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Influence of exercise training on cardiac remodeling after acute myocardial infarction – a PET/MRI study

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Abbreviations

AMI	Acute myocardial infarction
BSA	Body surface area
CAD	Coronary artery disease
CCTA	Coronary Computed Tomography Angiography
CHD	Coronary heart disease
CR	Cardiac rehabilitation
CVD	Cardiovascular disease
DGPR	Deutsche Gesellschaft für Prävention und Rehabilitation (German Society for Prevention and Rehabilitation)
ECG	Electrocardiography
EDV	End-diastolic volume
EF	Ejection fraction
ESV	End-systolic volume
ET	Exercise training
^{18}F-FDG	^{18} F-fluorodeoxyglucose
Gd	Gadolinium
HF	Heart Failure
IRENA	Intensivierte Reha-Nachsorge (intensive follow-up care after rehabilitation)
KARENA	Kardiovaskuläres Reha-Nachsorgeprogramm (cardiovascular rehabilitation follow-up program)
LGE	Late gadolinium enhancement
LV	Left ventricle
LVEDV	Left-ventricular end-diastolic volume
LVESV	Left-ventricular end-systolic volume
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
PET	Positron-Emission-Tomography
PCI	Percutaneous coronary intervention
RAAS	Renin-angiotensinogen-aldosterone system
SPECT	Single-Photon-Emissions-Computer-Tomography
STEMI	ST-segment elevation Myocardial Infarction
SV	Stroke volume
VO_{2peak}	Maximum oxygen uptake

1 Introduction

1.1 Myocardial infarction

Myocardial infarction (MI) is an acute manifestation of coronary artery disease (CAD) and coronary heart disease (CHD), which both belong to a group of illnesses that affect the heart and blood vessels, and are known as cardiovascular disease (CVD). (Steg et al., 2012; WHO, 2017).

CVD, including acute myocardial infarction (AMI), is not only the leading cause of death in Germany, but also worldwide (WHO, 2017). According to the German Federal Statistical Office, in 2014 38,9% of deaths in Germany were caused by CVD. Within CVD, CHD caused 14% of overall deaths and AMI 5,5% of overall deaths. The majority of deaths in patients suffering from CVD occurred in patients over the age of 65 (Statistisches Bundesamt, 2014).

The trigger for MI is ischemia, which most often is caused by a ruptured plaque leading to a thrombotic occlusion of the coronary artery (Davies, 2000; Thygesen et al, 2007). At the cellular level, ischemia leads to edema, inflammation and cell death in the form of coagulation necrosis. This process begins approximately 30 minutes after the onset of ischemia. After a few hours, myocytes that would normally be supplied with oxygen by the occluded artery, become necrotic. The size of the infarction is influenced by several factors, such as the extent of collateral blood vessels supplying the occluded area, ongoing or periodic vessel occlusion, myocardial preconditioning to ischemia and individual oxygen demand (Thygesen et al., 2007).

The primary symptom of coronary ischemia is ongoing chest pain that lasts over twenty minutes and is non-responsive to nitroglycerin (which acts as a vasodilating substance). Other non-specific symptoms include dyspnea, nausea, syncopia, fatigue, palpitations. However, an AMI can also present itself with atypical symptoms, especially in diabetics, women and the elderly (Thygesen et al., 2007; Steg et al., 2012).

Successful therapy requires a quick diagnosis of an AMI. The criteria for diagnosis of MI were defined in the “ESC guidelines for management of acute myocardial infarction in patients presenting with ST-Segment elevation” (Steg et al., 2012), which can be found in Table 1.

Table 1. Definition of acute myocardial infarction adapted from (Steg et al., 2012)

Elevation and/or fall of cardiac biomarker values (by preference troponin) with a minimum of one biomarker value >99th percentile of the upper reference limit And at least one of the following criteria: - Symptoms of ischemia - New significant ST-T changes or new left-bundle-branch-block in the ECG - Development of pathological Q-waves in the ECG - Cardiac imaging presenting a new loss of viable myocardium or regional wall motion abnormality - Identification of an intracoronary thrombus by angiography or autopsy

Cardiac death with previous ischemic symptoms, presumably new ECG changes or new LBBB, death occurring before blood cardiac biomarkers values are released or before cardiac biomarker values would be increased
Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

ECG = electrocardiography, LBBB = left bundle branch block, URL =upper reference limit

In the initial diagnosis of an AMI, an ECG plays an important role, as changes in the ST-segment, left bundle branch blocks and changes in the initial Q-wave are typical indicators. During the first hours of a MI, however, an ECG may not show these typical pathologies. Blood tests can help to detect an increase in cardiac biomarker values during the early phase of AMI. Troponin (T and I) are the most important biomarkers as they are highly sensitive and specific in detecting myocardial necrosis. When the probability for MI is high, such as in patients with an ST-segment elevation or a new left bundle branch block, reperfusion treatment should be performed without waiting for the results of the blood tests (Steg et al., 2012). If the diagnosis is still unclear, emergency imaging should be carried out. Coronary angiography is the imaging method of choice as it directly allows subsequent primary percutaneous coronary intervention (PCI). If a hospital does not have the capability to perform a coronary angiography, then a two-dimensional echocardiography should be performed to detect wall motion abnormalities. If wall motion abnormalities are found, the patient should be transferred to a hospital which can perform PCI immediately (Ibanez et al., 2017).

Symptoms presented during diagnostics should be treated as well, to not only provide relief to patients, but to also lower myocardial oxygen demand, as the myocardial workload and vasoconstriction are increased by pain. The recommended medication for symptom relief during the acute phase of MI include: titrated i.v.-opioids for pain-relief, tranquilizers in agitated patients, and oxygen if patients suffer from hypoxia, breathlessness or heart failure (Ibanez et al., 2017; Steg et al., 2012). Patients should also receive dual antithrombotic and antiplatelet medication as well as an intravenous anticoagulant as soon as possible (Ibanez et al., 2017; Steg et al., 2012).

The primary goal for patients suffering from AMI is the revascularization of the occluded artery. Each patient should preferably receive a mechanical revascularization by PCI. When PCI is contraindicated by other factors, pharmacological revascularization is an option. The standard procedure is to initiate treatment within the first twelve hours after symptom onset and diagnosis. However, even for a patient suffering from symptoms for more than twelve hours, if there is clinical or electrocardiographic evidence of ischemia, revascularization therapy will still be beneficial (Steg et al., 2012). The time between diagnosis of ST-segment elevation myocardial

infarction (STEMI) and the beginning of PCI should be no longer than 60 minutes. If a PCI center cannot be reached within 120 minutes, fibrinolytic therapy should be considered as revascularization therapy. During PCI the culprit lesion is dilated using balloon angioplasty. After the angioplasty, the guidelines suggest implanting a stent, preferably drug-eluting rather than bare-metal (Ibanez et al., 2017; Steg et al., 2012).

Upon successful revascularization therapy, the patient should follow a medication plan that includes dual antiplatelet and antithrombotic therapy using aspirin and an ADP-receptor inhibitor for 12 months. Ibanez et al. (2017) recommend initiating an early i.v. beta-blocker treatment in hemodynamically stable patients, previously treated with PCI, followed by a long-term oral therapy with beta-blockers. In case of contraindications for beta-blockers (e.g. obstructive airway disease or second- and third-degree atrioventricular block), the calcium-antagonist verapamil may be used in patients without heart failure (HF) or impaired left ventricular (LV) function. Statins and angiotensin-converting-enzyme-inhibitors (ACE-inhibitors)/angiotensin-receptor-blockers are also recommended. In a patient with an EF <40% and heart failure or diabetes, aldosterone-antagonists should be used (Ibanez et al., 2017; O'Gara et al., 2013; Steg et al., 2012).

After successful treatment of AMI an exercise-based cardiac rehabilitation (CR) program should be initiated. Long-term non-pharmaceutical strategies for post-MI patients focus on lifestyle changes, such as smoking cessation, diet and weight control, an increase in physical activity (in the form of structured exercise training (ET)), blood pressure management and psychosocial interventions such as stress reduction (Ibanez et al., 2017; O'Gara et al., 2013; Steg et al., 2012). Follow-up care is essential to encourage a patient to adhere to lifestyle modifications and prevent falling back into behavioral patterns that preceded the MI. Studies have shown that long-term adherence to life-style modification, especially ET, is necessary to maintain the positive effects on the impaired cardiovascular system following MI (Vona et al., 2004; Moholdt et al., 2011).

1.2. Cardiac remodeling

The International Forum on Cardiac Remodeling defines remodeling as follows:

> *"Cardiac remodeling may be defined as genome expression, molecular, cellular and interstitial changes that are manifested clinically as changes in size, shape and function of the heart after cardiac injury. The process of cardiac remodeling is influenced by hemodynamic load, neurohormonal activation and other factors still under investigation […]"* (Cohn et al., 2000, p. 570).

A common cause of severe cardiac injury is a MI, which triggers cardiac remodeling within a few hours after onset (Cohn et al., 2000; Erlebacher et al., 1984; Pfeffer, 1990; Sutton, 2000). The first hours of an MI are defined by edema, inflammation and coagulation necrosis leading to impaired contractile function and dyskinesis in the infarcted area (Pfeffer, 1990). Due to the loss of myocytes, the infarcted area is vulnerable to mechanical forces, such as an increased cardiac load, resulting in a thinning of the ventricular wall in the infarcted area. This is also known as infarction expansion. Infarction expansion not only leads to dilation of the infarcted area, but also to dilation in the non-infarcted myocardium. The process of ventricular dilation begins early after infarction and continues after infarction healing is completed (Pfeffer, 1990; Sutton, 2000).

The inflammatory phase of a MI is characterized by macrophages, neutrophils and monocytes inducing complex biochemical and intracellular signaling pathways that result in (a) a degradation in the extracellular matrix and collagen fibers, and neurohumoral activation; and (b) a limitation in infarction expansion and an induction of scar tissue formation (Frangogiannis, 2008; Frangogiannis, 2012; Sutton, 2000). The death of myocardial cells results in hemodynamic changes, namely hypotension and impaired systolic function, which activate the sympathetic nervous system and the renin-angiotensinogen-aldosterone-system (RAAS) and induces the secretion of natriuretic peptides. This complex process affects the non-infarcted myocardium, maintains stroke volume and circulation despite the loss of myocytes. Natriuretic peptides reduce cardiac preload and peripheral vascular resistance, and ameliorate pump function. Cardiac remodeling can initially be seen as an adaptive process to compensate for impaired cardiac function (Pfeffer, 1990; Sutton, 2000).

As mentioned above, infarction leads to ventricular dilation, which increases diastolic and systolic wall stress and an increase in ventricular volumes (Cohn et al., 2000; Pfeffer, 1990; Sutton, 2000). Ventricular dilation triggers the sympathetic, neurohumoral and RAAS system and acts as a strong stimulant for ventricular hypertrophy of the non-infarcted myocardium (Cohn et al., 2000; Pfeffer, 1990; Sutton, 2000). Hypertrophy of the myocardium can be seen as a buffer to increased wall stress and cardiac load while the necrotic infarcted area is being replaced by scar tissue, which is more resistant to mechanical forces (Sutton, 2000).

Despite the transient compensatory effect of an overactivated sympathetic nervous system and neurohumoral response after MI, long-term activation becomes detrimental and leads to further impaired cardiac function and heart failure, which is associated with a poor prognosis (Cohn et al., 2000; Hobbs et al., 2007; Cowie et al., 2000).

Monitoring a patient's cardiac remodeling is important in detecting heart failure at an early stage and initiating adequate therapy. To measure cardiac remodeling, parameters such as end-

diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), heart size and shape can be analyzed via echocardiography or cardiac imaging (e.g. magnetic-resonance imaging). EDV not only provides information about the diastolic filling of the ventricle, but also about the structural changes of the ventricle. ESV is determined by EDV and cardiac shortening (Cohn et al., 2000).

In addition, cardiac remodeling should not only be monitored, but also attenuated to prevent further heart failure progression. Next to optimal medication therapy, which has been shown to attenuate cardiac remodeling (Cohn et al., 2000), the possible effects of ET on cardiac remodeling, CAD and HF, have been an important research topic in sports medicine and cardiology (Haykowsky et al., 2007; Haykowsky et al. 2011; Jorge et al., 2011; Laughlin et al., 2012; Moholdt et al. 2011). Trials have shown that ET improves endothelial dysfunction on a systemic level, which is present in many patients following MI (Hambrecht et al., 2003; Vona et al., 2004). Moreover, ET can restore the imbalance of the autonomic nervous system, which is one of the main factors promoting cardiac remodeling as described above (Jorge et al., 2011; Malfatto et al., 1996; Rodrigues et al., 2014). Other trials analyzing whether ET ameliorates the complex inflammatory processes (which are offset during myocardial infarction) found a significant reduction in the inflammatory process which leads to *inter alia* decreased scar-thinning and risk for future cardiac events (Puhl et al., 2015; Milani et al., 2004). A meta-analysis from Haykowsky et al (2011) found that ET attenuated cardiac remodeling (Haykowsky et al., 2011). Current research is focusing on comparisons of different training methods such as aerobic interval training and moderate continuous training, as well as exercise duration and frequency, to determine the best possible ET program to improve cardiac remodeling long-term.

1.3. Cardiac rehabilitation

The importance of exercise-based cardiac rehabilitation (CR) is well-known. Several meta-analyses and reviews have shown that CR drastically reduces all-cause mortality and cardiac mortality in patients suffering from AMI and/or CHD (Anderson & Taylor, 2014; Ades, 2001; Doll et al., 2015; Hammill et al., 2010; Heran et al., 2011; Go et al., 2014; Lawler et al., 2011; Rauch et al., 2014).

ET has been found to ameliorate the prognoses in patients suffering from MI by attenuating cardiac remodeling, improving endothelial and cardiac function, enhancing exercise capacity, inhibiting sympathetic activity and lowering cardiovascular risk factors leading, not only to a higher long-term survival rate, but also to an increase in the quality of life (Bjarnason-Wehrens et al., 2009; Haykowsky et al., 2011; Fletcher et al., 2001; Giannuzzi et al., 2003).

Participation in a comprehensive CR program which includes ET has been shown to result in less adverse events such as reinfarction (Lawler et al., 2011) and readmission to hospitals (Heran et al., 2011). Moreover, it improves cardiac risk factors (Lawler et al., 2011). Thus, CR plays a pivotal role in prevention after MI.

Rehabilitation programs have several purposes. The main goal is to prevent further progression of a disease and improve the current state of a patient's health. Secondarily, it is helpful in reintegrating a person back into his or her social and professional life (Dietz, 2003; Bjarnason-Wehrens et al., 2009; Bjarnsason-Wehrens et al., 2007; Bundesarbeitsgemeinschaft für Rehabilitation, 2011; Bundesarbeitsgemeinschaft für Rehabilitation, 2005). A term often used in rehabilitation is "participation", which emphasizes the right of an individual suffering from an acute or chronic disease to be able to take part in social and professional activities.

Rehabilitation uses a multifactor approach to reinstate a person's health and participation. It consists of ET, prevention and lifestyle education, as well as psychological intervention, in order to strengthen a patient's coping mechanisms and encourage a healthy lifestyle (Dietz R, 2003; Bundesarbeitsgemeinschaft für Rehabilitation, 2005). As a long-term strategy to achieve the previously mentioned goals rehabilitation is divided into three phases, shown in Figure 1.

Figure 1. Phases of rehabilitation (adapted from Dietz R, 2003)

The Federal Collaboration for Rehabilitation and the German Society for Prevention and Rehabilitation (DGPR) establish recommendations for medical rehabilitation in Germany. The recommendations provided by these institutions set standards for the organization and structure of a CR program, content of CR and requirements for employees, facilities and equipment to ensure patient safety and to achieve the strongest benefit for a patient's health. In addition, the recommendations also address the critical need for a physical examination prior to the initiation of exercise programs. This includes exercise testing, and a review of medical history, electrocardiography and echocardiography (Reha Qualitätssicherung der Deutschen Rentenverischerung; Bjarnsason-Wehrens et al., 2007; Bundesarbeitsgemeinschaft für Rehabilitation, 2005).

There are several types of rehabilitation programs that patients can participate in. Most patients visit “inpatient” and “outpatient” rehabilitation centers, however, there are also newer models, such as home-based rehabilitation programs that have been successfully implemented (Fischer et al., 2012; Anderson &Taylor, 2014). The choice of a certain program type depends on several factors such as risk profile for future cardiac events and co-morbidities. In high-risk patients with instable cardiac function inpatient centers are recommended (Corrà et al., 2010). To date, the superiority of an inpatient, outpatient or a home-based program has not been demonstrated. According to a Cochrane review all programs are equally effective, at least in post-MI patients with low risk for future cardiac events (Anderson & Taylor, 2014).

When a patient finishes the cardiac rehabilitation program, follow-up care is usually performed by the patient’s general practitioner or cardiologist. In Germany, the German Pension Fund pays for exercise training programs such as IRENA (intensive rehabilitation follow-up care) or KARENA (coronary rehabilitation follow-up care) (Fischer et al., 2012; Reibis et al., 2014). In addition, regional “heart sport groups” organized by the DGPR, offer supervised ET following a rehabilitation program (Bundesarbeitsgemeinschaft für Rehabilitation, 2011).

1.3.1 Exercise training in cardiac rehabilitation

ET is a key component in CR. Specific recommendations for physical activity, as a part of a comprehensive rehabilitation program, are set forth in the national guidelines, which are provided by the DGPR.

The most recent guideline from the DGPR provides that ET in a patient with stable CAD should consist of aerobic endurance training (evidence level IA), dynamic resistance training (evidence level IB), and coordination and flexibility training (evidence level IIbC) (Bjarnason-Wehrens et al., 2009).

Before engaging in an exercise program, however, an extensive physical examination is needed to determine an individual’s risk of adverse cardiac events and current level of fitness (Fletcher et al., 2001; Perk et al., 2012). Based on the results of exercise testing, the exercise program should be adjusted to a patient’s current exercise capacity, exercise tolerance, risk factors and personal motivation (Bjarnason-Wehrens B et al., 2009; Fletcher et al., 2001; Bundesarbeitsgemeinschaft für Rehabilitation, 2005).

The current guideline from the Germany Society for Prevention and Rehabilitation suggests that training should be at about 40-80% of VO_{2peak} (maximum oxygen uptake), which is determined during previous exercise testing, and that patients should exercise at a moderate continuous intensity level (Bjarnsason-Wehrens et al., 2007; Smith et al., 2011). If training is not monitored

using VO_{2peak}, heart rate measurement is another means to monitor training intensity. The guideline recommends that training intensity should be at around 60-75% of patients' maximum heart rate, which can be measured using mobile heart rate monitors during training sessions (Bjarnason-Wehrens et al., 2009). In addition, a visual scale, such as the Borg Scale, is often used to determine exercise intensity and individual perceived exertion (Bjarnsason-Wehrens et al., 2007; Bjarnason-Wehrens et al., 2009; Fletcher et al., 2001). The scale ranges from six to twenty, beginning with almost imperceptible exertion to very hard exertion, and is measured in "received perception of exertion = RPE". A value from 11-14 is categorized as moderately strenuous training and should be the target range during training (Bjarnsason-Wehrens et al., 2007; Bjarnason-Wehrens et al., 2009; Borg, 1982; Borg, 1990).

Patients should engage in ET daily for at least thirty minutes during each exercise session. A minimum of five days of training per week is a common recommendation. This recommendation, however, only applies to patients with stable cardiac function and low-to-medium risk of an adverse cardiac event. To ensure patient safety, patients should begin training moderately and gradually increase the duration, frequency and intensity of the training (Bjarnason-Wehrens et al., 2009; Fletcher et al., 2001; National Clinical Guideline Centre, 2013; Smith et al., 2011). Fletcher et al. (2001) propose walking for 10 minutes a day and gradually increasing duration and intensity. Patients with low-to-moderate risk, and sufficient cardiovascular fitness following myocardial infarction may begin training with a more strenuous exercise regimen (Fletcher et al., 2001; National Clinical Guideline Centre, 2013).

In addition to endurance training, some cardiac patients, specifically those with sufficient left ventricular function and exercise tolerance, can also participate in dynamic resistance training. Concerns regarding a high increase in blood pressure, arrhythmia or AMI, caused by strength training, have been dismissed by several studies and guidelines (Bjarnason-Wehrens et al., 2004; Pollock et al, 2000). The increase in blood pressure depends on resistance load, load intensity, repetition count and duration of the exercise (Bjarnason-Wehrens et al., 2004). When applied correctly in a professional and supervised setting with an adequate intensity and repetition count, the increase in blood pressure is comparable to that found during aerobic endurance training (Bjarnason-Wehrens B et al., 2004; Pollock et al., 2000). However, patients with a high risk for adverse cardiac events, impaired cardiac function, multi-morbidity and low exercise tolerance should not engage in this training method (Bjarnason-Wehrens et al., 2004; Pollock et al., 2000). Before initiating dynamic resistance training, an extensive physical examination is necessary and patients should first engage in aerobic ET for a few weeks (Bjarnason-Wehrens et

al., 2004; Pollock et al., 2000). Useful equipment for dynamic strength training can be elastic bands or free weights (Balady et al., 2007; Fletcher et al., 2001).

Although the current guideline from the DGPR suggests integrating exercises for muscle coordination and flexibility, there is less evidence for the benefit of these exercises compared to aerobic endurance and dynamic strength training (IIbC). (Bjarnsason-Wehrens et al., 2007; Bjarnason-Wehrens et al., 2009). Improving muscle coordination and flexibility, however, has the added benefit of strengthening a patient's capability to manage activities of every-day life (ADL), e.g. carrying groceries, gardening, cleaning, etc.

1.4. Cardiac imaging

Non-invasive cardiac imaging has been of great importance in diagnosing CVD, including CAD and the extent of a MI. Furthermore, cardiac imaging plays a pre-eminent role in determining the prognosis of patients suffering from MI, CHD and HF. Non-invasive cardiac imaging includes echocardiography, magnetic resonance imaging (MRI), single-photon-emissions-computer-tomography (SPECT), coronary computed tomography angiography (CCTA) and positron-emissions-tomography (PET) (Herrmann et al., 2018). Each of these imaging techniques has its own set of indications, advantages and disadvantages. A PET-scan, for example, assesses myocardial viability reliably, estimates the severity of CAD and determines myocardial blood flow (Nekolla et al., 2009). PET scans have proven to be important in molecular imaging, a new imaging field that identifies biological processes with the help of radioactive tracers. Molecular imaging may provide novel information for future treatment of CVD. PET imaging is sensitive in measuring inflammation, angiogenesis and sympathetic nerve function (Nekolla et al., 2009; Pan, 2016). Furthermore, PET scans can help in diagnosing high-risk CAD patients for future adverse events such as MI, who can then benefit from PCI (Rischpler et al., 2013; Sawada, 2006).

In contrast, a MRI, has the advantage of depicting myocardial anatomy and measuring cardiac function, ventricular volumes and characterization of soft tissue, as well as the transmurality and size of a MI and cardiac remodeling. A MRI is also feasible in detecting myocardial viability (Nekolla et al., 2009; Pontone et al., 2017; Wintersperger et al., 2015; Arai, 2011b; Rischpler et al., 2015).

In the past few years new imaging techniques have evolved in cardiovascular research. Hybrid PET/CT imaging is common in oncology and has also gained importance in the cardiological field (Rischpler et al., 2013). Hybrid PET/MRI is another prospective imaging method that has become more common in research and may play a stronger role in diagnostics in patients suffering from CAD and/or MI. A hybrid PET-MRI combines the advantages of both imaging techniques in one

session: a reliable assessment of cardiac function, cardiac morphology, infarction size using MRI; and the assessment of viability, inflammation and perfusion using a PET scan (Krumm et al., 2018; Pan, 2016).

Although both PET and MRI, and hybrid PET-MRI scans, currently do not play a role in imaging patients with AMI, they can fulfill an important function after revascularization therapy as they "[…] *provide detailed evaluation of infarcted myocardium, edema extent, area at risk and salvaged myocardium in acute myocardial infarction […]"* (Krumm et al., 2018). Moreover, a study, performed by Rischpler et al. (2016) using a hybrid ^{18}F-FDG-PET/MRI system, suggests that the uptake of ^{18}F-FDG in the myocardium after revascularization therapy correlates with adverse cardiac function after six months (Rischpler et al., 2016). Thus, combined PET/MRI imaging can deliver useful and additional information for both diagnosis and prognosis in CVD.

1.4.1 Principle of magnetic resonance imaging

MRI makes use of the magnetic moment, also known as spin, that naturally occurs in the human body. Since hydrogen nuclei (^{1}H) (which consists out of one proton) are found in a high concentration in water and fat, its magnetic spin is used to produce images. (Berger, 2002; Ridgway, 2010). Normally, the hydrogen protons spin on their own axis with the axes aligned in random directions. A magnetic resonance system produces a magnetic field, with different field strengths, known as Tesla. When placed into a magnetic field, the hydrogen protons align towards or against this magnetic field, producing a magnetic vector (Berger, 2002; Ridgway, 2010). When energy in the form of radiofrequency waves (pulse) are used in the direction of the vector, the direction of the spins is altered. When the radiofrequency pulse is turned off, the protons return to their original state and the original magnetic vector is aligned again. This process is known as relaxation.

During the relaxation phase, a signal is transmitted that is detected by the magnetic resonance system and computed into images. Since tissues relax at different speeds, these different relaxation times are used to create an image:

> *"[…] The time taken for the protons to fully relax is measured in two ways. The first is the time taken for the magnetic vector to return to its resting state and the second is the time needed for the axial spin to return to its resting state. The first is called T1 relaxation, the second is called T2 relaxation […]"* (Berger, 2002, p. 35).

One MRI scan consists of several radiofrequency pulse sequences that create an image of the tissue of interest. In cardiovascular imaging, MRI has a high spatial resolution and can accurately produce a contrast between different tissues (Tseng et al., 2016). A MRI has the capability to determine ventricular function, volumes and wall motion with the help of the cine technique, and thus, allows an examination of a patient's cardiac function (Tseng et al., 2016). Contrast agents, such as gadolinium (Gd), can also be used to enhance MRI imaging. These contrast agents are injected intravenously and distribute quickly into the extravascular space. They do not, however, permeate intact cell membranes due to their charge and size (Arai, 2011a). The distribution of gadolinium after about five-to-twenty minutes post-intravenous injection is known as late gadolinium enhancement (LGE) and it produces a hyper-enhanced imaging signal caused by the accumulated gadolinium in the depicted tissue (Gerber et al., 2000). LGE can show the infarcted area during the acute and chronic phase of infarction: in an acute setting LGE accurately depicts the transmurality of an infarction. After scar formation LGE can be used to depict scar size. LGE-MRI can also be used to determine myocardial viability (Abdel-Aty et al., 2011b; Rischpler et al., 2013).

As briefly explained above, each imaging technique has its advantages and disadvantages. Hybrid imaging techniques such as PET/MRI, PET/CT or echocardiography/MRI-fusions aim at combining the advantages of each technique to measure cardiac parameters, such as morphology, structure and remodeling even more precisely. Accurate imaging may influence patient treatment and outcome as (a) more patients can be identified who could benefit from certain treatments and (b) identifying changes in cardiac structure, function, metabolism or remodeling may allow for better monitoring of previous, current and future treatments. Consequently, successful monitoring could improve a patient's treatment by allowing important adaptions in a patient's individual therapy more quickly than in standard follow-up imaging. A meta-analysis by Haykowsky et al. (2011) showed that many trials used echocardiography to determine cardiac remodeling parameters, whereas SPECT or MRI, as well as left ventriculography, were not as common (Haykowsky et al., 2011). Compared to an MRI, echocardiography, however, strongly depends on sonographic conditions and is not as accurate in measuring morphology and mechanical function (Bauer et al., 2008). Thus, MRI may be superior in measuring cardiac remodeling parameters and impact future exercise recommendations for patients following MI.

The benefits of providing ET after MI as a part of patient rehabilitation have thoroughly been examined in terms of systemic effects, which include improvements in exercise capacity, endothelial function and autonomous nervous system (Kavanagh et al., 2002; Hambrecht et

al., 2003; Martinez et al., 2011). Many interventional trials have examined whether structured ET impacts cardiac remodeling. Most of these trials confirmed the positive effects of ET on cardiac remodeling by changing the factors initiation of ET, duration, frequency and type of ET (Giallauria et al., 2008; Giallauria et al., 2013; Giannuzzi et al., 2003). In retrospect, however, it remains unclear whether participation in current CR programs designed by the DGPR and in leisure time exercise behavior as recommended in CR programs attenuate cardiac remodeling as well, especially when examining self-reported leisure time ET.

Not only ET following MI can change cardiac remodeling, ET prior to an MI could limit infarction size and thus affect cardiac remodeling as well. In humans, prospective studies answering this question are not available due to ethical reasons. In animal trials, however, ET has been found to be able to limit infarction size, thus some authors presume a similar effect could be present in humans suffering from MI (de Waard & Duncker, 2009; Frasier et al., 2011; Freimann et al., (2005)

2 Objective

The primary aim of this observational study was to determine whether ET in the first six months following MI can ameliorate cardiac remodeling, as measured by a cardiac MRI-scan. Cardiac remodeling parameters included left-ventricular end-diastolic volume, left-ventricular end-systolic volume, stroke volume and ejection fraction. In comparison to interventional studies, which manipulate the parameter ET, e.g. by changing exercise duration, frequency or intensity, to analyze the influence of ET on cardiac remodeling (Giallauria et al., 2008; Giallauria et al., 2013; Giannuzzi et al., 2003), this retrospective study examined whether patients (a) participated in a CR program including ET as recommended by the DGPR and (b) analyzed exercise behavior and adherence to ET recommendations following a CR program. Cardiac remodeling parameters were measured with the use of an MRI scan.

In addition, the effect of self-reported exercise prior to MI on initial infarction size and infarction volume, which were measured by late-gadolinium enhancement during the MRI-scan, was analyzed.

The following hypotheses were proposed:

- Self-reported exercise training and participation in CR programs following myocardial infarction can attenuate cardiac remodeling parameters (ΔLVEDV, ΔLVESV) measured by an MRI scan
- Self-reported exercise training prior to myocardial infarction can lead to a smaller initial infarction size (LGE%) and volume (ml) measured by an MRI scan

3. Methods

3.1. Study population

From May to October 2014, 29 patients were selected to participate in this study. The inclusion criteria for this study were the following:

- First acute myocardial infarction (AMI), defined as: ongoing chest pain >20 min, electrocardiographic (ECG) changes, such as ST-segment elevation or new left-bundle block, and elevated cardiac enzyme levels.
- Treatment of AMI with percutaneous coronary intervention (PCI) upon hospital admission.
- No contraindication for a simultaneous PET/MRI, e.g. ferromagnetic material implants, implanted cardioverter-defibrillator, pacemakers, claustrophobia, allergies to contrast agents, low creatinine clearance <50ml/min, hemodynamic instability or pregnancy.
- 18 years of age and capable of giving written informed consent.

A simultaneous PET/MRI scan was performed 5 ± 1.4 (mean ± SD) days after a successful PCI. The pain to balloon time was 4,5h (median, 25th percentile 2,4h, 75th percentile 13,3h). The second scan, MRI-only, was planned to take place after six to nine months following PCI. After their second scan, patients received a questionnaire from the *Center for Preventive and Sports Medicine* at the University Hospital *Klinikum rechts der Isar* in Munich, assessing the patients' participation in exercise training (ET) before and post-MI, and their participation in a rehabilitation program.

Written informed consent was obtained from each patient before participation in this study. This study was approved by the ethics committee of the Technical University Munich and was performed in accordance to the ethical standards defined in the Declaration of Helsinki.
Of the original 29 patients, 26 (24 men, 2 women), gave written informed consent to participate**.**

3.2. Questionnaire

The C*enter for Preventive and Sports Medicine* developed a questionnaire consisting of 29 questions concerning demographic characteristics, cardiovascular risk factors, ET prior to an MI, medication and rehabilitation measures post-MI, and ET during the first six months after MI. The questionnaire included multiple-choice, closed and open-ended questions.

Data regarding age, weight, height/stature, cardiovascular risk factors and medication post-MI were collected to assess both general and cardiovascular characteristics of the study population.

Information on rehabilitation measures, more specifically, participation in a rehabilitation program post-MI was also gathered. Patients were asked whether they participated in a rehabilitation program, whether their participation was inpatient or outpatient, and when and how long they participated in the rehabilitation program. This information was gathered to determine whether patients suffering from MI received the follow-up care specified in current treatment guidelines from the European Society of Cardiology and the German Society for Prevention and Rehabilitation (Bjarnason-Wehrens et al., 2009).

The questionnaire also asked about the patients' participation in leisure time ET before suffering from an MI. The questionnaire aimed to document the extent, frequency and type of exercise in order to analyze whether participation in regular ET prior to myocardial infarction influences the initial infarction size (LGE%) and initial infarction volume (ml).

To examine whether ET post-MI affects cardiac remodeling (measured by cardiac functional parameters) information on ET during the first six months, including cardiac rehabilitation, following an MI was gathered. Furthermore, the duration of ET in minutes per week and frequency of ET per week was assessed. The questionnaire also documented the type of exercise patients engaged in: aerobic endurance training, technical/rhythmic sports, rehabilitative sport programs or other types of ET. Different exercise types were categorized by example. A meta-analysis by Haykowsky et al. (2007) showed that aerobic exercise training is superior to a combination of aerobic and strength training in attenuating cardiac remodeling of heart failure patients (Haykowsky et al., 2007). Thus, collecting data on the type of ET performed by patients after MI is important. This information on patients' exercise behavior was used to analyze whether patients adhered to exercise recommendations from current guidelines. These guidelines suggest engaging in aerobic endurance training on at least five days a week, preferably daily, for a minimum of thirty minutes at a moderate intensity (Bjarnason-Wehrens B et al., 2009; Jones et al., 2013; National Clinical Guideline Centre, 2013; Smith et al., 2011).

Follow-up telephone interviews were conducted with patients who either failed to return the questionnaire or returned it incomplete, requiring clarification. The original questionnaire can be found in the appendix.

3.3. Imaging

PET/MRI-imaging was performed by the *Department of Nuclear Medicine* at the University Hospital *Klinikum Rechts der Isar* in Munich. The images were acquired using a hybrid system Biograph mMR scanner (Siemens Healthcare GmbH, Erlangen, Germany) (Rischpler et al., 2016). The cardiac parameters in this study were the following: LVEDV, LVESV, SV, EF. Additionally,

infarction size, infarction volume and LV-volume were measured. Each of these parameters was measured at the first and second scan. ^{18}F-FDG uptake was only measured in the first scan. After completion of the second scan, the data was sent to the *Center for Preventive and Sports Medicine* at the University Hospital *Klinikum rechts der Isar* for further analysis.

3.3.1. Positron-emission-tomography/magnetic resonance imaging

The first scan (T1) was performed as a simultaneous PET/MRI scan using the previously mentioned hybrid imaging system. On the day prior to the scan patients received a low-carbohydrate diet followed by 12 hours of fasting to prevent a physiological uptake of ^{18}F-FDG in cardiomyocytes. On the day of the scan unfractionated heparin was injected (50 IU/kg body weight) 30 minutes before a standardized dose of ^{18}F-FDG was administered intravenously (Rischpler et al., 2016). Approximately 145 ± 51 minutes after intravenous injection of ^{18}F-FDG a PET scan was initiated. The PET scan was performed in 3D-mode, emission data was corrected and the collected images were reconstructed using a 3D attenuation-weighted ordered-subsets expectation maximization iterative reconstruction algorithm (AW-OSEM 3D) (Rischpler et al., 2016).

To obtain T1- weighted MRI images and evaluate late gadolinium enhancement (LGE%), 0.2 mmol/kg body weight Gadopentetat-Dimeglumin was injected into each patient (Magnograf®; Marotrast GmbH, Jena, Germany) (Rischpler et al., 2016). After 10 minutes the MRI scan was initiated. To acquire images, ECG triggering was performed, and patients were advised to hold their breath. With the use of steady-state free precision (SSFP) cine sequences systolic function was examined (Rischpler et al., 2016). The second MRI-only scan (T2) was performed six to nine months post-MI to measure once-again the aforementioned parameters.

3.3.2. Imaging analysis

For regional analysis LGE and ^{18}F-FDG images were lined up correspondingly using the MunichHeart/m^{3}p software and the 17-segment model of the American Heart Association (AHA) was used on these images (Rischpler et al., 2016). Manual delineation on short axis images was performed, with the help of the MunichHeart/MR software, to determine the degree of late gadolinium enhancement in the left ventricle (Rischpler et al., 2016).

3.4. Statistical analyses

Data was analyzed using IBM SPSS 23 (IBM Corp, Armonk, NY, USA).

Descriptive statistics (mean values ± and standard deviations, median values + 25th and 75th percentile) were calculated for all variables. Normal distribution was analyzed by graphical

analysis using histograms, P-Plots and Q-Q-Plots and cross-checked with numerical analysis using the Kolmogorov-Smirnov test.

To determine a possible influence of ET post-MI on cardiac remodeling parameters, the study sample (n=26) was divided into two groups based on their median duration of performed exercise/week. The median value of ET among all patients was 212 minutes/week, thus ET of 200 minutes/week was used to separate patients into two different exercise groups. Group 1 consisted of 12 patients with ET of less than 200min/week per week vs. Group 2 consisted of 14 patients achieving more than 200min/week of ET.

As most variables were not normally distributed within the groups, non-parametric tests, such as the Mann-Whitney-U test for independent variables, were carried out to detect significant differences between the two exercise groups in the following variables.

Independent variables in the group comparisons were patient characteristics; including age, weight (kg), height (cm), body-mass-index (BMI, m^2/kg) and body surface area (BSA, m^2), as well as imaging data; including pain-to-balloon time (h), ^{1st} scan (days after PCI), ^{2nd} scan (days after PCI).
In categorical variables, such as sex, cardiovascular risk factors and medication post-MI, a cross-table and calculation of Chi-squared (χ^2) was carried out to detect a significant difference in these variables between the group 1 ET <200min/week and group 2 ET >200min/week. The significance level was set to $p < 0,05$.

Most cardiac remodeling data were not normally distributed; therefore, the non-parametric Mann-Whitney-U test was carried out for group comparisons of independent variables: ΔLVEDV, ΔLVESV, ΔEF, ΔSV, Δinfarction volume, Δinfarction size as well as ΔLV volume. Since the data was not normally distributed, the Spearman's Rho correlation coefficient was calculated in order to assess the relationship between ET in min/week and remodeling parameters ΔLVEDV, ΔLVESV, ΔEF, ΔSV, Δinfarction volume, Δinfarction size, ΔLV volume. The significance level was set to $p< 0.05$.

The second aim of this study was to examine the potential influence of ET prior to an MI on initial infarction size and initial infarction volume. After data from the questionnaire concerning regular participation in ET prior to MI was analyzed, the study sample (n=26) was divided once again into two new groups. Regular exercise training was seen as participating in ET at least once to twice. The No-ET-group consisted of 14 patients, who engaged in either no ET or sporadically at most. The ET-group consisted of 12 patients who engaged in ET on a regular basis. The patient distribution among these groups was not the same as in the post-MI groups ET<200min/week

and ET>200min/week. A descriptive analysis was also performed on these data sets. Normal distribution was tested as previously mentioned for these data sets, and non-parametric tests were used to compare the independent variables, infarction size and volume between the two groups.

4. Results

4.1. Patient characteristics, cardiovascular profile, imaging data

The overall patient characteristics and their cardiovascular profile can be found in Table 1. Table 2 shows the same parameters for each exercise subgroup.

Table 2. Patient demographics, cardiovascular profile, imaging data in overall patient population post MI

Patient demographics and cardiovascular profile overall	mean ± standard deviation
Age (years)	62.2 ± 13.7 [34-85]
Gender	
Male	24
Female	2
Weight (kg)	84 ± 13.6
Height (cm)	176 ± 8
Body mass index (kg/m^2)	26.9 ± 3.5
Body surface area (m^2)	2.00 ± 0.18
Cardiovascular risk factors	
Hypertension	12 (46.2%)
Dyslipidemia	16 (61.5%)
Diabetes	2 (7.7%)
History of smoking	13 (50%)
Positive family history	10 (38.5%)
Medication 6 months post-MI	
ACE-inhibitors/AT-1-inhibitors	23 (88%)
ß-inhibitors	22 (84%)
statins	22 (84%)
anti-thrombotic medication (e.g. ASS)	26 (100%)
Pain to balloon time (h)*	
Mean ± SD	10 ± 12 [2.1-55.7]
Median	4,5
Lower Quartile	2,4
Upper Quartile	13,3
Interquartile range	19,9
1st scan (days after PCI)*	
Mean ± SD	4.8 ± 1.4 [3-8]
Median	5
Lower Quartile	4
Upper Quartile	5,3
Interquartile range	1
2nd scan (days after PCI)*	
Mean ± SD	254 ± 70.5 [171-479]
Median	236
Lower Quartile	201
Upper Quartile	293
Interquartile range	92

Variables presented as n (%) or mean ± standard deviation (SD) as well as median + lower/upper quartile and interquartile range, values in square brackets represent the range of values; ACE-inhibitors=

*angiotensinogen-converting-enzyme-inhibitor, AT-1-inhibitor= angiotensin-1-inhibitor, ASS= acetylsalicylic acid, PCI = percutaneous coronary intervention, *= values not normally distributed, therefore median and mean values are presented.*

Post-MI patients were divided into two subgroups based on their participation in ET per week. Table 2 presents the previously shown patient demographics, cardiovascular profile and imaging data between the two groups.

Table 3. Patient demographics, cardiovascular profile, imaging data in exercise subgroups post MI

Patient demographics and cardiovascular profile in exercise groups	Group 1 ET <200min/week n=12	Groupe 2 ET >200min/week n=14	*p-value*
Age (years)	63.7 ± 14.7 [38-85]	60.9 ± 13.2 [34-85]	0.595
Gender			
Male	10	14	0.112
Female	2	0	
Weight (kg)	87.5 ± 16	80.5 ± 9.9	0.280
Height (cm)	178 ± 9	175.4 ± 8.6	0.501
Body mass index (kg/m^2)	27.8 ± 4.1	26.1 ± 2.7	0.436
Body surface area (m^2)	2.04 ± 0.20	1.96 ± 0.15	0.481
Cardiovascular risk factors			
Hypertension	6 (50%)	6 (42.9%)	0.408
Dyslipidemia	6 (50%)	10 (71.4%)	0.595
Diabetes	1 (8.3%)	1 (7.4%)	0.674
History of smoking	6 (50%)	7 (50%)	1.000
Positive family history	4 (33.3%)	6 (42.9%)	0.628
Medication 6 months post MI			
ACE-inhibitors /AT-1-inhibitors	11 (91.7%)	12 (85.7%)	0.191
ß-inhibitors	9 (75%)	13 (92.9%)	0.399
statins	9 (75%)	13 (92.9%)	0.399
Antithrombotic medication (e.g ASS)	12 (100%)	14 (100%)	
Pain to balloon time (h)*			
Mean ± SD	12.5 ± 15.5	7.4 ± 7.4	0.347
Median	6.3	4.5	
Lower Quartile	2.7	2.2	
Upper Quartile	18.3	8.2	
Interquartile Range	15.6	6.1	
1st scan (days after PCI) *			
Mean ± SD	4.8 ± 1.5	4.8 ± 1.4	0.494
Median	5	5	
Lower Quartile	3	4	
Upper Quartile	5	5	
Interquartile Range	2	1	
2nd scan (days after PCI) *			
Mean ± SD	25 ± 83	253 ± 61	0.940
Median	240	234	
Lower Quartile	196	208	
Upper Quartile	287	298	

Interquartile Range	91	90

*Variables presented as n (%) or mean ± standard deviation (SD); values in square brackets represent the range of values; ACE-inhibitors= angiotensinogen-converting-enzyme-inhibitor, AT-1-inhibitor= angiotensin-1-inhibitor, ASS= acetylsalicylic acid, PCI = percutaneous coronary intervention, significant differences between group 1 and group 2 are marked as *p <0,05*

4.2. Cardiac rehabilitation and exercise training post-myocardial infarction

Participation in a cardiac rehabilitation program in the overall patient sample was 88.5 % (n=23). The median initiation of these programs was 14 days after suffering an MI and with a median duration of 21 days. Table 3 shows the participation, initiation and duration of cardiac rehabilitation programs for each subgroup.

Looking at participation in ET as a whole, five patients did not engage in any exercise, nine patients engaged in regular exercise training once to twice a week, and eleven patients engaged in exercise three days a week or more. The median duration of exercise training per week was 212 minutes.

Table 4. Rehabilitation data

	Group 1 ET < 200min/week	Group 2 ET >200min/week	*p-value*
Rehabilitation			
No rehabilitation	1 (8.3%)	2 (14.3%)	
Inpatient program	11 (91.7%)	10 (71.4%)	0.781
Outpatient program	0	2 (14.3%)	
Initiation (days after MI)			
Mean ± SD	12 ± 8 [CI 6.2 -17.8]	14 ± 4,7 [CI 11.1-16.8]	
Median	14	14	
Upper Quartile	18	18	0.648
Lower Quartile	6	9	
IQR	12	9	
Duration (days)			
Mean ± SD	17.5 ± 9.5 [CI 10.7-24.3]	20.4 ± 2.1 [CI 18.9-21.8]	
Median	21	21	
Upper Quartile	21	21	0.981
Lower Quartile	15.8	21	
IQR	5	0	

Variables presented as n (%) or mean ± standard deviation (SD) as well as median, range and quartiles, MI = myocardial infarction, IQR = interquartile range, CI = confidence interval; p-values calculated using non-parametric Mann-Whitney-U test for group comparisons in independent variables

The most common types of exercise in both groups were brisk walking (n=13), cycling (n=7) and strength-endurance-flexibility training (n=5). Less common were ergometer training (n=2), Nordic walking (n=2), tennis (n=2), gymnastics (n=2), swimming (n=1), light jogging (n=1), cross-trainer (n=1) and participation in a heart sport group (n=1). The frequency and duration of ET for the subgroups can be found in Table 4. Exercise frequency and duration show significant

differences between the two groups, namely *p= 0.001* for exercise frequency and *p= <0.001* for exercise duration.

Table 5. Exercise frequency (x/week) and duration (min/week) between the subgroups

	Group 1 ET < 200min/week	Group 2 ET > 200min/week	*p-value*
Exercise frequency			
Mean ± SD	1.8 ± 2.1 [CI 0.2- 3.3]	3.8 ± 1.4 [CI 2.8-4.7]	
Median	1.5	3	
Upper Quartile	2.6	5	0.001*
Lower Quartile	0	3	
IQR	2.6	2	
Exercise duration			
Mean ± SD	63 ± 67.3 [CI 14.9-111.1]	368.2 ± 142.5 [CI 272.2-463.9]	
Median	55	330	
Upper Quartile	116.3	510	<0.001
Lower Quartile	0	260	
IQR	116.3	250	

*SD = standard deviation, IQR = interquartile range, CI = confidence interval; p-values calculated using a non-parametric Mann-Whitney-U test for group comparisons in independent variables, significant differences between groups marked as *p <0.05*

4.3. The effect of exercise training on cardiac remodeling

To determine whether exercise training influences cardiac remodeling, the median value of the changes in LVEDV, LVESV, EF, SV, infarction size, infarction volume and LV-volume from the first scan (T1) and the second scan (T2) were compared between the two groups.

The only parameter showing a significant difference between the two subgroups was ΔLVEDV. The median value of LVEDV increased from T1 to T2 in Group 1 by 13.7 ml (25th percentile 5ml, 75th percentile 27,5ml). In contrast, the median value of LVEDV in Group 2 decreased from T1 to T2 by -1.4 ml (*p* 0.017, 25th percentile -11 ml, 75th percentile 6ml*).* The parameters LVESV, EF and SV did not show any significant changes from T1 to T2 in each group and there was no significant difference between the groups in these three variables (*p* 0.374, 0.462, 0.231 respectively). Infarction size, infarction volume and LV-volume did not decrease significantly.
A Spearman's Rho correlation analysis only found a significant association between the variables ET in min/week and ΔLVEDV (r -0.43, *p* 0.027). There was no significant correlation between ET min/week and other cardiac remodeling parameters ΔLVESV, ΔEF, ΔSV.

The changes in cardiac remodeling parameters from T1 to T2 can be found in Table 5. Changes in infarction parameters from T1 to T2 can be found in Table 6.

Table 6. Cardiac remodeling parameters at T1, T2 and difference from T1 to T2 (T2-T1)

	Group 1 ET <200min/week	Group 2 ET >200min/week	*p-value*
LVEDV			
T1			
Mean ± SD	123± 30 [CI 104.5-142.6]	135 ± 40 [CI 112.8-158]	
Median	112.5	133	
Upper Quartile	148	150	0.297
Lower Quartile	101	110	
IQR	47	40	
T2			
Mean ± SD	137 ± 30 [CI 118-155.8]	131 ± 40 [CI 108-154.5]	
Median	134	134.4	
Upper Quartile	166	142	0.560
Lower Quartile	110	99.5	
IQR	56	43	
ΔLVEDV (T2-T1)			
Mean ± SD	13 ± 18 [CI 1.8-25]	- 4 ± 19.5 [CI -15.5 - +7]	
Median	13.7	- 1.4	
Upper Quartile	27.5	6	0.017*
Lower Quartile	5	- 11	
IQR	22	17	
LVESV (ml)			
T1			
Mean ± SD	69 ± 25 [CI 53-84.5]	71 ± 30 [CI 54-88.5]	
Median	64	69	
Upper Quartile	85	87	0.899
Lower Quartile	47	46	
IQR	38	40.5	
T2			
Mean ± SD	77 ± 34 [CI 55.7-99]	71 ± 31 [CI 53-89]	
Median	66.8	63.7	
Upper Quartile	104	85	0.742
Lower Quartile	49.	51	
IQR	55	34	
Δ LVESV (T2-T1)			
Mean ± SD	9 ± 18 [CI -2.6 - +20]	-0.25 ± 19.5 [CI -11.5 -+11]	
Median	5.7	6	
Upper Quartile	26	14.8	
Lower Quartile	-4	-17.9	0.374
IQR	30	32	
EF (%)			
T1			
Mean ± SD	45 ± 11 [CI 38-52]	48 ± 9 [CI 43-54]	
Median	45.5	45.2	
Upper Quartile	53.7	57.8	0.705
Lower Quartile	38.8	40.8	
IQR	14.8	17	
T2			
Mean ± SD	45 ± 15 [CI 35.6-54.5]	47 ± 10 [CI 41-52.7]	
Median	50	48	
Upper Quartile	58.2	54	1.000
Lower Quartile	29.8	40	
IQR	28.4	14	
Δ EF (T2-T1)			
Mean ± SD	-0.12 ± 8.6 [CI -5.6 - +5.4]	-1.7 ± 10 [CI -7.5 - +3.9]	

Median	3.2	-4.3	
Upper Quartile	5.7	3.2	0.462
Lower Quartile	-7.6	-9	
IQR	13	12.6	
SV (ml)			
T1			
Mean ± SD	55 ± 14 [CI 45.7-64]	64 ± 14 [CI 55.6-72.5]	
Median	54.3	66	
Upper Quartile	65.3	77.4	0.160
Lower Quartile	51.3	47.8	
IQR	14	29.6	
T2			
Mean ± SD	59 ± 19 [CI 47.6-71.4]	60 ± 16 [CI 50.5-69.5]	
Median	57.3	60.9	
Upper Quartile	72.8	74.7	0.899
Lower Quartile	46.3	45.4	
IQR	26.6	29.3	
ΔSV (T2-T1)			
Mean ± SD	4.6 ± 16 [CI -5.3- +14.6]	-3 ± 12 [CI -9.7- +3.9]	
Median	2.9	-1.8	
Upper Quartile	11.5	7.5	0.231
Lower Quartile	-3.9	-15.1	
IQR	15.4	22.7	

*SD= standard deviation; IQR = interquartile range, CI = confidence interval, LVEDV = Left-ventricular end-diastolic volume, LVESV = left-ventricular end-systolic volume, EF = Ejection fraction, SV = stroke volume, significant differences between groups marked as *p <0.05*

Table 7. Infarction parameters from T1 to T2 and change between T1 to T2

	Group 1 ET <200min/week	Group 2 ET >200min/week	*p-value*
Infarction size (LGE%)			
T1			
Mean ± SD	24 ± 13 [CI 15.3-32.3]	17.6 ± 9 [CI 12.2-23.1]	
Median	23.3	16.5	
Upper Quartile	31.6	24.3	0.231
Lower Quartile	7.4	6.7	
IQR	21.3	32.5	
T2			
Mean ± SD	18 ± 12.6 [CI 10.1-26.1]	12 ± 8 [CI 7.7-16.6]	
Median	15.2	11.9	
Upper Quartile	29.6	17.1	0.274
Lower Quartile	7.7	4.2	
IQR	21.8	13	
Δ infarction size (T2-T1)			
Mean ± SD	-5.7 ± 3.5 [CI -7.9- -3.4]	-5.5 ± 5 [CI -8.3- -2.7]	
Median	-6.1	-3.9	
Upper Quartile	-2.6	-1.3	0.820
Lower Quartile	-7.8	-9.1	
IQR	5.3	7.8	
Infarction volume (ml)			
T1			
Mean ± SD	31 ± 19 [CI 19.1-43.3]	22 ± 15.4 [CI 13.2-30.9]	
Median	29.9	18.9	
Upper Quartile	42.3	28.8	0.212
Lower Quartile	14.9	9.4	

IQR	27.4	19.4	
T2			
Mean ± SD	17 ± 12.6 [CI 9.2-25.2]	12 ± 8 [CI 7-16.3]	
Median	12.9	11.9	
Upper Quartile	21.8	16.2	0.322
Lower Quartile	8	4.5	
IQR	13.8	11.8	
Δ Infarction volume (T2-T1)			
Mean ± SD	-14 ± 8 [CI -19.4- -8.7]	-10 ± 10 [CI -16.2- -4.5]	
Median	-14.5	-5.4	
Upper Quartile	-6.8	-2.9	0.176
Lower Quartile	-20.2	-17.2	
IQR	13.4	14.2	
LV volume (ml)			
T1			
Mean ± SD	132 ± 34 [CI 110.7-154.8]	118 ± 22 [CI 105.6-131.6]	
Median	132.9	113.5	
Upper Quartile	148.4	133.3	0.231
Lower Quartile	103.6	101.5	
IQR	44.8	31.8	
T2			
Mean ± SD	100 ± 29 [CI 81.5-118.9]	95 ± 14 [CI 87.6-103.9]	
Median	99.6	98.2	
Upper Quartile	116.9	106.3	0.781
Lower Quartile	74.3	85	
IQR	42.7	21.4	
Δ LV volume (T2-T1)			
Mean ± SD	-32 ± 19 [CI -44.5- -20.6]	-23 ± 18 [CI -33.3- 12.6]	
Median	-33	-18.6	
Upper Quartile	-19.6	-11.5	0.145
Lower Quartile	-39.5	-32.2	
IQR	19.8	20.7	

*SD= standard deviation; IQR = interquartile range, CI = confidence interval, LV = left-ventricular volume, significant differences between groups marked as *p <0.05*

Figure 2 shows the distribution of ΔLVEDV in each subgroup and between the groups. As mentioned previously this was the only parameter where a statistical significance between the two subgroups was found.

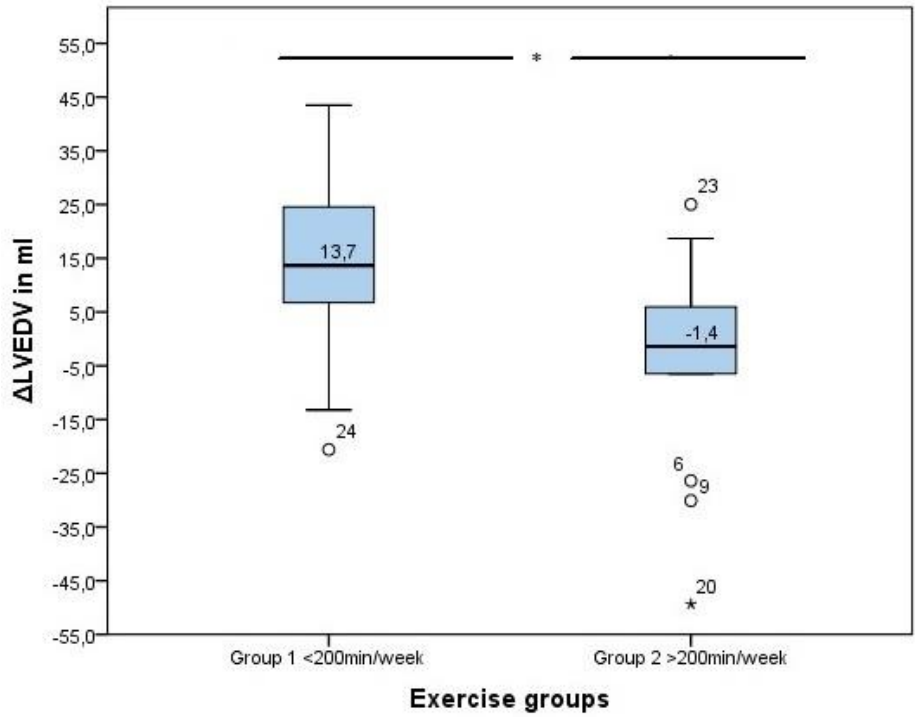

*Figure 2. Difference in ΔLVEDV (ΔLVEDV = T2 LVEDV-T1 LVEDV) between group 1 and group 2 ; Variables presented as median values of ΔLVEDV, LVEDV = left ventricular end diastolic volume, * p <0.05*

4.4. The influence of exercise training prior to myocardial infarction on initial infarction size and volume

The initial infarction size and infarction volume between the No-ET-group and the ET-group were calculated and are shown in figures 3 and 4, as well as table eight and nine. A Mann-Whitney-U-Test for comparison of median values showed no significant difference between the two groups. (*p* 0.118 for infarction size and 0.131 for infarction volume).

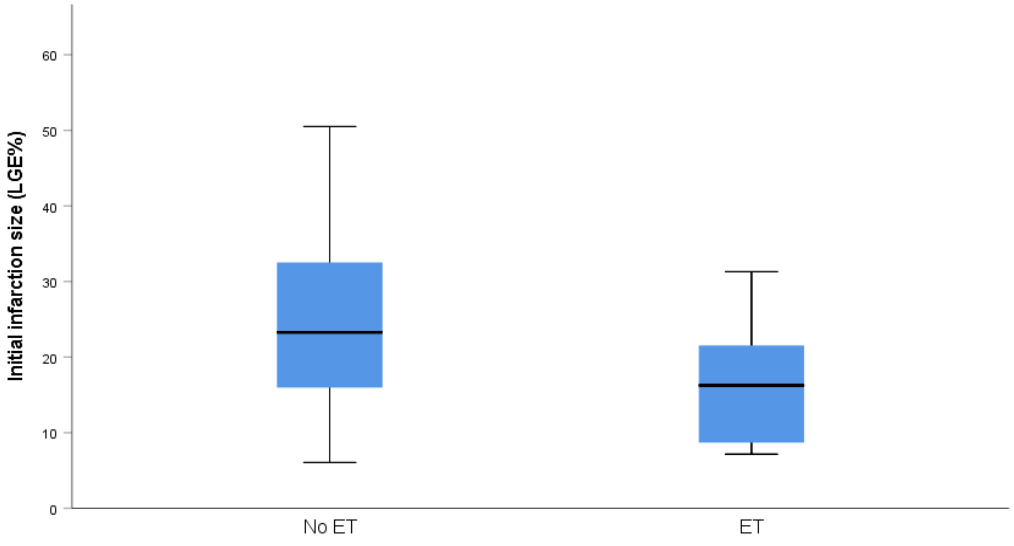

Figure 3. Initial infarction size between group No-ET and group ET. Box-plot and whiskers depict distribution of values for initial infarction size (LGE%, late-gadolinium-enhancement in %)

Table 8. Initial infarction size between group No-ET and group ET

Infarction size (LGE %)	No ET (n=14)	ET (n=12)
Median	23.3	16.0
Minimum	6.1	7.2
Maximum	50.5	31.2
Upper Quartile	34.0	22.9
Lower Quartile	14.2	8.5
IQR	19.8	14.4

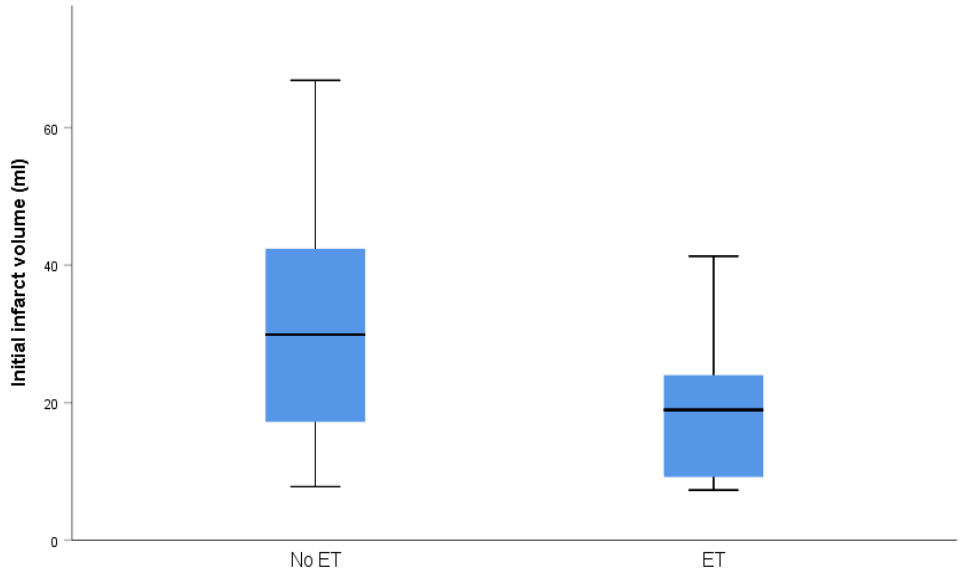

Figure 4. Initial infarction volume between group No-ET and group ET. Box plot and whiskers depict distribution of values for initial infarction volume (ml= milliliters)

Table 9. Initial infarction volume group No-ET and group ET

Infarction volume (ml)	No ET (n=14)	ET (n=12)
Median	29.9	18.9
Minimum	7.8	7.3
Maximum	66.9	41.3
Upper Quartile	15.6	9.0
Lower Quartile	44.6	24.3
IQR	31.1	15.4

5. Discussion

As mentioned previously, the primary aim of this study was to determine whether exercise training post-MI, performed in the CR programs according to German guidelines, as well as exercise behavior following CR, can ameliorate cardiac remodeling measured by EDV, ESV, LV-EF and SV. Secondarily, we analyzed whether habitual ET prior to MI affects initial infarction size

and infarction volume. A questionnaire was developed by the *Center for Preventive and Sports Medicine* from the University Hospital *Klinikum rechts der Isar* to analyze exercise behavior before and after MI. The *Department for Nuclear Medicine* from the University Hospital *Klinikum rechts der Isar* performed imaging analysis to measure the cardiac remodeling parameters. To compare the effects of ET on cardiac remodeling we divided our patients into two exercise groups, based on the median value of ET in minutes per week, resulting in group 1 exercising <200min/week and group 2 exercising >200min/week. For analysis of exercise behavior prior to MI and its influence on initial infarction size and volume, we divided the patients into two groups, namely group No-ET and group ET, based on their participation in exercise.

5.1. Participation in rehabilitation programs and exercise behavior post-myocardial infarction

This observational study analyzed participation in rehabilitation programs post MI and exercise behavior in the first six to nine months post MI in 26 patients suffering from AMI and treated with PCI.

Of the 26 patients participating in this study, 23 attended a rehabilitation program. The majority (n=21) took part in an inpatient center, only two participated in outpatient centers. The distribution of patients in inpatient and outpatient centers in our study is in alignment with statistical analyses from the German Society for Pension Insurance (Deutsche Rentenversicherung Bund, 2018). In 2016, only 14% of rehabilitation services were performed in outpatient centers. Of all outpatient rehabilitative services, only 3% (women) and 9% (men) were used for cardiac rehabilitation (Deutsche Rentenversicherung Bund, 2018; Fischer et al., 2012).

Despite the small sample size in this study, the majority (88.5%) participated in a CR program. This rate is high in comparison to other European countries, as shown in the EUROSPIRE III survey from 2009 (Kotseva et al., 2009). This survey analyzed medical records of approximately 14,000 patients and interviewed almost 9000 patients suffering from CHD throughout Europe. Their aim was to evaluate whether the guidelines and prevention programs for cardiovascular patients were sufficiently implemented throughout Europe. The inclusion criteria were the following: elective or emergency CABG, elective or emergency PTCA, STEMI or NSTEMI, troponin-negative acute myocardial ischemia, with emergency CABG and PTCA including emergency treatment for patients with AMI.

Kotseva et al. (2009) found that less than half of eligible patients for cardiac rehabilitation programs received recommendations to participate in a rehabilitation program; of these

patients, 75% attended at least half of the provided rehabilitation sessions. Thus, only 1/3 of the eligible patients attended a minimum of half of the rehabilitation sessions (Kotseva et al., 2009). In the most recent EUROSPIRE IV survey (2016) the number of patients who received recommendations to attend a CR program increased to 50.7% of patients. Of these patients, 81.3% attended at least half of the sessions. Despite this slight increase in patients receiving advice to participate in a CR program and the number of patients attending half of the sessions, the implementation of CR in clinical practice is still insufficient and unsatisfying. In comparison, patients in our study showed a high participation rate, with 23 out of 26 patients (88.5%), in a CR program. It may be possible that recommendation, organization and accessibility of rehabilitation programs in the area our patients were treated in, namely Munich, Germany, is implemented better than in other regions across Europe. When looking into the application process for CR programs it is also possible that insurance companies in Germany may approve applications more quickly or more often than insurance companies in other European countries.

This study did not investigate the exact number of exercise sessions attended during CR (in contrast to the EUROSPIRE study). Thus, it cannot be said how high the participation rate in ET sessions were during the CR program. As most patients participated in inpatient CR programs it may only be presumed that the likelihood of attaining most ET sessions was high due to *e.g.* a higher group mentality and motivation to attend ET sessions.

Financial aspects may also play a role in the underutilization of CR programs. One of the patients in this study, who was self-employed, did not participate in a CR program because he was not able to cover the costs of such a program. Thus, it is possible, that when under a private health insurance plan, the number of patients not participating in a CR program may be higher. However, this is an assumption, that was not analyzed in this study and should be considered in future research.

Not only is participation in CR programs lacking, adherence to recommendations concerning an increase in physical activity, specifically exercise training, is meager.

Kotseva et al. (2009) found:

> "[…] *Increased physical activity after their coronary event was reported by 59.1% of patients, and 23.9% reported to have been following specific advice from a health or exercise professional. A small minority (12.0%) attended a fitness or leisure centre or joined a community-walking group. Just less than half of the patients (48.0%) increased their everyday physical activity. The majority of patients reported mild (57.8%) or no (12.1%) physical activities outside work. Moderate (vigorous activity at least 20 min once or twice a week)*

> *and intensive (vigorous activity at least 20min three or more times a week) activity was reported by 16.4 and 13.8%, respectively. Only 33.8% of patients reported doing some regular exercise to increase their physical fitness* […] " (Kotseva et al., 2009, p. 127)

Furthermore, only 62% of the German patients in the EUROSPIRE survey stated that they increased their amount of physical activity after MI, which is only slightly above the average of 59,1%. Physical activity and ET are not the same:

> *"Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure beyond resting expenditure. Exercise is a subset of physical activity that is planned, structured, repetitive, and purposeful in the sense that improvement or maintenance of physical fitness is the objective. Physical fitness includes cardiorespiratory fitness, muscle strength, body composition, and flexibility, comprising a set of attributes that people have or achieve that relates to the ability to perform physical activity."* (Thompson et al., 2003, p. 3109).

Since our study did not analyze changes in physical activity described as an increase in energy expenditure, e.g. by gardening, house work, cycling or walking as forms of transportation, etc., the general increase in physical activity and movement in our patient sample cannot be compared to the participants of the EUROSPIRE trial. Thus, we cannot say if patients solely changed their exercise behavior or the total amount of physical activity.

When looking at regular ET, only 30% of all cardiac patients in the EUROSPIRE III survey stated that they participated in regular ET post-MI. Although the patients participating in the EUROSPIRE III survey belonged to a geographically selected area and were treated mainly in academic hospitals, implementation of guideline recommendations for coronary patients were, according to the authors of the survey, likely to be even worse than reported (Kotseva et al., 2009). The most recent EUROSPIRE IV survey (2016) showed little improvement in terms of exercise behavior. Although the majority of patients stated they had increased their physical activity level, only four out of ten patients exercised vigorously once a week or more for at least twenty minutes (Kotseva et al., 2016).

In comparison, in our study group, five patients did not engage in any form of ET in the first six to nine months post- MI, five patients exercised less than 150 minutes a week, and 16 patients exercised more than 150 minutes a week. Thus, roughly 1/3 of our patients did not engage in

the recommended amount of ET per week. These results reflect the results of the EUROSPIRE surveys III and IV from 2009 and 2016.

In secondary and tertiary prevention for cardiac patients, most guidelines recommend a minimum of 30 minutes of moderate intensity ET on at least five days a week, preferably daily (Bjarnason-Wehrens et al., 2009; Giannuzzi et al., 2003; Jones et al., 2013; National Clinical Guideline Centre, 2013; Bjarnason-Wehrens et al., 2007; Eckel et al., 2014; Perk et al., 2012). When comparing adherence to ET recommendations in current guidelines, most of our patients (58%) met these recommendations. However, the intensity level of the patients cannot be determined as ET was self-reported and not monitored. Overestimation of individual participation in ET and exercise expenditure is considered likely, based on other trials (Shephard, 2003).

5.2. The impact of exercise training after myocardial infarction on cardiac remodeling

This study hypothesizes that ET following MI attenuates cardiac remodeling. Over the past decades many positive effects of ET initiated after MI have been demonstrated: e.g., an improvement in cardiopulmonary fitness, exercise capacity, autonomic and endothelial functions, and a reduction in morbidity and mortality (Fletcher et al., 2001; Hambrecht et al., 2003; Heran et al., 2011; Keteyian et al., 2008; Leon et al., 2005; Jorge et al., 2011). The exact impact of ET on cardiac remodeling is still unclear, especially in terms of the correct training modality, frequency, intensity and duration.

In this retrospective analysis it was found that one parameter significantly improved between the two exercise groups, ET<200min/week and ET >200min/week. LVEDV decreased by a median of -1.4 ml (mean -4.3 ml ± 19.5) from the first to the second scan in the group ET >200min/week. Whereas, patients in the ET <200min/week showed a median increase from the first to the second scan of 13.7 ml (mean 13.4 ± 18). LVESV showed a slight increase in ET >200min/week of median 6.1 ml (mean -0.25 ml ± 19.5) and in ET <200min/week of median 5.7 ml (mean 8.7 ml ± 18). The changes in LVESV were, however, non-significant. Other secondary parameters measured, such as EF and SV, did not show an improvement from the first to the second scan. In contrast, patients exercising regularly for the first six months post-MI showed a stronger decrease in EF and SV than patients not exercising. Surprisingly, stroke volume even increased in patients in the ET <200min/week group compared to the ET >200min/week.

The improvement in EDV is in line with a meta-analysis conducted by Haykowsky et al. (2011), which analyzed the effect of ET on cardiac remodeling begun shortly after myocardial infarction.

The authors concluded that exercise training can attenuate cardiac remodeling, measured via EDV and ESV, but the beneficial effect depends upon the time of initiation of exercise training post-MI, as well as the duration of the exercise program: "*The largest changes in LV remodeling were obtained when programs began after around 1-week post MI hospital discharge and lasted for 6 months* […]" (Haykowsky, 2011, p. 5). Furthermore, when looking at ESV, which according to White et al. (1987) is an important predictor for mortality post-MI, "*each one-week delay in initiation exercise training would require an additional month of training to obtain a comparable reduction in ESV*" (Haykowsky et al., 2011, p. 5;White et al., 1987,).

In this study sample most patients did not initiate CR until two weeks (or later) after MI. Thus, the initiation of the CR program may already have been too late to have a larger impact on cardiac remodeling. Roughly, 80% of patients in this study stated that they engaged in ET on a regular basis in the first six months after cardiac rehabilitation. However, most patients performed exercise without supervision or a specific program. The type of training, duration, frequency and intensity, as well as a lack of supervision may be reasons why the beneficial effects on cardiac remodeling were not as prominent in this patient group.

In Germany, supervised ET usually only takes place for the duration of CR programs, which last about three to four weeks (Bjarnsason-Wehrens et al., 2007). After finishing rehabilitation, patients have the possibility to take part in supervised heart sport programs such as IRENA, KARENA or "Herzsport" (Fischer et al., 2012). These programs offer a minimum of one training session per week under the care of a doctor and a professional trainer. Up to 90 sessions over a period of 30 months are financially covered by health insurance or governmental institutions (Bundesarbeitsgemeinschaft für Rehabilitation, 2011). Patients can continue exercising in these groups at their own cost.

In this study, only one patient participated in a coronary heart sport group. This patient showed a decrease in EDV by 30,1 (ml), in ESV by 37,5 (ml) and an increase in EF by 21,2 (%). Although results of only one patient are too weak to draw any conclusions, this single case illustrates that ET may have larger effects on cardiac remodeling when participating in longer, supervised ET programs in comparison to those exercising without supervision. The improvement in cardiac remodeling parameters in this patient suggests that more focus and resources need to be applied to long-term supervised exercise training programs.

Giallauria et al. (2008) studied the effects of ET on cardiac remodeling in post-MI patients suffering from mild left ventricular dysfunction. Sixty-one patients were divided into a training or control group. ET was performed three times a week in the training group and consisted of a five-minute warm-up and cool-down, and a 30-minute session on a bicycle-ergometer at 60-70%

of VO_2-peak, which was previously determined in an initial exercise performance test. The program lasted for six months. At the six-month follow-up, EDV and ESV had decreased in the training group and were much lower compared to the control group. In contrast, EDV and ESV increased in the control group. This randomized-controlled study demonstrates the anti-remodeling effect of a six-month exercise program in post-MI patients and the necessity to extend the duration of exercise programs following MI (Giallauria et al., 2008).

Other studies, however, were not able to confirm a beneficial effect of ET on cardiac remodeling. Kubo et al. (2004) examined the exercise activity at the ventilatory threshold in patients with extended anterior myocardial infarction and reduced ejection fraction (EF <45%). These patients were divided into an exercise group and a control group. The training program was initiated approximately four weeks after myocardial infarction and lasted for 12 weeks. Patients engaged in walking on a treadmill or using a bicycle ergometer for 20 minutes twice a day, three times a week under supervision. They trained at their ventilatory threshold (anaerobic threshold), which was determined during exercise performance testing before beginning the training program. These results showed an increase in EDV and ESV in the exercise group, but not in the control group, where EDV and ESV decreased. The authors concluded that training at individual ventilatory threshold in patients with extended anterior myocardial infarction further provoked cardiac remodeling, and that these patients should not initiate training until the healing process of the infarction was completed (approximately two to three months) (Kubo et al., 2004).

In our study, significant group differences regarding weekly exercise frequency (p = 0.001*)* and exercise duration (p <0.001) suggest that other training parameters such as type of exercise and exercise intensity may play an important role in influencing cardiac remodeling. EDV was the only parameter which showed a significant difference between the two groups namely that group 2 >200min ET/week showed an improvement in EDV compared to group 1 < 200min ET/week. It is possible that other cardiac remodeling parameters, such as EF, SV, LV-Volume or ESV may also be improved by changing certain exercise parameters. Across both groups, many patients engaged in the same type of exercise, e.g. brisk walking or cycling. This could indicate that exercise duration and frequency play an important role in improving EDV, however, they do not affect the other remodeling parameters. In addition, another training parameter has not been considered, namely training intensity. Training intensity may not only be able to achieve even better improvements in EDV, it may also be the pivotal parameter in improving the other cardiac remodeling parameters.

The role of exercise intensity is currently being investigated in several studies. As described previously, most guidelines recommend continuous training at a moderate-intensity level in

primary and secondary prevention (Fletcher et al., 2001; Balady et al., 2007; Bjarnsason-Wehrens et al., 2007; Bjarnason-Wehrens et al., 2009; National Clinical Guideline Centre, 2013). Several trials testing aerobic interval training, also known as high-intensity interval training (HIIT), in patients suffering from MI, CHD and/or HF, however, are on-going (Ellingsen et al., 2017; Hannan et al., 2018; Wisløff et al., 2007; Støylen et al., 2012, Rognmo et al. 2004).

A study performed by Wisløff et al. (2007) compared the effects of aerobic interval training (AIT) with moderate-intensity continuous training (MCT) on cardiac remodeling in post-MI elderly patients with stable HF (age 75,5 ± 11,1 years). Patients were randomly divided into either the AIT-, MCT- or a control group and engaged in "uphill" treadmill walking. The AIT and MCT groups each participated in two supervised exercise sessions and one unsupervised session at home. The control group engaged in one supervised exercise session once every three weeks. In the AIT group each supervised training lasted for 38 minutes and consisted of a 10-minute warm up at 50-60% of VO_{2peak} (= about 60-70% of peak heart rate), followed by four four- minute intervals at 90-95% of peak heart rate. Between each four-minute interval patients engaged in a three-minute active pause at 50-70% peak heart rate. Each training session ended with a three-minute cool down at 50-70% peak heart rate. The MCT group on the other hand walked for 47 minutes at 70-75% of peak heart rate without any pauses or increased intervals. The home-based training consisted of outdoor uphill walking. Patients were instructed to follow the same training protocol as on the treadmill. To monitor exercise intensity, patients carried a heart rate monitor and the Borg scale was used during and after each training session. To achieve peak heart rate in each session, speed and inclination of the treadmill was adjusted during each training session.

The results of this study were remarkable: "*Twelve weeks of AIT induced reverse LV remodeling. LV diastolic and systolic diameters declined by 12% and 15% and estimated LV end-diastolic and end-systolic volumes by 18% and 25%, respectively […]*" (Wisløff et al., 2007, p. 3090). The authors also found that systolic function recovered immensely, with an increase in EF by 10%. In contrast, there was no change in systolic function in patients in the MCT group. The same effect was seen for diastolic function (Wisløff et al., 2007). As the study included patients being infarction free for 12 months, it should be assessed whether these effects can also be found in patients recently suffering from an MI, as exercise capacity seems to play a pivotal role in attenuating cardiac remodeling.

In comparison the results of a large randomized controlled and multicenter SMART-EX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure, 2017) was not able to detect a superiority of HIIT over MCT. In this trial, 231 patients suffering from stable and optimally treated heart failure with reduced ejection fraction (NYHA II-III) were randomly

divided into three groups, namely HIIT, MCT and RRE (recommendation for regular exercise) groups. The programs lasted for 12 weeks. The primary endpoint was the change in left-ventricular end-diastolic diameter (LVEDD) as the parameter for cardiac remodeling. The HIIT group engaged in three supervised exercise sessions per week on a treadmill or bicycle. The training sessions consisted of four four-minute intervals aiming at 90-95% of maximum heart rate followed to three-minute active recovery periods at moderate intensity. HIIT sessions lasted for 38 minutes including warm- up and cool- down. Patients training in the MCT group engaged in the same amount of supervised training sessions on a treadmill or bicycle. However, the aim was to train at 60-70% of maximum heart rate. Training sessions lasted 47 minutes. The RRE group received recommendations on regular home training without supervision and met once every three weeks for a supervised training session at 50-70% of maximum heart rate. During the follow-up period after completion of the 12-week training period, telephone contact was made every four weeks to detect adverse clinical events and to animate physical activity. Of the 231 patients, 207 were included in the final analysis. The main result of this study was that HIIT was not superior to MCT. However, it must be noted that 51% of patients in the HIIT group did not meet the prescribed exercise intensity and underperformed. In addition, 80% of patients in the MCT group exercised above their prescribed exercise intensity. Moreover, the improvements seen in the LVEDD, as a parameter for cardiac remodeling, shown after 12 weeks of supervised ET, were not maintained after 52 weeks, suggesting patients did not adhere to exercise recommendations when training without supervision. The authors concluded, that further studies are needed to test whether HIIT is superior to MCT, due to the fact, that training intensity over 90% was not met by a sufficient number of patients (Ellingsen et al., 2017)

The use of aerobic interval training in patients suffering from recent MI needs to be investigated further in the future, as the adequate intensity, frequency and duration of ET remains unclear.

5.3. Effect of self-reported exercise training prior to myocardial infarction on infarction size and volume

As mentioned previously, the effect of self-reported ET prior to MI on infarction size and volume has not been tested in prospective studies in humans. Our goal was to determine whether ET prior to MI is able to limit the size of the infarction as well as the infarction volume.

In our study patients engaging in ET prior to MI regularly (≥ 1x/week) showed smaller infarction sizes and lower infarction volumes compared to sedentary patients. However, a comparison of these results between the two groups showed no statistical significance. Despite the lack of statistical significance, a graphical analysis showed a visual tendency towards smaller infarction

sizes and volumes in physically active patients. It is possible that the results may be statistically significant in a larger sample size, as this group of patients (n=26) was quite small.

Another possible reason for these non-significant results may lie in the frequency of ET. Of the 12 patients who engaged in ET, only three patients exercised three times per week or more, the other nine patients exercised once or twice a week. Despite engaging in ET on a regular basis, a frequency of once or twice a week may be too little to significantly affect initial infarction size and volume.

In an animal trial performed by Brown et al (2003), female rats were randomly divided into a sedentary and an exercise group. Over 20 weeks, the exercise group engaged in wheel running began with two weeks of running at a 10% grade for 20 meters per minute at initially five minutes a day increasing to 30 minutes per day. Over the following six weeks, exercise duration and speed were increased to 35 m/min for twenty minutes. After twenty weeks the left anterior descending artery was occluded, and ischemia lasted for one hour followed by a two- hour reperfusion therapy. In contrast to the sedentary group, the exercise group showed smaller infarction sizes, which suggests that the heart of trained rats is more resistant to ischemia. In addition, Brown et al. found that the non-infarcted myocardium surrounding the ischemic area showed better blood flow in the exercise group, suggesting that regular ET over a longer period of time results in sustained cardiac function during the ischemic period. Upon reperfusion the previously ischemic area showed a higher blood flow in exercising rats than in sedentary rats (Brown et al., 2003). Thus, ET prior to MI may not only reduce infarction size, but also ensure cardiac pump function of the non-infarcted myocardium during an ischemic period. When comparing this animal study to the results in our study, it becomes obvious that a structured ET regimen, with an increase in exercise duration and intensity is needed to possibly achieve similar results in humans. As patients did not adequately answer questions concerning exercise intensity and duration prior to myocardial infarction, it cannot be determined that they trained at the correct intensity or duration to achieve significantly smaller infarction sizes and volumes.

Freiman et al. (2005) showed that six weeks of swim training in rats prior to MI resulted in a 40% reduction in infarction size four weeks after MI. In their study, rats were divided into an exercise and sedentary group. The exercise group engaged in swim training for six days a week beginning at 15 min per session and increasing to 90 min on the sixth day and continuing this training duration until the end of the training period. In addition, "[the] *area of the viable muscle, and thickness of the interventricular septum were both significantly larger in ExMI, by 23% and 9%, respectively*." (Freimann et al., 2005, p. 933). The authors concluded that ET prior to MI may influence cardiac remodeling positively after MI, namely by arteriogenesis. The authors found

that only the exercise group showed a higher arteriole density "*suggesting that prior exercise training conditioned the myocardium for enhanced arteriogenesis in response to MI* […]" (Freimann et al., 2005, p. 936) and that this pre-conditioning may limit infarction-size.

The frequency and duration of ET may play an eminent role on infarction size and infarction volume. Median values for infarction size in the ET group was 16% LGE and 23% in the No-ET group. Although these results were non-significant in statistical analyses, they do show a trend towards smaller infarction sizes. The same goes for infarction volume with a median value of 18 ml in the ET-group and 29ml in the No-ET group. As only three patients exercised three times a week or more and the majority of patients in the ET-group exercised once or twice a week, it may be possible that with the use of a structured ET regimen on a regular basis, a relevant pre-conditioning limiting infarction size and volume may also be possible in humans. However, trials with larger patient numbers are needed to further analyze this hypothesis.

In the study performed by de Waard et al. (2009), a running-wheel was used as the training method instead of swimming. Mice were divided into an exercise group and a sedentary group. The exercise group engaged in two weeks of voluntary wheel-running. After inducing MI, the mice were once again split up into an exercise group, which engaged in wheel-running for up to 8 weeks, and a sedentary group, resulting in four groups: exercise-infarction-exercise, exercise-infarction-sedentary, sedentary-infarction-exercise and sedentary-infarction-sedentary. Unlike Freiman et al. (2005), de Waard et al. did not find an influence of prior ET on infarction size. However, mice engaging in prior wheel-running showed a decrease in post-infarction mortality from 40% to 20% and improved LV-function. The authors proposed that the decrease in mortality may have been because *"the increased infarct thickness acted to reduce systolic wall stress and thereby prevented cardiac rupture, thus enhancing post-MI survival in mice that had been subjected to prior exercise […]*" (de Waard & Duncker, 2009, p. 934). The authors further concluded, that although exercise may not be able to prevent acute infarction in patients with a high risk of MI, it may have an impact on post-myocardial cardiac function and survival (de Waard & Duncker, 2009).

These animal studies demonstrate that ET prior to MI, in other words lifestyle modifications prior to cardiac injury, may be important non-pharmacological means of protection against the negative outcomes of a MI. In addition, more detailed analysis of ET prior to MI in terms of exercise intensity, type, frequency and duration is necessary. As many patients did not answer these questions sufficiently in this retrospective analysis, a deeper insight to each of these parameters and their possible influence on infarction size and volume was not achieved.

6. Study limitations

The most important limitation in this study was the use of a self-constructed questionnaire as it lacked validation: questionnaires represent subjective evaluations, and participants tend to overestimate themselves, especially when it comes to physical activity (Shephard, 2003). This overestimation can influence data immensely and lead to significance in data analysis, when there is none and vice versa. In analyzing the effects of exercise training, questionnaires often look at frequency, duration, intensity and modality. Intensity itself is difficult to measure using a questionnaire, unlike in interventional studies where intensity is often measured by heart rate, peak oxygen intake or as an absolute value. In a questionnaire, intensity is often stated in absolute terms and then transformed into a metabolic equivalent. As Shephard (2003) explained, patients tend to overestimate themselves and conversion calculations are based on young individuals, not the elderly, which limits the validity of these calculations (Shephard, 2003). The flaws of questionnaires limit their validity and their significance and show the necessity to develop new research methods to accurately answer these questions.

Further limitations in this study were the small sample size and the heterogeneity in age and sex. The more heterogenous the sample, the more difficult it is to extrapolate results to a larger population, especially when questionnaires are the main method of collecting data. In addition, data generated from small sample sizes is often not normally distributed, which can influence statistical analysis, unlike larger sample sizes, where data tends to be more normally distributed.

To gain more insight into participation in exercise training during the duration of cardiac rehabilitation programs, it would have been useful to contact the attended rehabilitation centers as well and include this data, so that not only effects of exercise training before and after an MI can be analyzed, but also the effects of training implemented during the healing process following an MI.

Finally, it must be mentioned that this study was an observational study, thus there was no active intervention. An intervention study may be able to show more reliable and controlled effects of exercise training on cardiac remodeling as training mode, duration, frequency and can be defined precisely during the intervention program and performed uniformly among patients.

7. Conclusion

Despite its limitations, the results of this retrospective analysis suggest that exercise training may become an important factor in ameliorating cardiac remodeling in patients suffering from MI. There is no doubt that timely percutaneous intervention and revascularization therapy, as

well as optimal pharmacological therapy, are the most important treatment strategies in AMI. In the future, long-term cardiac remodeling may be ameliorated further by ET. However, the frequency, duration, modality and intensity of ET remain to be determined in future research. Many patients often lead a sedentary lifestyle before myocardial infarction, which is why long-term programs must aim to ensure that ET, with appropriate intensity and frequency, becomes a habit and is not neglected after a short time.

Research focusing on exercise prior MI in a larger study population is needed to further confirm effects in humans. The slight, although non-significant, trend in this study sample towards smaller infarction sizes suggests that even if myocardial infarction cannot be prevented in all patients, these patients will still benefit from exercise training prior to a MI. Thus, it is important to promote lifestyle modifications, especially exercise behavior.

The prevention of MI and its secondary diseases is a major task not only for the medical community, but also for governments. The consequences of physical inactivity as well as the socioeconomic and medical costs are well-known. Underutilization of cardiac rehabilitation programs and a lack of information about disease-prevention are common in industrialized countries. The results of this study show that participation in ET before and after MI is not as high as it should be. Despite the high participation in a cardiac rehabilitation program in this study, it is surprising that the number of patients complying with the recommendations of current guidelines for regular exercise is not very large. Long-term follow-up care in Germany needs to aim at making exercise a habit and not a short-term activity. Increasing the duration and number of supervised ET programs may be an important step in adherence to exercise recommendations.

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9. Appendix

9.1. Questionnaire

Klinikum rechts der Isar

Technische Universität München

Zentrum für Prävention, Ernährung und Sportmedizin
Klinikum Rechts der Isar
Technische Universität München
Ismaninger Straße. 22, Bau 523
81675 München

Klinikum rechts der Isar
Anstalt des öffentlichen Rechts

Nuklearmedizinische Klinik

und Poliklinik

Univ.-Prof. Dr. M. Schwaiger

Direktor

Sehr geehrte Teilnehmer/innen,
wir bitten Sie, alle Fragen sorgfältig durchzulesen und möglichst genau zu beantworten.
Die Ergebnisse aus dem Fragebogen helfen uns, einen Einblick in die Therapie und den Behandlungsverlauf Ihres Herzinfarktes zu gewinnen.
Die Befragung bezieht sich auf die ersten sechs Monate nach dem Herzinfarkt.

Fragebogen zur Therapie nach akutem Herzinfarkt

Name: _____

Geb.-Datum: _____ **Geschlecht: weiblich** ☐ **männlich** ☐

Größe: _____ **Gewicht:** _____**kg**

Liegen (oder lagen) folgende Risikofaktoren vor?	**Ja**	**Nein**
1) Bluthochdruck	☐	☐
2) Erhöhte Blutfette (Cholesterin oder Triglyceride)	☐	☐
3) Zuckerkrankheit (Diabetes)	☐	☐
4) Arterienverkalkung am Herzen (koronare Herzerkrankung)	☐	☐
5) Haben Sie vor Ihrem Herzinfarkt geraucht?	☐	☐
Wenn ja, wie lange und viele Zigaretten pro Tag? _____		
6) Gibt es in Ihrer Familie weitere Fälle von Herzinfarkten?	☐	☐

Wenn ja, bei welchen Familienmitgliedern? In welchem Alter fand der Infarkt statt?

_____

7) Waren Sie vor Ihrem Herzinfarkt sportlich aktiv? Wenn ja, welchen Sportarten sind Sie nachgegangen? Wie oft haben Sie pro Woche trainiert und wie lange (in Minuten/Woche)? Mit etwa welcher Intensität haben Sie trainiert?_____

_____

___

_____

___

_____

___

Welche der Medikamente nehmen Sie ein?	**Ja**	**Nein**
1) ACE-Hemmer (z.B. Ramipril)	☐	☐
2) Betablocker (z.B. Bisoprolol, Metoprolol)	☐	☐
3) AT1-Blocker (z.B. Losartan)	☐	☐
4) Ca^{2+}-Kanal-Blocker (z.B. Verapamil)	☐	☐
5) Statine (z.B. Simvastatin)	☐	☐

6) Andere _____

_____

_____

_____

Fragen zu Rehabilitations-Maßnahmen

1) Welche Versorgungsformen haben Sie in Anspruch genommen?

Ambulant ☐ Stationär ☐

2) In welcher Reha-Klinik/ambulanten Versorgung waren Sie?

_____

3) Wie viele Tage nach dem Herzinfarkt begann Ihre Therapie in der Reha-Einrichtung?

_____

4) Wie lange nahmen Sie an der Reha-Maßnahme teil? (Angabe in Wochen)

_____

5) Wie oft haben Sie in den ersten 6 Monaten **nach der Reha** durchschnittlich in der Woche Sport getrieben?

_____

6) Welchen körperlichen Aktivitäten sind Sie nachgegangen?

Körperliche Aktivität	Welche Sportart? Ungefähr wie schnell/intensiv?	Durchschnittliche Dauer/Woche (Angabe in Minuten)	MET (vom Arzt ausgefüllt)
Ausdauersport (z.B. spazieren gehen, laufen, schwimmen, Rad fahren, Fitnesskurse, Ergometertraining)			
Technische oder rhythmisch orientierte Sportartarten (z.B. Tanzen, Reiten, Golf)			
Rehabilitationssport (z.B. Herzsportgruppe)			
andere Sportarten			

MET Total:

Vielen Dank für Ihre Teilnahme!

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