90 (±19)	89 (±21)	89 (±19)	98 (±10)	98 (±11)	89 (±14)	89 (±13)	89 (±11)	94 (±13)	
Vaues are mean (± SD)												

Table 6: Results group control/TM: pre – post – follow-up (part 2)

Table 6: Results Group Control/TM (CTM): pre - post - follow-up												
		Epochs										p-value:
Parameter	Group	Baseline	Stand 1	Stand 2	Stand 3	Stand 4	Stand 5	Recovery 1	Recovery 2	Recovery 3	Recovery 4	pre - post - follow-up
Stroke volume [ml]	CTM pre (n=11)	61 (±9)	61 (±10)	62 (±9)	62 (±8)	60 (±10)	60 (±10)	70 (±8)	74 (±13)	74 (±13)	60 (±6)	0.640
	CTM post (n=11)	64 (±13)	59 (±8)	57 (±9)	58 (±8)	59 (±10)	59 (±10)	71 (±12)	73 (±14)	75 (±14)	66 (±13)	
	CTM follow-up (n=11)	64 (±9)	60 (±6)	58 (±6)	57 (±6)	58 (±7)	58 (±10)	70 (±12)	72 (±12)	72 (±12)	65 (±11)	
Stroke index [ml/m^2]	CTM pre (n=11)	30 (±5)	30 (±6)	31 (±6)	31 (±4)	30 (±6)	30 (±6)	35 (±4)	37 (±5)	36 (±6)	30 (±4)	0.644
	CTM post (n=11)	32 (±8)	29 (±5)	29 (±6)	29 (±5)	29 (±6)	29 (±6)	35 (±6)	36 (±7)	38 (±7)	33 (±8)	
	CTM follow-up (n=11)	32 (±6)	30 (±5)	29 (±5)	29 (±4)	29 (±6)	29 (±6)	35 (±6)	36 (±6)	36 (±6)	33 (±6)	
Cardiac output [l/min]	CTM pre (n=11)	4.3 (±0.7)	4.4 (±0.6)	4.4 (±0.5)	5.0 (±1.1)	4.4 (±0.6)	4.4 (±0.4)	5.3 (±0.9)	5.4 (±1.2)	5.2 (±1.0)	4.2 (±0.6)	**0.003**
	CTM post (n=11)	4.2 (±0.9)	4.6 (±0.7)	4.3 (±0.6)	4.4 (±0.5)	4.4 (±0.5)	4.3 (±0.5)	5.2 (±1.0)	4.8 (±0.9)	4.9 (±1.1)	4.3 (±1.1)	
	CTM follow-up (n=11)	4.0 (±0.7)	4.3 (±0.5)	4.3 (±0.6)	4.3 (±0.7)	4.2 (±0.4)	4.2 (±0.5)	4.6 (±0.9)	4.6 (±1.0)	4.5 (±0.8)	4.0 (±0.6)	
Cardiac index [l/(min*m^2)]	CTM pre (n=11)	2.1 (±0.4)	2.4 (±0.7)	2.4 (±0.6)	2.3 (±0.2)	2.3 (±0.5)	2.3 (±0.5)	2.6 (±0.5)	2.6 (±0.5)	2.6 (±0.5)	2.1 (±0.3)	**0.003**
	CTM post (n=11)	2.1 (±0.5)	2.3 (±0.4)	2.1 (±0.3)	2.2 (±0.3)	2.2 (±0.3)	2.2 (±0.3)	2.6 (±0.6)	2.4 (±0.5)	2.4 (±0.6)	2.1 (±0.6)	
	CTM follow-up (n=11)	2.0 (±0.4)	2.2 (±0.2)	2.1 (±0.3)	2.1 (±0.3)	2.1 (±0.3)	2.1 (±0.2)	2.3 (±0.5)	2.3 (±0.5)	2.2 (±0.4)	2.0 (±0.4)	
Total peripheral resistance [dyne*s/cm^5]	CTM pre (n=11)	1909 (±525)	1676 (±521)	1681 (±479)	1625 (±431)	1921 (±538)	1933 (±508)	1369 (±79)	1383 (±312)	1520 (±261)	1898 (±468)	0.848
	CTM post (n=11)	1894 (±544)	1596 (±396)	1774 (±402)	1887 (±267)	1953 (±438)	1950 (±453)	1510 (±497)	1620 (±479)	1570 (±454)	1891 (±554)	
	CTM follow-up (n=11)	1781 (±420)	1665 (±379)	1675 (±441)	1638 (±436)	1886 (±328)	1906 (±378)	1569 (±380)	1565 (±379)	1615 (±421)	1858 (±348)	
Total peripheral resistance index [dyne*s*m^2/cm^5]	CTM pre (n=11)	3876 (±1141	3469 (±1359	3470 (±1236	3334 (±1047	3944 (±1375	3959 (±1272	2746 (±277)	2838 (±784)	2974 (±819)	3893 (±1280	0.471
	CTM post (n=11)	3826 (±1233	3248 (±810)	3604 (±815)	3623 (±857)	3976 (±921)	3936 (±1006	3059 (±1124	3265 (±1005	3160 (±938)	3833 (±1319	
	CTM follow-up (n=11)	3617 (±1038	3346 (±729)	3355 (±790)	3282 (±782)	3790 (±625)	3839 (±736)	3176 (±868)	3140 (±693)	3245 (±813)	3760 (±835)	
Vaues are mean (± SD)												

The diagrams of parameters with significant changes or that are otherwise relevant to this diploma thesis are below. The diagrams of all other parameters can be found in the appendix.

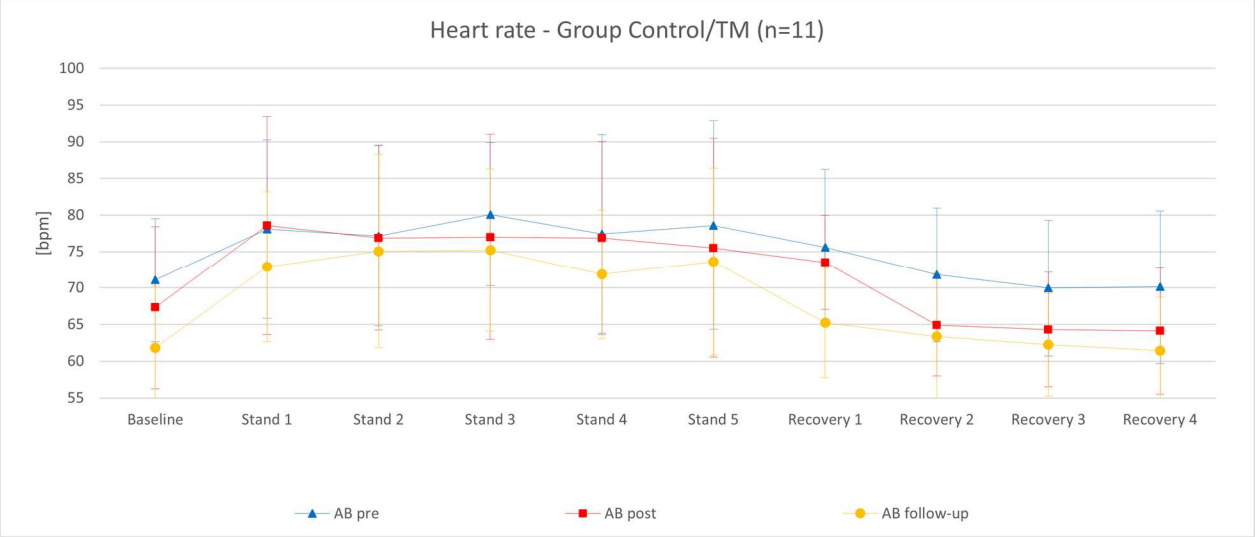

Figure 15: Heart rate (pre-post-follow-up). This figure shows the changes of the heart rate parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was significant (p=0.017) between pre and post and follow-up.

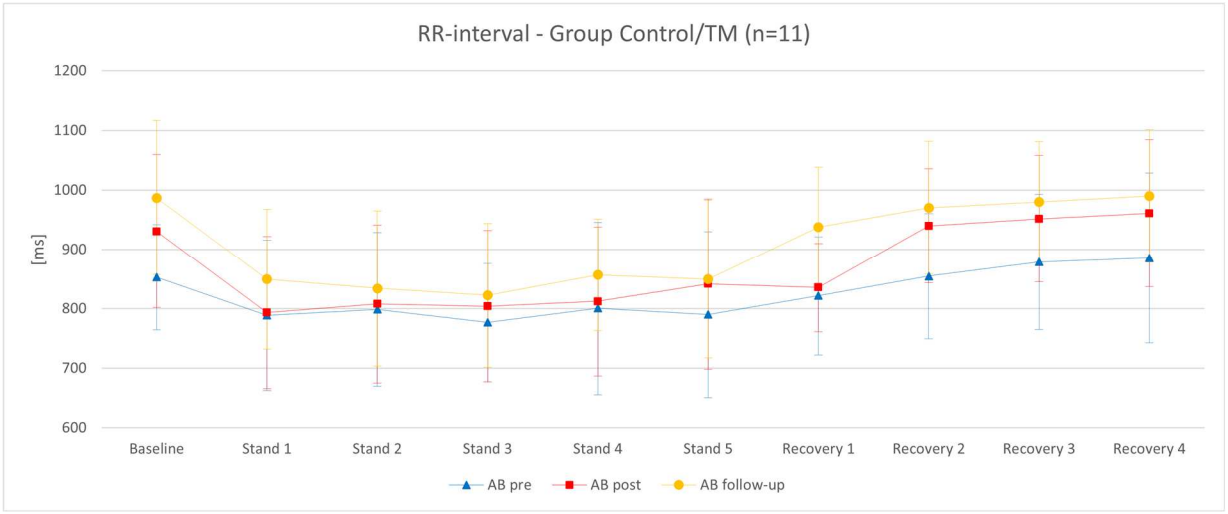

Figure 16: RR-interval (pre-post-follow-up). This figure shows the changes of the RR-interval parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was significant (p=0.002) between pre and post and follow-up.

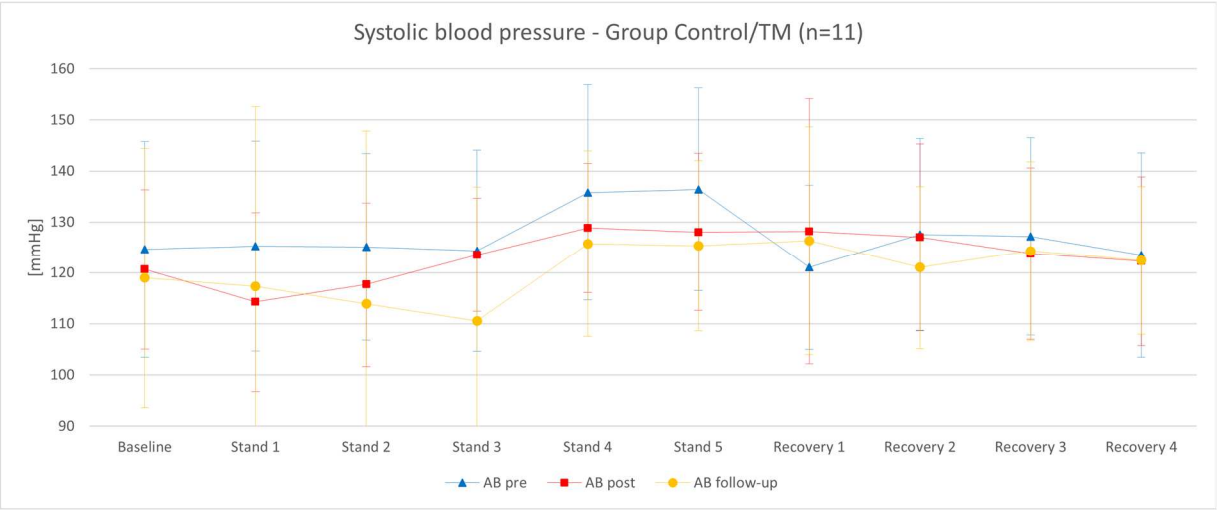

Figure 17: Systolic blood pressure (pre-post-follow-up). This figure shows the changes of the systolic blood pressure parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was not significant (p=0.418) between pre and post and follow-up.

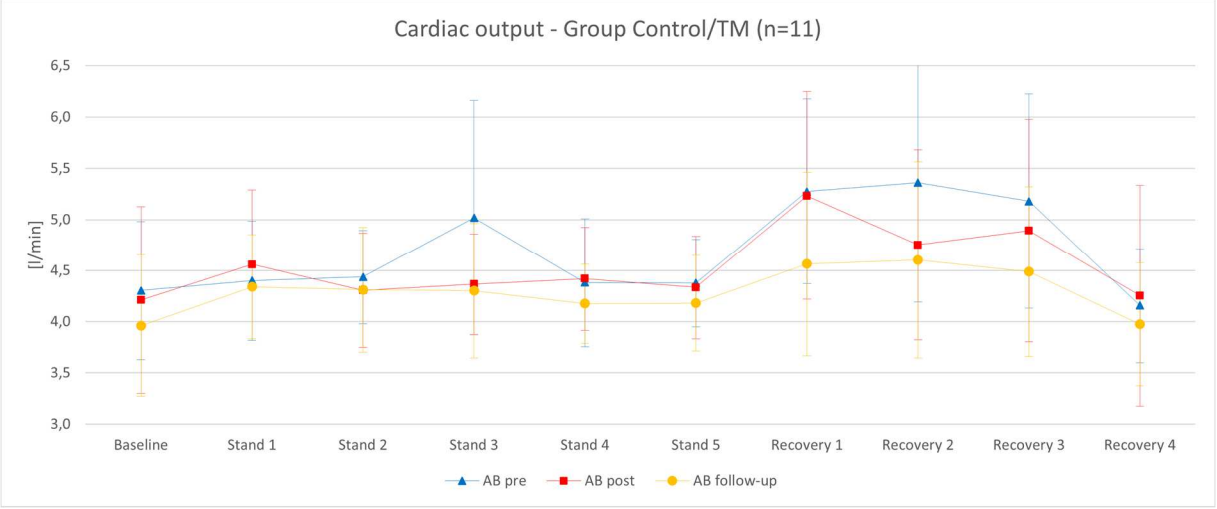

Figure 18: Cardiac output (pre-post-follow-up). This figure shows the changes of the cardiac output parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was significant (p=0.003) between pre and post and follow-up.

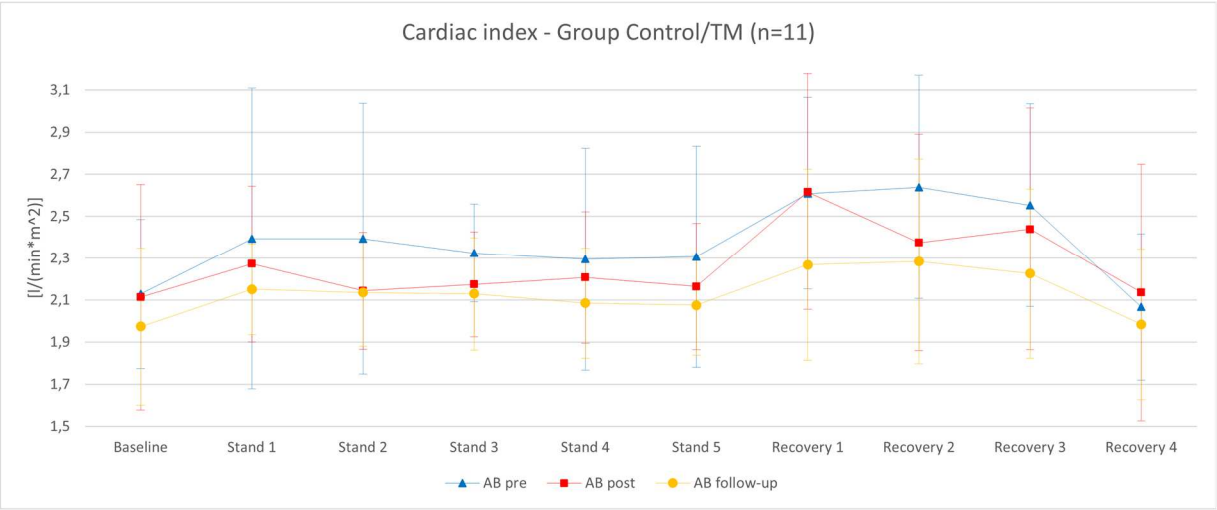

Figure 19: Cardiac index (pre-post-follow-up). This figure shows the changes of the Cardiac index parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was significant (p=0.003) between pre and post and follow-up.

The comparison of the mean values of all participants that completed all measurements shows that there has been a significant change of the values HR ($p = 0.017$), RR-Interval ($p = 0.002$), CO ($p = 0.003$) and CI ($p = 0.003$).

5. Discussion

The main findings of this study concerning the cardiovascular parameters of group control and group TM are that there has been a significant improvement of the parameter systolic blood pressure and a marginal trend of a heart rate decrease ($p = 0.58$) while the RR-interval, which is closely related to the heart rate, significantly increased in both groups within a month. However, the magnitude of the changes was almost equal in both groups. Hence, the primary outcome is, that by adding Transcendental Meditation (TM) to the one-month in-patient cardiac rehabilitation program, no additional short-term improvements of the cardiovascular parameters could be observed. Interestingly however, one month after the rehabilitation (follow-up) the parameters heart rate and RR-interval kept declining and also the cardiac output and cardiac index dropped significantly in the total study population.

So far (spring 2021) only one other study has investigated the effects of meditation on patients undergoing cardiac rehabilitation. Bokhari et al. (93) published a paper in 2019 that included 56 African-Americans which underwent a 12-week cardiac rehabilitation program and divided them in the following groups: CR (cardiac rehabilitation), TM (Transcendental Meditation), CR+TM, control group (usual care alone). They found significant improvements of the myocardial flow reserve (MFR) after 12 weeks, particularly in the groups that practiced TM (CR+TM [+20.7%], TM [+12.8%], CR [+5.8], control [-10.3%]). While no additional benefits were found within one month in the current study, these results indicate that the practice of TM might affect the cardiac rehabilitation positively in the longer term. Alike the sources cited in the chapter "1.5.2.2. Evidence based benefits of TM" the durations of the clinical trials that found a positive effect were noticeable longer than our trial was. The mean duration was 5.6 months (considering all cited studies that are related to cardiovascular parameters and are not elder than 1987 in chapter 1.5.2.2., except for the summary of Walton et al.(52)) (55,59–64,68–70). This circumstance suggests that there might be a positive effect resulting from the practice of TM that tends to unfold its positive effects rather in the long-term.

Further, it should be mentioned that Bokhari et al. (93) assessed the myocardial flow reserve (MFR) with a ^{13}N-ammonia positron emission tomography (PET). The assessment of MFR through a PET is considered as a quite sensitive and specific (both are at about 90%) method to evaluate cardiovascular changes in patients suffering on chronic coronary syndrome (94–96). This might

explain why the authors found a significant effect despite a rather short period in between the measurements.
To quantify the effect through TM more precisely future trails should comprise a bigger variety of groups like a control group, a rehabilitation group, a TM group and a TM+rehabilitation group. However, a plain control group that does not receive any rehabilitative care after suffering a cardiac event would be ethically not justifiable.

Further findings of this study show that patients undergoing a one-month cardiac rehabilitation after a cardiac event benefit considerably from the rehabilitation program. Moreover, the positive effect even increased one month after the rehabilitation. The decline of the resting heart rate reduces coronary vascular events and through that also cardiovascular mortality (97). When looking at the Heart Rate changes in Figure 15 it seems like the heart rate recovers continuously quicker from standing when moving back into supine position comparing pre to post to follow-up. This suggests that the so-called heart rate recovery (HRR) improves as well. The HRR is the heart rate drop within one minute after physical exercise. Although we did not particularly include the HRR in our assessment, this would be an interesting cardiac parameter for future investigations as it serves as a valid predictor of long-term cardiac survival and mortality. Moreover, it reflects the activity of the autonomic system since the heart rate is primarily controlled by the vagus nerve (98–100). The decline of the cardiac output and the cardiac index must not be misinterpreted as a loss of heart performance. It is mainly a consequence of the heart rate reduction as the stroke volume barely changes.

This pilot study is the first of its kind in Europe investing this topic and so far the second study worldwide. All testing has been precisely performed using state-of-the-art devices. Hence, the results und study structure can be used as basis for further investigation.

5.1 Limitations

Some factors should be mentioned that could be optimized. First, the rehab patients receive a multitude of interventions every day already. Beyond physical exercises, participants can also choose from a variety of relaxation methods (see chapter “3.1 Setting and Location. Second, adding further interventions to the rehab schedule, might ironically induce stress in turn, as patients are increasingly challenged to stick to their timetable. Third, when patients start with the rehab program

they are commonly in quite poor condition. It seems likely that they will benefit exceedingly from any kind of rehabilitation intervention in succession to surgery or a cardiac event. Hence, a more reasonable study design for future investigation would comprise on the one hand more study groups (e.g. control-group, TM-group, rehab-group and TM+reha-group) and on the other hand a long-term follow-up (preferable of at least six months).

As already elaborated in detail in the discussion part above, the time-factor seems to be the biggest limitation of our study. As literature research revealed an average study duration of 5.6 months of the citated trials, this indicates that the investigation of the effects of TM on the cardiovascular systems only makes sense in the longer-term. If the study duration is rather short, as it was in our trial, an assessment device with a higher sensitivity would be advisable.

We are aware of the fact that an adaption of the medication, the consumption of caffeinated drinks and the consumption of nicotine could have considerable effects on the cardiovascular system and the measured parameters. But as these disruptive factors can hardly be controlled, we were not capable to consider them in this trial. The easiest way to minimize this source of error is randomization (as we did) and a bigger study population. Additionally, participants could get strongly instructed to abstain from nicotine and caffeine (at least at the day of testing).

5.2 Conclusion

The results of our study show that by adding TM to the cardiac rehabilitation program the additional benefits seem negligible in the short-term. However, as literature indicates, there seems to be a positive effect in the longer-term. More investigation has to be conducted to clarify if TM could affect the cardiac rehabilitation outcome positively in the long-term.

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7. Appendix

7.1 Study-schedules

Oktober 2019 Dienstags-Gruppe KONTR_I

KW	Montag	Dienstag	Mittwoch	Donnerstag	Freitag	Samstag	Sonntag
	30	1	2	3	4	5	6
40		Aufnahme DGKS: Info Arzt: Formulare ThRÖ?	7:00 Blutabnahme Ab 09:00 Anfangsmessung* (90min) 24hEKG + Stuhlgefäß				
	7	8	9	10	11	12	13
41	24h EKG/Stuhl* 16:00-16:30						
	14	15	16	17	18	19	20
42	24h EKG/Stuhl* 16:00-16:30						
	21	22	23	24	25	26	27
43	24h EKG/Stuhl* 16:00-16:30						
	28	29	30	31	1	2	3
44	Ab 09:00 Endmessung* (90min) 24hEKG + Stuhlgefäß	Entlassung					

* 24hEKG-Raum

Figure 20: The study-schedule of control group control. The measurements are highlighted in yellow. At day 2 and 25 main measurements were conducted and in between on day 7, 14 and 21 only 24-hour-ECG and stool samples were taken.

Oktober 2019 Dienstags-Gruppe TM_I

KW	Montag	Dienstag	Mittwoch	Donnerstag	Freitag	Samstag	Sonntag
	30	1	2	3	4	5	6
40		Aufnahme DGKS: Info Arzt: Formulare ThRÖ?	7:00 Blutabnahme Ab 09:00 Anfangsmessung* (90min) 24hEKG + Stuhlgefäß		Einführung** 16:00-17:30 18:15-19:15	Einzelgespräche** 10:00-12:00 13:00-16:00 Meditation** 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30 Gruppengespräch** 18:15-19:15
	7	8	9	10	11	12	13
41	Meditation** 07:00-07:30 17:00-17:30 24h EKG/Stuhl*16:00-16:30 Gruppengespräch** 18:15-19:15	Meditation** 07:00-07:30 17:00-17:30 Gruppengespräch** 18:15-19:15	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30 Wird selbständig durchgeführt	Meditation** 07:00-07:30 17:00-17:30 Wird selbständig durchgeführt
	14	15	16	17	18	19	20
42	Meditation** 07:00-07:30 17:00-17:30 24h EKG/Stuhl*16:00-16:30 Gruppengespräch** 18:15-19:15	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30 Wird selbständig durchgeführt	Meditation** 07:00-07:30 17:00-17:30 Wird selbständig durchgeführt
	21	22	23	24	25	26	27
43	Meditation** 07:00-07:30 17:00-17:30 24h EKG/Stuhl*16:00-16:30 Gruppengespräch** 18:15-19:15	Meditation** 07:00-07:30 17:00-17:30 *	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30	Meditation** 07:00-07:30 17:00-17:30 Wird selbständig durchgeführt	Meditation** 07:00-07:30 17:00-17:30 Wird selbständig durchgeführt
	28	29	30	31	1	2	3
44	Ab 09:00 Endmessung* 24hEKG + Stuhlgefäß Meditation** 07:00-07:30 17:00-17:30 Gruppengespräch**18:15-19:15	Entlassung					

* 24hEKG-Raum
** Andachtsraum

Figure 21: The study-schedule of intervention group TM. The measurements are highlighted in yellow. At day 2 and 25 main measurements were conducted and in between on day 7, 14 and 21 only 24-hour-ECG and stool samples were taken. All activities concerning mediation are written in red letters between day 4 and 28.

7.2 Diagrams of the remaining parameters

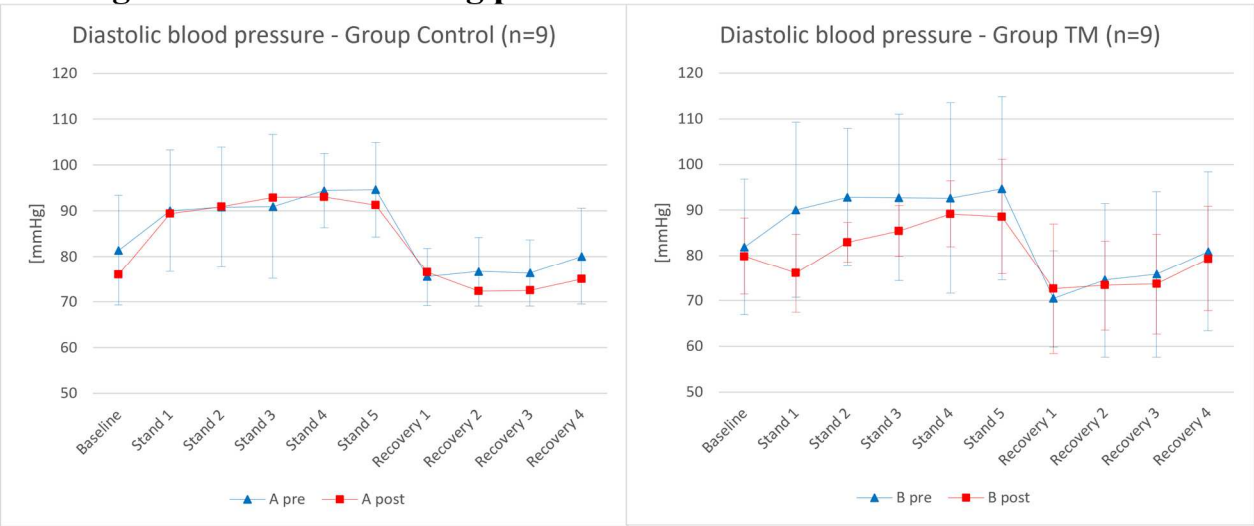

Figure 22: Diastolic blood pressure (pre-post). This figure shows the change of the diastolic blood pressure parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). No significant (p=0.433) change of this parameter between pre and post could be found in both groups and there was no significance (p=0.928) between the groups.

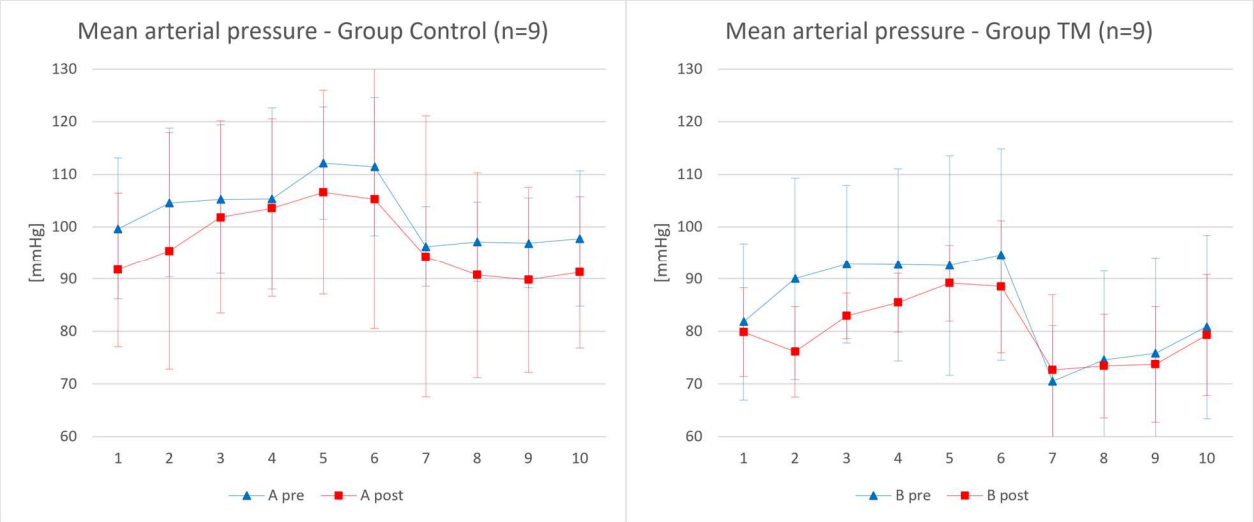

Figure 23: Mean arterial pressure (pre-post). This figure shows the change of the mean arterial pressure parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). No significant (p=0.088) change of this parameter between pre and post could be found in both groups and there was no significance (p=0.754) in between the groups.

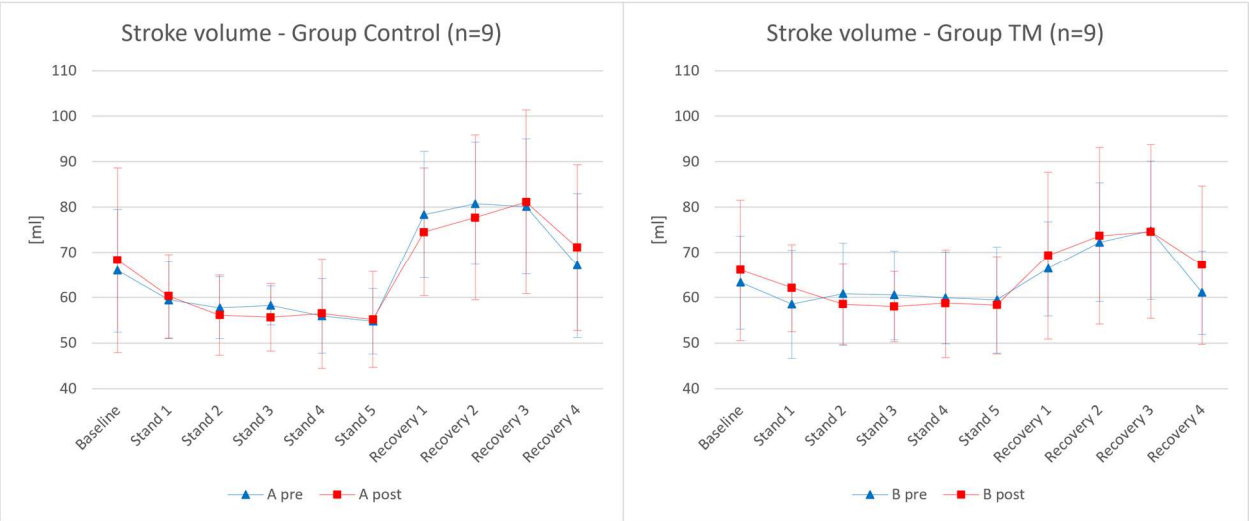

Figure 24: Stroke volume (pre-post). This figure shows the change of the stroke volume parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). No significant (p=0.926) change of this parameter between pre and post could be found in both groups and there was no significance (p=0.799) in between the groups.

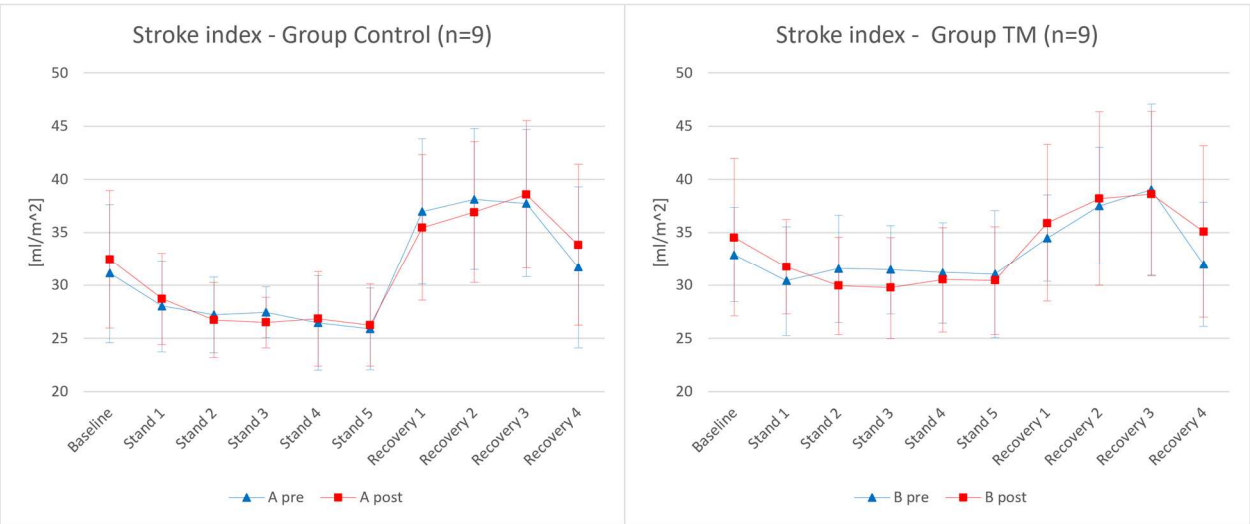

Figure 25: Stroke index (pre-post). This figure shows the change of the stroke (volume) index parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). No significant (p=0.797) change of this parameter between pre and post could be found in both groups and there was no significance (p=0.839) in between the groups.

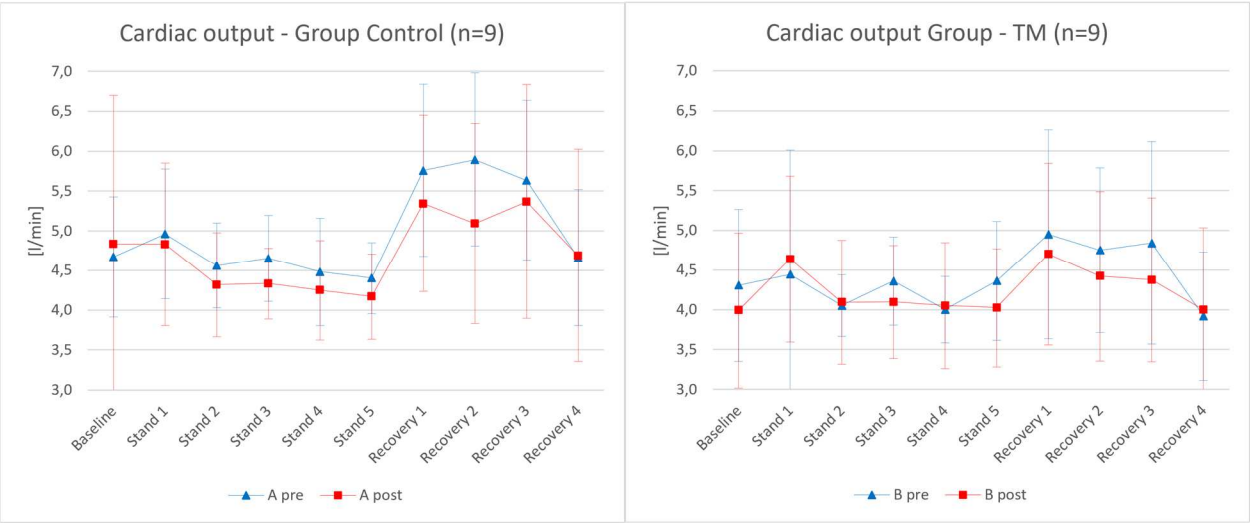

Figure 26: Cardiac output (pre-post). This figure shows the change of the cardiac output parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). No significant (p=0.290) change of this parameter between pre and post could be found in both groups and there was no significance (p=0.630) in between the groups.

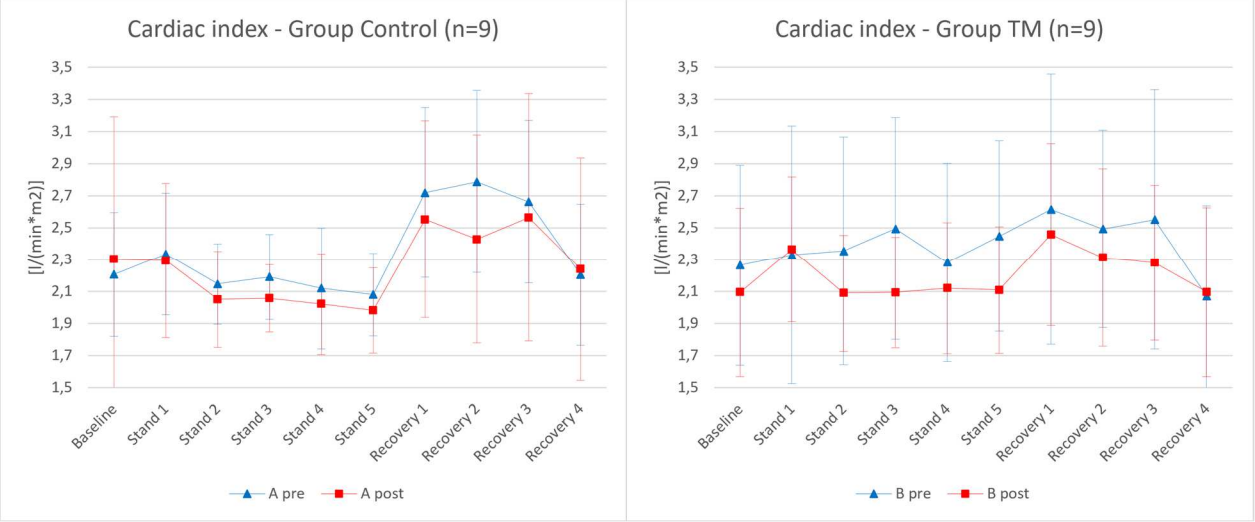

Figure 27: Cardiac index (pre-post). This figure shows the change of the cardiac index parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). No significant (p=0.217) change of this parameter between pre and post could be found in both groups and there was no significance (p=0.822) in between the groups.

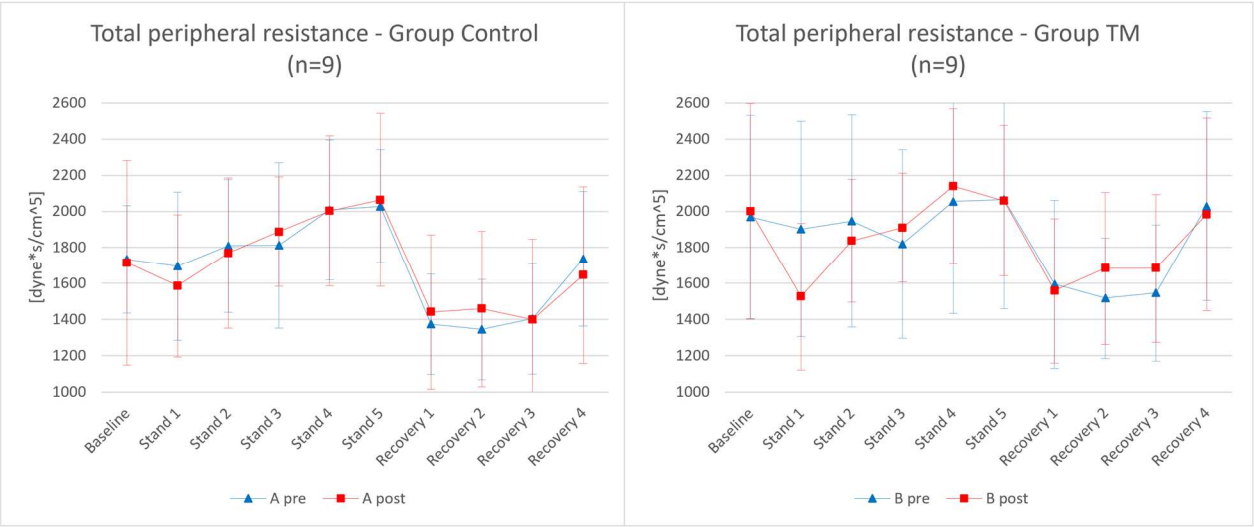

Figure 28: Total peripheral resistance (pre-post). This figure shows the change of the total peripheral resistance parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM. The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). No significant (p=0.627) change of this parameter between pre and post could be found in both groups and there was no significance (p=0.769) in between the groups.

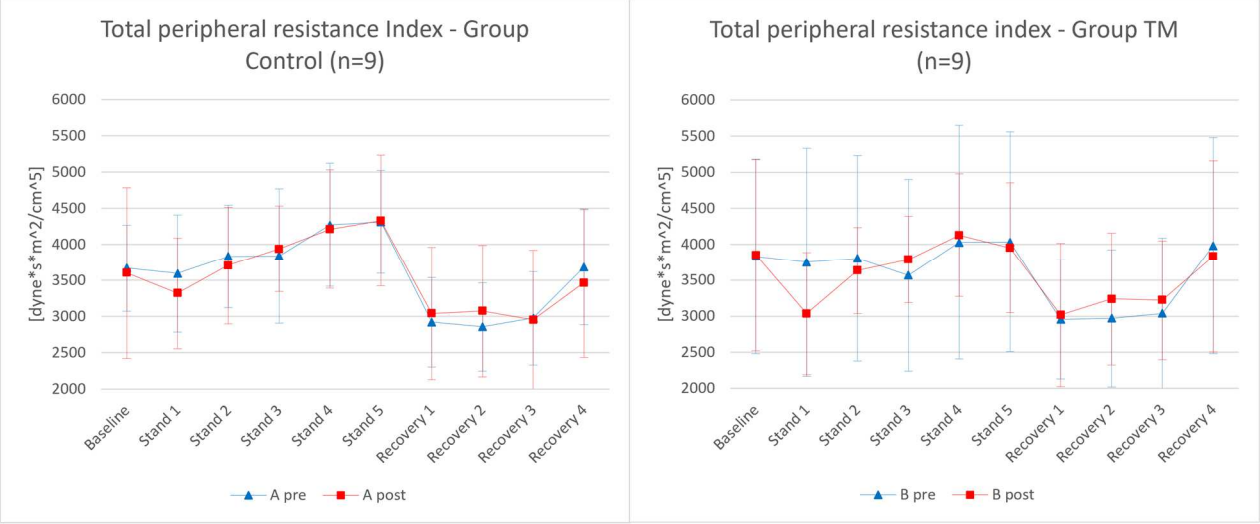

Figure 29: Total peripheral resistance Index (pre-post). This figure shows the change of the total peripheral resistance index parameter between the pre and post measurement. The blue line represents the mean values of the pre-measurement and the red line the mean values of the post-measurement. On the left side are the values of group control and on the right side of group TM The scales on the y-axis are identical. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). No significant (p=0.308) change of this parameter between pre and post could be found in both groups and there was no significance (p=0.769) between the groups.

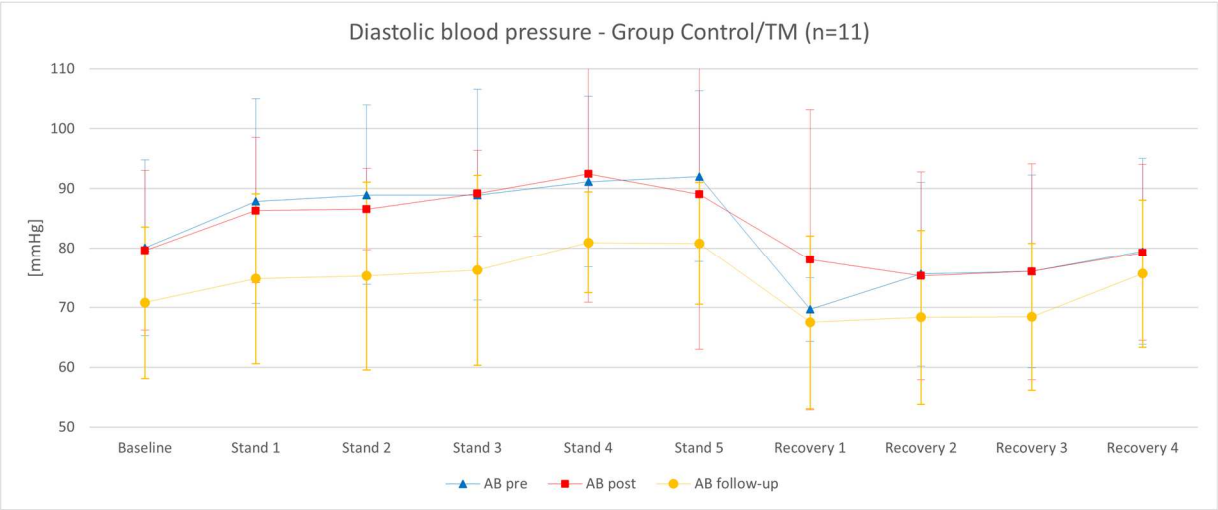

Figure 30: Diastolic blood pressure (pre-post-follow-up). This figure shows the changes of the diastolic blood pressure parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was not significant (p=0.227) between pre and post and follow-up.

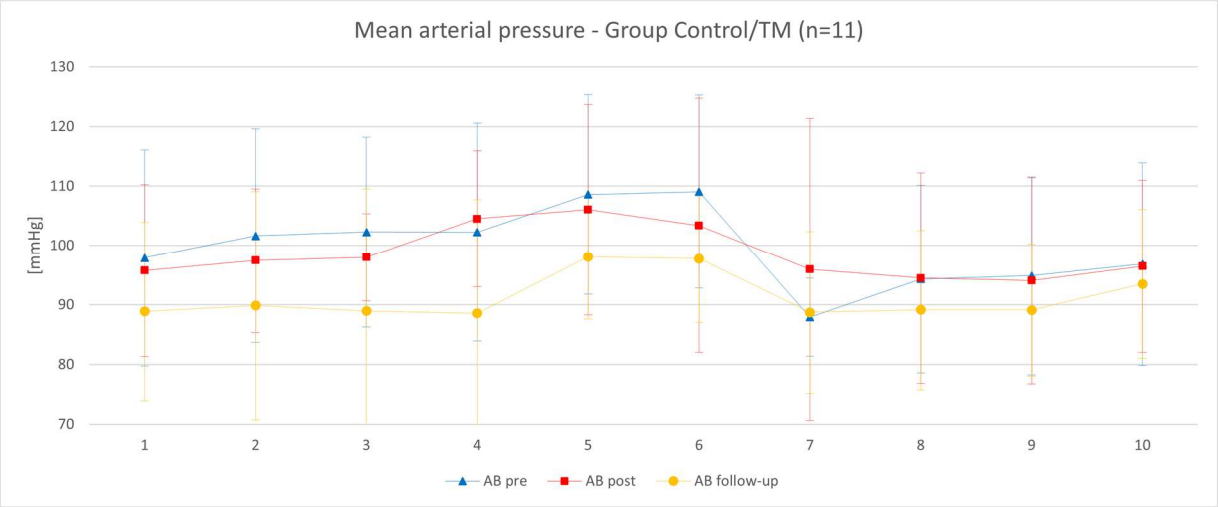

Figure 31: Mean arterial pressure (pre-post-follow-up). This figure shows the changes of the mean arterial pressure parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was not significant (p=0.296) between pre and post and follow-up.

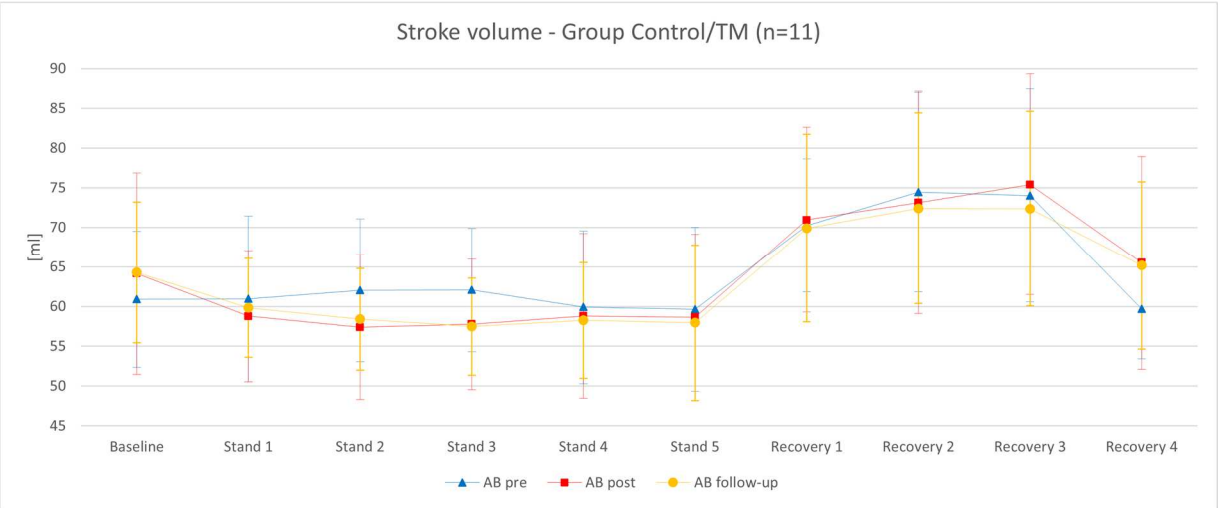

Figure 32: Stroke volume (pre-post-follow-up). This figure shows the changes of the stroke volume pressure parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was not significant (p=0.640) between pre and post and follow-up.

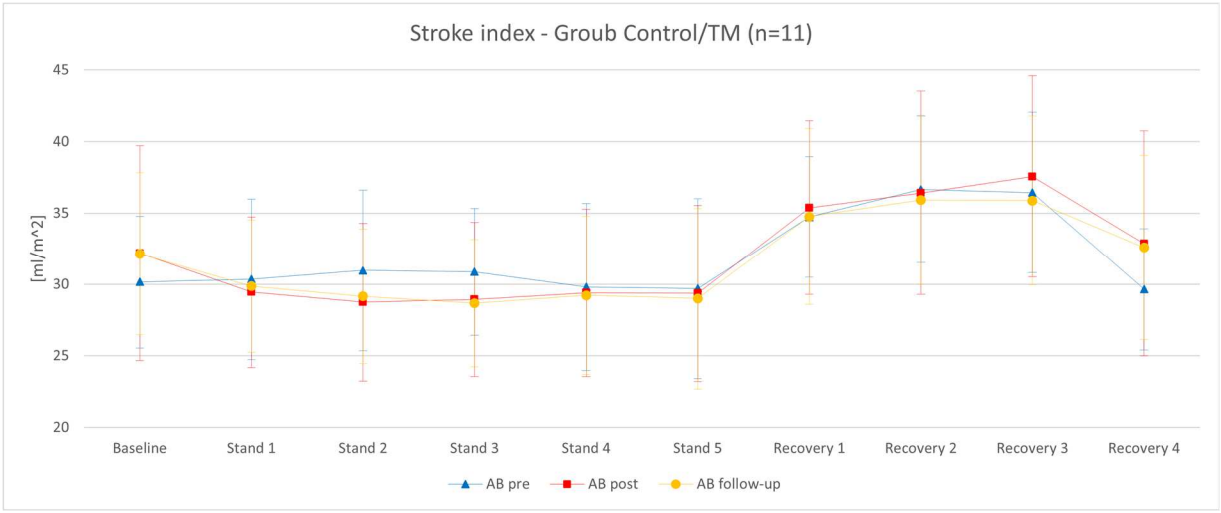

Figure 33: Stroke index (pre-post-follow-up). This figure shows the changes of the stroke (volume) index parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was not significant (p=0.644) between pre and post and follow-up.

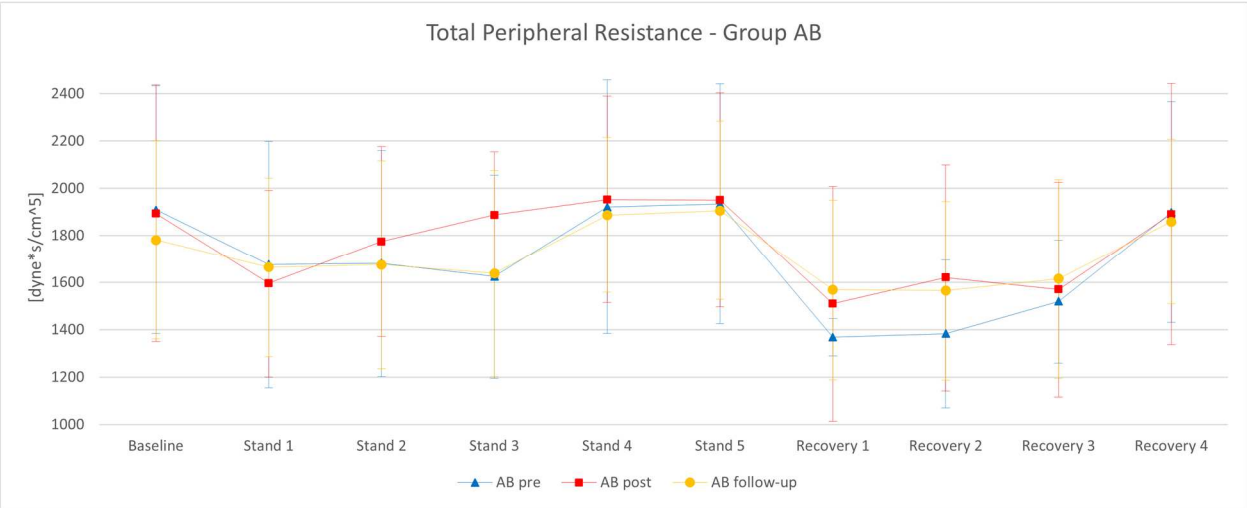

Figure 34: Total peripheral resistance (pre-post-follow-up). This figure shows the changes of the total peripheral resistance parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was not significant (p=0.848) between pre and post and follow-up.

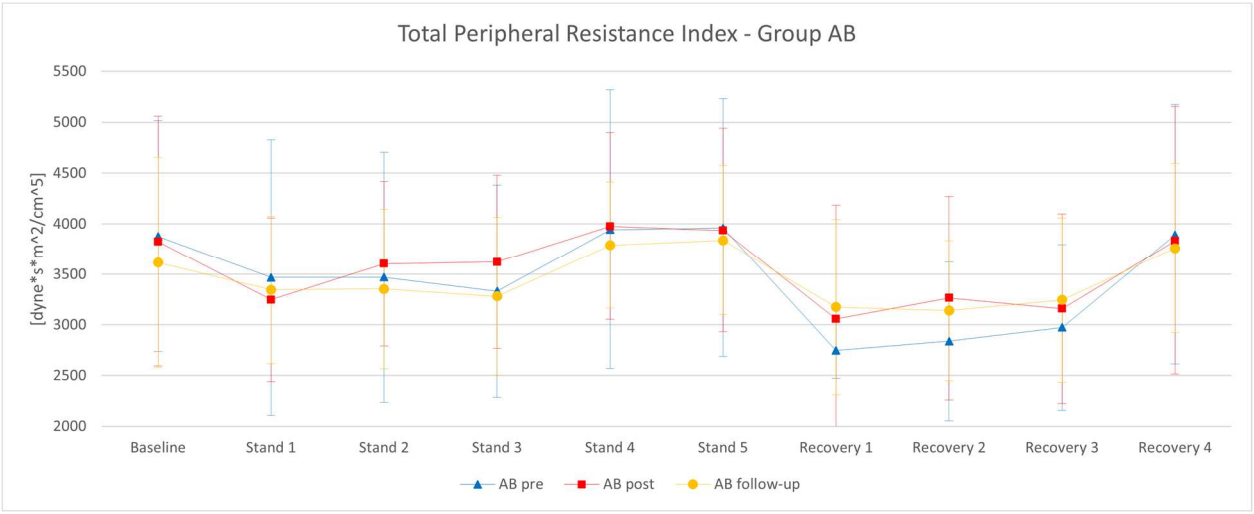

Figure 35: Total peripheral resistance index (pre-post-follow-up). This figure shows the changes of the total peripheral resistance index parameter between the pre, post and follow-up measurement. The blue line represents the mean values of the pre-measurement, the red line the mean values of the post-measurement and the yellow line the mean values of the follow-up measurement. The epochs represent the periods while resting in supine position (Baseline), standing (Stand 1 – 5) and recovery again in supine position (Recovery 1-4). The change of this parameter was not significant (p=0.471) between pre and post and follow-up.

7.3 Ethics

Ethikkommission

Medizinische Universität Graz

Auenbruggerplatz 2, A-8036 Graz
ethikkommission@medunigraz.at
Tel.: +43 / 316 / 385-13928, Fax: -14348

VOTUM
gültig bis 16.07.2020

EK-Nummer:	31-443 ex 18/19
Studientitel:	Transcendental Meditation and yoga: short- and long-term effects in cardiac rehabilitation patients – a pilot study
Prüfer:	Dr. Petra Mächler SKA Rehabilitationszentrum St. Radegund für Herz-Kreislauferkrankungen
Sponsor:	Medizinische Universität Graz, Lehrstuhl für Physiologie
Ansprechpartner:	Assoz. Prof. Dr. Nandu Goswami, 8010 Graz, Neue Stiftingtalstraße 6/V
CRO:	-
Antragsteller:	Medizinische Universität Graz, Lehrstuhl für Physiologie
Ansprechpartner:	Assoz. Prof. Dr. Nandu Goswami, 8010 Graz, Neue Stiftingtalstraße 6/V

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 21.06.2019 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 07.06.2019, begutachtet im 'expedited Review' am 21.06.2019	
✓ Cover Letter CoverLetter 1	07.06.2019
✓ Antragsformular ECS	07.06.2019
✓ Originalprotokoll TMY_Rehab_Studienprotokoll_vers1_07.06.2019 1	07.06.2019
Informed Consent Form TMY_Rehab_Einwilligungserklärung_vers1_07.06.2019 1	07.06.2019
✓ Sonstiges: Declaration of conformity-Nexus10 MKII-Rev6 1	07.06.2019
✓ Sonstiges: Fragebogen_ASTS POMS_vers1_07.06.2019 1	07.06.2019
✓ Sonstiges: Fragebogen_PSQI_vers1_07.06.2019 1	07.06.2019
✓ Sonstiges: Fragebogen_PSQ20_vers1_07.06.2019 1	07.06.2019
✓ Sonstiges: Gebührenbefreiung 1	07.06.2019
✓ Sonstiges: BioTrace-NeXus-ZScore-V1.0 1	07.06.2019
✓ Sonstiges: Fragebogen_STAI-Y6_vers1_07.06.2019 1	07.06.2019
✓ Sonstiges: Nexus-10-User-Manual 1	07.06.2019
✓ Sonstiges: Fragebogen_SF36_Ver1_07.06.2019 1	07.06.2019
Dokumente eingegangen am 03.07.2019 (in der nächsten Begutachtung mitbegutachtet)	
✓ Cover Letter	03.07.2019
✓ Antragsformular ECS unterschrieben	20.06.2019
✓ Informed Consent Form 2	03.07.2019
Dokumente eingegangen am 10.07.2019, begutachtet im 'expedited Review' am 16.07.2019	
✓ Letter of Authorization	10.07.2019

Die Ethikkommission geht - rechtlich unverbindlich - davon aus, dass es sich um keine klinische Prüfung nach AMG bzw. MPG handelt.

Es handelt sich um eine Studie im Rahmen einer Diplomarbeit.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 16. Juli 2019

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.Dr.Hans Dimai
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

Medizinische Universität Graz, Auenbruggerplatz 2, A-8036 Graz, www.medunigraz.at

7.4 Measurement protocol

Pilotstudie: TMY-Studie St. Radegund

MEASUREMENT PROTOCOL

PRE ASSESSMENT

DATE of measurement: _____

TIME of measurement: _____

PATIENT-ID: _____

Group: _____

Intervention: _____

Weather and Temperature:

Changes in Medication:

Comments:

Hair sample for cortisol measurements:

Pulse Wave Velocity:

Retinal Imaging – Patient #:

FMD/FMS:

TMG:

Supine-to-stand Test:

MEASUREMENT PROTOCOL

POST ASSESSMENT

DATE of measurement: _____

TIME of measurement: _____

PATIENT-ID: _____

Group: _____

Intervention: _____

Weather and Temperature:

Changes in Medication:

Comments:

Hair sample for cortisol measurements:

Pulse Wave Velocity:

Retinal Imaging – Patient #:

FMD/FMS:

TMG:

Supine-to-stand Test:

7.5 Participant´s information and consent

Patienteninformation und Einwilligungserklärung zur Teilnahme an der wissenschaftlichen Studie

"Transzendentale Meditation[1] and Yoga: Kurz- und Langzeit Effekt in Herz-Rehabilitations-Patienten – eine Pilotstudie" (TMY_Rehab)

Sehr geehrte Patientin, sehr geehrter Patient!

Wir laden Sie ein an der oben genannten wissenschaftlichen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen Gespräch.
Die Teilnahme an dieser Studie ist freiwillig und kann jederzeit ohne Angabe von Gründen durch Sie beendet werden.
Wissenschaftliche Studien sind notwendig, um verlässliche neue Forschungsergebnisse zu gewinnen. Unverzichtbare Voraussetzung für die Durchführung einer wissenschaftlichen Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser Studie schriftlich erklären. Bitte lesen Sie sich den folgenden Text daher sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur

- wenn Sie Art und Ablauf der wissenschaftlichen Studie vollständig verstanden haben,
- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser wissenschaftlichen Studie im Klaren sind.

Zu dieser wissenschaftlichen Studie sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

[1]Transzendentale Meditation: eine eigene Richtung im Bereich der Meditation nach dem Gelehrten Maharishi Mahesh Yogi

1. Was ist der Zweck der wissenschaftlichen Studie?

Herz-Kreislauf-Erkrankungen sind die häufigste Todesursache in Österreich. Die ESC-Richtlinien empfehlen eine Herzrehabilitation nach koronaren Ereignissen (akutes Koronarsyndrom, Myokardinfarkt usw.) mit dem höchsten Evidenzgrad.
Arzneimitteltherapeutische und nicht-pharmakologische Maßnahmen wie ein gezieltes und individuelles Trainingsprogramm, Stressmanagementprogramme, Ernährungsberatung, Raucherentwöhnung, etc. reduzieren die kardiovaskuläre Wiedererkrankung. Der Abbau von psychosozialem Stress gilt neben dem körperlichen Training und der Ernährung als einer der Hauptfaktoren in der kardiologischen Rehabilitation.
In dieser Studie werden Transzendentale Meditation (TM) und Yoga zur regulären Rehabilitationstherapie hinzugefügt, um die Effizienz dieser Methoden zu untersuchen und möglicherweise die Lebensqualität von Patienten zu verbessern. Das große Ziel dieses Projekts ist es, zu untersuchen, wie Meditations- oder Yogaeinheiten, die zusätzlich zum üblichen Rehabilitationsprogramm angeboten werden, die Funktionen der Blutgefäße sowie das Mirkobiom (Mikroorganismen (z.B. Bakterien) im Darm / Darmflora) und das Stresslevel beeinflussen.

2. Wie läuft die wissenschaftliche Studie ab?

Diese wissenschaftliche Studie ist eine Kooperation vom SKA Rehabilitationszentrum St. Radegund für Herz-Kreislauferkrankungen zusammen mit dem Lehrstuhl für Physiologie an der Medizinischen Universität Graz durchgeführt. Es werden dreißig PatientInnen an dieser Studie teilnehmen. Durch ein zufälliges Auswahlverfahren werden die Patienten/innen auf drei Gruppen zu je 10 Patienten/innen aufgeteilt und **erhalten zusätzlich zu Standard Rehabilitations Behandlungen** folgende Behandlung:

A: die Kontrollgruppe erhält nur die Standard Rehabilitationsbehandlungen. Diese umfassen ein individuell zusammengestelltes Sportprogramm sowie Seminare/Vorträge, als auch Physiotherapie (je nach Bedarf) und natürlich diverse medizinische Untersuchungen
B: Interventionsgruppe I erhält zusätzlich zu der Standardtherapie Meditations-Einheiten. Nach einigen Einheiten zur Einschulung finden diese zwei Mal pro Tag statt. Einmal in der Früh und einmal am Abend für rund 20 Minuten.

C: Interventionsgruppe II erhält zusätzlich zur Standardtherapie Yoga-Einheiten. Ebenfalls 2x20 Minuten pro Tag.
Die Standard Rehabilitationsbehandlungen bestehen vor allem aus einem individuell zusammengestelltem Bewegungsprogramm, aber auch aus diversen Seminaren und medizinischen Untersuchungen. Gruppe B und C erhalten zusätzlich dazu Meditationseinheiten bzw. Yogaeinheiten. Ihre Teilnahme an dieser klinischen Studie wird pro Untersuchungstermin rund 2 Stunden dauern. Dabei werden an 5 Zeitpunkten verschiedene wissenschaftliche Messungen durchgeführt die hier kurz beschrieben werden. Pro Messtermin werden wir etwa X Stunden Ihrer Zeit in Anspruch nehmen.

Um den Status ihrer Gefäße (Elastizität, Reaktionsfähigkeit) Testen zu können werden wir bei Ihnen drei nicht-invasive (keine Nadeln oder Spritzen) Messungen durchführen. Eine Ultraschallmessung am Oberarm (Flow Mediated Dilatation – Abbildung 2). Die Blutflussgeschwindigkeit wird mittels Blutdruckmanschetten gemessen (Abbildung 3), dabei wird eine am Oberkörper und eine am Bein befestigt und fühlt sich für Sie an wie eine gewöhnliche Blutdruckmessung. Bei der dritten Messung wird mittels einer Kamera ein Foto von den Gefäßen in Ihrem Auge gemacht (Abbildung 4).

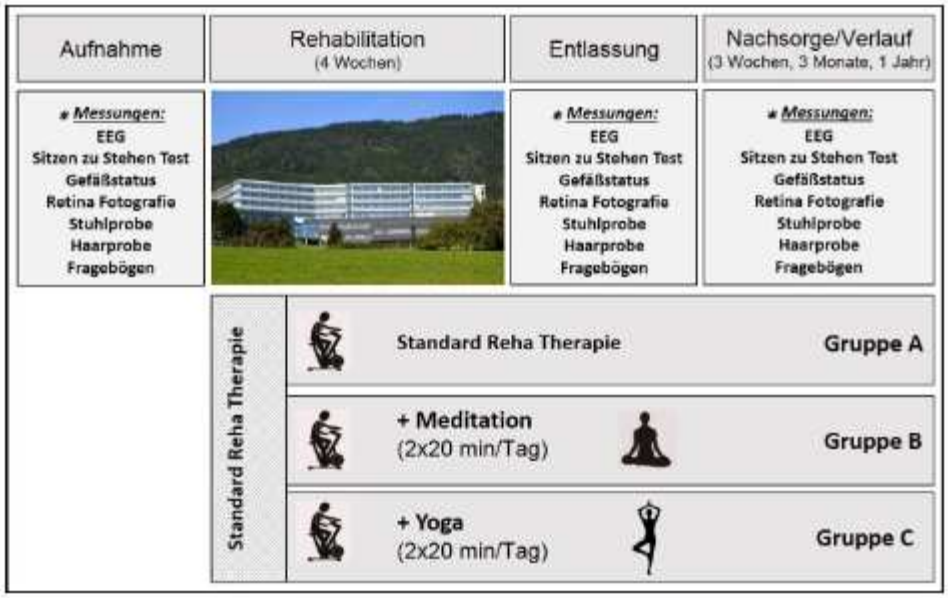

Abbildung 1: Ablauf der wissenschaftlichen Studie. Die Messzeitpunkte für die wissenschaftlichen Messungen sind: zu Beginn der Rehabilitation, am Ende der Rehabilitation und nach 3 Wochen, 3 Monaten und 1 Jahr nach Ende der Rehabilitation

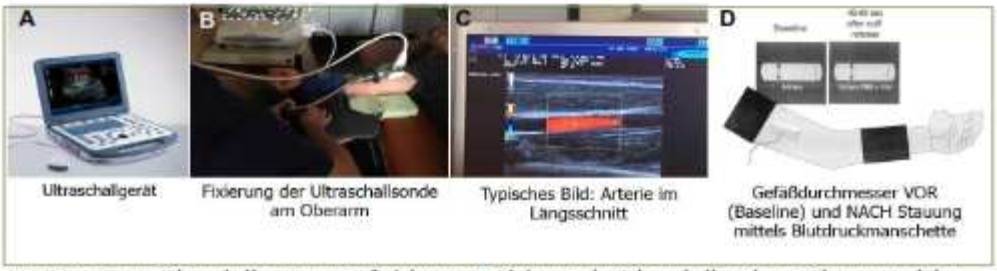

Abbildung 2: A. Ultraschallgerät zur Aufzeichnung **B.** Fixierung der Ultraschallsonde am Oberarm und der Blutdruckmanschette am Handgelenk **C.** Typisches Bild der Brachialarterie im Längsschnitt **D.** Veränderung des Gefäßdurchmessers.

Abbildung 3: Messgerät zur Berechnung der Pulswellengeschwindigkeit und Platzierung der Manschetten am Oberarm und Oberschenkel

Abbildung 4: Retina-Kamera. Mit einer kleinen, einfachen Kamera (rechts) wird von den Gefäßen in Ihren Augen ein Foto gemacht (links). Alles was Sie spüren wird beim Entstehen des Fotos ein Blitz sein.

Um zu sehen wie die unterschiedlichen Therapien sich auf ihr Gehirn auswirken, werden wir eine Elektroenzephalografie (EEG) bei Ihnen durchführen. Dabei handelt es sich um eine Kappe (ähnlich einer Badehaube) an der Kontakt-Elektroden (mit Kontaktgel welches keine Spuren hinterlässt) befestigt sind, die Ihre Hirnströme und Signale messen können. Die EEG Messung soll vor, während und nach der Meditation stattfinden.

Abbildung 5: Elektroenzephalografie (EEG) Programm und das Gerät sowie die Montage am Kopf.

Um ihr Stresslevel zu testen werden Sie gebeten verschiedene Fragebögen zu beantworten. Diese werden folgende Punkte behandeln: Schlafqualität, Lebensqualität, individuelles Stresslevel, momentanes Empfinden (Stimmungsskala) und Ängstlichkeits-Level. Zusätzlich werden Haarproben genommen um das Stress-Hormon Cortison darin zu messen – dafür werden mindestens 10g Haare benötigt (1 Haarsträhne). Dabei entspricht jeder Zentimeter an gewonnenem Haar einem vergangenen Monat.

Sie werden auch gebeten zu jedem der 5 Messtermine eine Stuhlprobe abzugeben.

Zur Messung der Herz-Kreislaufregulation bei Positionsänderungen wird ein Sitzen zu Aufstehen Test durchgeführt. Dabei werden Werte wie Blutdruck und die Herzleistung (Task Force Monitor, Abbildung 7), die Muskelaktivität an der Wade über die Haut und die Gefäßreaktion in der Wade über die Haut (Abbildung 6b) gemessen, sowie der Blutfluss im Gehirn mit einem Ultraschall-Gerät miterfasst (Abbildung 6a und 8). Alle angewandten Methoden sind ***nicht invasiv*** (das heißt es werden nur ***Klebeelektroden auf der Haut*** verwendet und ***keine Nadeln*** oder Spritzen, es gibt auch im Rahmen dieser Messung keine Blutabnahme) ***und nicht schmerzhaft***. Sie werden – wie in Abbildung 1 dargestellt – insgesamt zu 5 Messterminen gebeten an einem solchen ***Sitzen zu Aufstehen Test*** (Abbildung 6) teilzunehmen. Insgesamt bekommen Sie zwei Blutdruckmanschetten angelegt, eine am rechten Oberarm, die zweite am linken Mittelfinger. Zur Messung des EKGs und anderer Herz-Kreislaufwerte werden 8 Elektroden auf Ihrem Oberkörper befestigt. Dazu kommen noch 3 Klebeelektroden auf den Waden zur Vermessung der Muskeln.

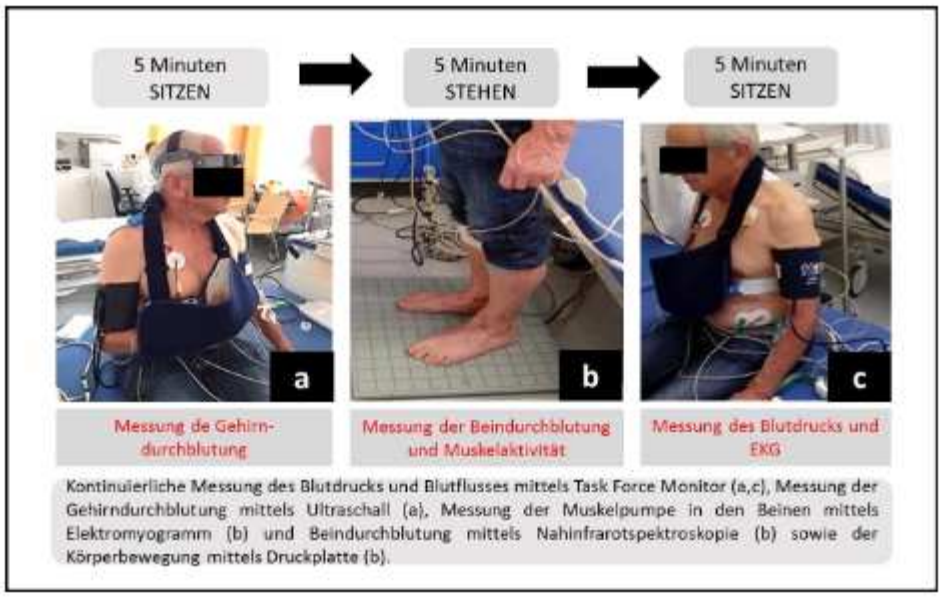

Abbildung 6: *Ablauf des Sitzen zu Aufstehen Tests.* Ein Proband befindet sich in der Ausgangslage, in sitzender Position ruhig für **5 Minuten** (A). Danach wird er gebeten aufzustehen und für **5 Minuten ruhig zu stehen** (B). Anschließend wird der Proband gebeten sich für **weitere 5 Minuten wieder zu setzen** (C). Dabei steht der Proband auf einer Druckplatte, die Körperschwankungen aufzeichnet.

Abbildung 7: Task Force Monitor®

Abbildung 8: Transkranialer Doppler zur Messung des Blutflusses ins Gehirn

Alle Messungen von den Patienten in der Gruppe A-C werden verglichen, um zu erforschen, ob Meditation oder Yoga im Vergleich zur Standardbehandlung zu einem zusätzlichen Vorteil in der kardialen Rehabilitation und Stressreduktion bieten kann. ***Im Rahmen der Untersuchungen finden keine zusätzlichen Blutuntersuchungen statt. Die Ergebnisse Ihrer Routine-Blutanalysen werden aber in die Studie einbezogen.***

3. Worin liegt der Nutzen einer Teilnahme an der wissenschaftlichen Studie?

Es ist möglich, dass Sie durch Ihre Teilnahme an dieser wissenschaftlichen Studie keinen direkten Nutzen für Ihre Gesundheit ziehen. Es werden jedoch Messwerte der Herzleistung, der Gefäße und ihres Stresslevels bestimmt, welche Ihnen zugänglich gemacht werden.

4. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Im Rahmen der Studie werden keine Medikamente verabreicht. Während des Steh-Tests kann es kurzzeitig zu einem Schwindelgefühl kommen. Im Fall einer Allergie durch die Klebeelektroden kann es zu einer Rötung an dem entsprechenden Hautareal kommen.

5. Hat die Teilnahme an der wissenschaftlichen Studie sonstige Auswirkungen auf die Lebensführung und welche Verpflichtungen ergeben sich daraus?

Die Studie hat keine Auswirkungen auf Ihre Lebensführung. Sollten Sie bei den Kontrollterminen verhindert sein und diesen Termin nicht wahrnehmen können, bitten wir Sie umgehend, uns davon zu informieren.

6. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Sollten im Verlauf der wissenschaftlichen Studie irgendwelche Symptome, Begleiterscheinungen oder Verletzungen auftreten, müssen Sie diese dem Studienleiter mitteilen. Bei schwerwiegenden Begleiterscheinungen (wie z.B. Schmerzen bei der Durchführung der Übungen oder Schwindel) bitte umgehend.

7. Wann wird die wissenschaftliche Studie vorzeitig beendet?

Sie können jederzeit, auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der klinischen Studie ausscheiden ohne dass Ihnen dadurch irgendwelche Nachteile für Ihre weitere medizinische Betreuung entstehen.

8. In welcher Weise werden die im Rahmen dieser wissenschaftlichen Studie gesammelten Daten verwendet?

Bei den Daten, die über Sie im Rahmen dieser klinischen Studie erhoben werden, ist grundsätzlich zu unterscheiden zwischen

1) Personenbezogene Daten,
anhand derer Sie direkt identifizierbar sind (z.B. Name, Geburtsdatum, Adresse...)
verbleiben an der Herzchirurgie und werden nach der ambulanten Nachkontrolle (nach 3 Monaten) gelöscht.

2) Pseudonymisierte (verschlüsselten) Daten,
bei denen alle Informationen, die direkte Rückschlüsse auf Ihre Identität zulassen, werden durch einen Code (z. B. eine Zahl) ersetzt.

Der Code wird von den verschlüsselten Datensätzen streng getrennt und nur an Ihrem Prüfzentrum aufbewahrt. Zugang zu Ihren nicht verschlüsselten Daten haben der Prüfarzt und andere Mitarbeiter des Prüfzentrums, die an der klinischen Studie oder Ihrer medizinischen Versorgung mitwirken. Die Daten sind gegen unbefugten Zugriff geschützt. Zusätzlich können autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des Sponsors sowie Beauftragte von In- und/oder ausländischen Gesundheitsbehörden und jeweils zuständige Ethikkommissionen in die nicht verschlüsselten Daten Einsicht nehmen, soweit dies für die Überprüfung der ordnungsgemäßen Durchführung der klinischen Studie notwendig bzw. vorgeschrieben ist. Diese Personen unterliegen einer strengen Geheimhaltungspflicht.

Eine Weitergabe der Daten erfolgt nur in verschlüsselter Form. Auch für etwaige Publikationen werden nur die verschlüsselten Daten verwendet.

Sie können Ihre Einwilligung zur Erhebung Ihrer Daten jederzeit widerrufen. Nach Ihrem Widerruf werden keine weiteren Daten mehr über Sie erhoben. Die bis zum Widerruf erhobenen Daten können allerdings weiter im Rahmen dieser klinischen Studie verwendet werden.

Aufgrund der gesetzlichen Vorgaben haben Sie außerdem, sofern dies nicht die Durchführung der klinischen Studie beeinträchtigt, das Recht auf Einsicht in die von Ihnen erhobenen Daten und die Möglichkeit der Berichtigung, falls Sie Fehler feststellen.

Sie haben auch das Recht, bei der österreichischen Datenschutzbehörde eine Beschwerde über den Umgang mit Ihren Daten einzubringen (www.dsb.gv.at).

Sämtliche Personen, die Zugang zu Ihren verschlüsselten und nicht verschlüsselten Daten erhalten, unterliegen im Umgang mit den Daten dem österreichischen Datenschutzgesetz in seiner gültigen Fassung sowie der Datenschutz-Grundverordnung (DSGVO).

Auch die Dauer der Speicherung Ihrer Daten ist durch Rechtsvorschriften geregelt.

Falls Sie Fragen zum Umgang mit Ihren Daten in dieser klinischen Studie haben, wenden Sie sich zunächst an Ihren Prüfarzt. Dieser kann Ihr Anliegen ggf. an die Personen, die am Prüfzentrum für den Datenschutz verantwortlich sind, weiterleiten.

Kontakt Datenschutzbeauftragte/r: datenschutz@medunigraz.at

9. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser klinischen Prüfung entstehen für Sie keine zusätzlichen Kosten.

10. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser wissenschaftlichen Studie stehen Ihnen Ihr Studienleiter und seine Mitarbeiter gern zur Verfügung. Auch Fragen, die Ihre Rechte als Proband und Teilnehmer an dieser wissenschaftlichen Studie betreffen, werden Ihnen gerne beantwortet.

Name der Kontaktpersonen:
Dr. Petra Mächler vom Rehabilitationszentrum St. Radegund
03132/23511 oder email: ska-rz.radegund@pensionsversicherung.at

Assoz. Prof. Dr. Nandu Goswami vom Lehrstuhl für Physiologie, Med Uni Graz
0316 380 4278 oder email: nandu.goswami@medunigraz.at

11. Werden andere behandelnde Ärzte von der Teilnahme an der wissenschaftlichen Studie informiert werden?

Nein