Aus der Klinik für Kardiologie
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DISSERTATION

Speckle-tracking derived strain imaging and its use in evaluating right ventricular function in patients with ST-segmental elevation infarction. A new prognostic tool?

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Abbreviations

ACC – American College of Cardiology

AHA – American Heart Association

AMI – acute myocardial infarction

AT – antithrombotic therapy

CAD – coronary artery disease

CBF – Campus Benjamin Franklin (Charité)

CK – creatine kinase

CK-MB – creatine kinase, muscle-brain type

CMR – cardiac magnetic resonance imaging

DES – drug eluting stent

EACVI – European Association of Cardiovascular Imaging

ECG - electrocardiogram

ESC – European Society of Cardiology

FAC – fractional area change

HFrEF – heart failure with reduced ejection fraction

ICD – implantable cardioverter defibrillator

IVSd – interventricular septal end diastole

LAD – left anterior descending artery

LAsV – left atrial systolic volume

LBBB – left bundle branch block

LCA – left coronary artery

LCX – left circumflex artery

LV – left ventricle

LVAD – left ventricular assistant device

LVEF – left ventricular ejection fraction

LV-GLS – left ventricular global longitudinal strain

LVIDd - left ventricular internal diameter end diastole

LVIDs - left ventricular internal diameter end systole

LVM – left ventricular mass

LVOT – left ventricular outflow tract

LVPWd – left ventricular wall end diastole

MR – mitral regurgitation

MRI – magnetic resonance imaging

NSTEMI – non-ST-segment elevation myocardial infarction

NYHA – New York Heart Association

PASP – systolic pulmonary artery pressure

PCI – percutaneous coronary intervention

PDA – posterior descending artery

RAsV – right atrial systolic volume

RCA – right coronary artery

RIMP – right sided index of myocardial performance

RMD – Ramus marginalis dexter

ROC – receiver operator curve

ROI – region of interest

RV – right ventricle

RVEF – right ventricular ejection fraction

RVFAC – right ventricular fractional area change

RV-FWS – right ventricular free wall strain

RV-GLS – right ventricular global longitudinal strain

RV-SSR – right ventricular peak systolic strain rate

SD – standard deviation

STE – speckle-tracking echocardiography

STEMI - ST-segment elevation myocardial infarction

TAPSE – tricuspid annular plane systolic excursion

TAPSV – tricuspid annular plane systolic velocity

TDI – tissue Doppler imaging

TR – tricuspid regurgitation

TTE – transthoracic echocardiography

VTI – velocity time integral

WHF – World Health Federation

WHO – World Health Organization

Abstract

Background

In cases of right ventricular (RV) involvement, adverse prognoses have been observed in patients with acute ST-segment elevation myocardial infarction (STEMI). Speckle-tracking (STE) derived strain measurements are promising for the characterization of right ventricular function. The prognostic relevance of these new parameters remains unclear. The aim of this study is to assess the value of RV strain and the strain rate derived by STE in patients with acute STEMI who have undergone percutaneous coronary intervention (PCI).

Method

We recruited 99 STEMI patients who received post-acquisition echocardiography analysis after PCI between January of 2015 and January of 2016. RV dimensions and function, including two-dimensional strain and strain-rate, were measured. RV strain was analyzed as free wall strain and global longitudinal strain. After a mean follow-up period of 25 months several outcome parameters were collected. To our knowledge, this is the first study evaluating the prognostic value of two-dimensional RV STE derived strain vs. tricuspid annular plane systolic excursion (TAPSE) in patients with STEMI and primary PCI on GE ultrasound machines and software.

Results

RV strain showed significant correlation with TAPSE. RV-GLS was higher in patients with impaired LVEF. TAPSE showed comparable results, however, 80% of the patients with impaired RV-GLS (> -13%, n = 11) had normal TAPSE (≥ 17 mm).

Out of the 74 patients we interviewed, seven died (9.5%) during follow-up. RV strain was significantly higher in patients who died. TAPSE was lower in these patients, although the difference was not statistically significant. In a ROC analysis for RV-GLS, a cut-off of -13 showed a sensitivity of 86% and a specificity of 91% for the prediction of death during the two-year follow-up. For RV-FWS we identified a cut-off at -19 with similar sensitivity but lower specificity (83%) for the same endpoint. TAPSE was not useful for the prediction of death during follow-up. Multivariate analysis identified RV-GLS as an independent predictor of death during follow-up (OR 1.36, 95%-CI 1.01 – 2.50, p = 0.043). Exceeding the cut-off of -13 was associated with a 24.66-fold increased risk of death. RV-FWS and TAPSE did not show independent predictive value for the endpoint death.

Conclusion

RV strain is an important predictor of mortality in STEMI patients. TAPSE and RV strain rate were not effective at predicting mortality. RV-GLS shows superior prognostic value compared to TAPSE and should be implemented in echocardiographic routine evaluations of patients with STEMI.

Hintergrund

Bei Patienten mit ST-Strecken Hebungsinfarkt (STEMI) mit rechtsventrikulärer (RV) Beteiligung wurde eine ungünstige Prognose beschrieben. Die Messung von strain und strain rate mittels "speckle-tracking Echokardiografie" (STE), ermöglicht eine genauere Beschreibung der globalen und regionalen Myokardfunktion. Die prognostische Relevanz dieser neuen Messgrößen ist bisher unklar. In dieser Studie untersuchen wir den prognostischen Nutzen von RV strain mittels STE, bei Patienten mit akutem STEMI und Z.n. perkutaner Koronarintervention (PCI).

Methoden

Rekrutiert wurden insgesamt 99 STEMI-Patienten zwischen Januar 2015 und Januar 2016. Alle Patienten erhielten nach PCI eine Echokardiographie. Dabei wurden die RV Dimensionen und Funktion inklusive 2d strain und strain rate beurteilt. Analysiert wurde der RV strain aller sechs RV Segmente sowie der der freien Wand. Nach einem durchschnittlichen Follow-up von 25 Monaten wurden einige Outcome-Parameter erhoben. Unseres Wissens nach ist dies die erste mit GE Geräten und Software durchgeführte Studie, die den prognostischen Wert von RV strain mittels STE bei STEMI-Patienten beurteilt.

Ergebnisse

RV strain zeigte eine gute Korrelation mit TAPSE. Bei Patienten mit eingeschränkter LVEF zeigte sich ein höherer RV-GLS. Vergleichbare Ergebnisse wurden bei der TAPSE erzielt, jedoch hatten 80% der Patienten mit eingeschränktem RV-GLS (> -13%, n = 11) eine normale TAPSE (≥ 17 mm).

Von den 74 befragten Patienten, verstarben 7 (9.5%) während des Follow-ups. Die Verstorbenen hatten initial einen signifikant höheren RV strain. TAPSE war bei diesen Patienten niedriger, jedoch war hier der Unterschied zu den Überlebenden nicht statistisch signifikant. In einer ROC Analyse für RV-GLS, zeigte ein Cutoff von -13 eine Sensitivität von 86% eine Spezifität von 91% für die Vorhersage der Sterblichkeit innerhalb von zwei Jahren nach dem initialen Myokardinfarkt. Für RV-FWS wurde für den gleichen Endpunkt ein Cutoff von -19 mit gleicher Sensitivität bei geringerer Spezifität (83%) identifiziert. TAPSE zeigte sich in unseren Analysen nicht als hilfreich für die Sterbevorhersage während des Follow-ups. Eine multivariable logistische Regression identifizierte RV-GLS als unabhängigen Prädiktor für das Versterben während des Follow-ups (OR 1.36, 95%-CI 1.01 – 2.50, p = 0.043). Eine Überschreitung des Cutoffs von -13 ist assoziiert mit einem 24,66-fach erhöhten Sterberisiko während des Follow-ups. RV-FWS und TAPSE konnten nicht als unabhängige Prädiktoren hierfür identifiziert werden.

Zusammenfassung

RV strain ist ein wichtiger Prädiktor für die Mortalität von STEMI-Patienten. TAPSE und RV strain rate waren nicht effektiv für die Vorhersage der Sterblichkeit. RV-GLS schneidet als prognostisches Instrument bei Patienten mit STEMI im Vergleich zu TAPSE besser ab und sollte in der stationären Routineevaluation integriert werden.

1 Introduction

1.1 Acute myocardial infarction

Epidemiology

According to the World Health Organization (WHO), ischaemic heart disease is the leading cause of death, and has been on the top ten list for the last 15 years. Ischaemic heart disease was the cause for well over nine million deaths in 2016 alone[2]. In chronic ischaemic heart disease, also called coronary artery disease (CAD), a progressive deposition of cholesterol in the coronary artery walls leads to atherosclerotic plaque formation. Ultimately, this leads to stenosis and a slowly decreasing oxygen supply to the heart muscle. Over the course of the disease, an acute coronary syndrome can occur when an atherosclerotic plaque ruptures and the resulting thrombus completely seals the coronary artery. This leads to a sudden reduction in oxygen supply in the heart muscle and causes acute myocardial infarction (AMI). Every sixth man and every seventh woman in Europe will die from myocardial infarction[3]. The incidence of acute myocardial infarction varies greatly between European countries, with a mean incidence of 190/100.000 hospital admissions per year[4].

Based on electrocardiographic (ECG) characteristics, acute myocardial infarction is further subdivided into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). This distinction is particularly relevant for therapy decisions and prognosis, whereby STEMI requires faster therapeutic actions as all cardiac muscle layers are typically ischaemic. ST-segment myocardial infarction causes 80/100.000 hospital admissions per year in Europe[4].

Significant differences have been described in the epidemiological data and clinical presentation between men and women. Even though the mortality rate of acute myocardial infarction has decreased overall, the decline in mortality rate has been less in women compared to men[5]. This has been attributed to the fact that women with AMI often present with atypical and more unspecific symptoms, including dyspnea, nausea, vomiting, and diaphoresis[6,7]. On the other hand, women who undergo percutaneous coronary intervention are generally older than men[8]. This age gap has been attributed, at least in part, to the protective effect of estrogens and other sex hormones in premenopausal women[9].

Pathophysiology

On the pathological level, acute myocardial infarction is defined as the presence of myocardial cell necrosis as a result of prolonged ischaemia[10]. In the fourth universal definition of myocardial infarction, an expert consensus paper from the European Society of Cardiology (ESC), American College of Cardiology (ACC), American Heart Association (AHA) and World Heart Federation (WHF), five types of myocardial infarction are distinguished according to their etiology.

The most frequent reason for acute coronary ischaemia is the atherothrombotic occlusion of a coronary artery due to CAD. When a plaque ruptures, a thrombus forms, which partially or completely obstructs the remaining lumen of the coronary artery (Type 1). Type 2 myocardial infarction is defined as an acute mismatch of oxygen demand and supply not caused by a ruptured atherosclerotic plaque: Stable plaques themselves usually progress slowly enough in size for the underlying myocardium to adapt and collateral pathways to form. However, an acute increase in cardiac oxygen demand (e.g. acute tachycardia due to atrial fibrillation) or an acute decrease in oxygen supply (e.g. acute bleeding, vasospasm) can often not be sufficiently compensated by arteriosclerotically narrowed coronary arteries. This can lead to Type 2 myocardial infarction. (*Figure 1*).

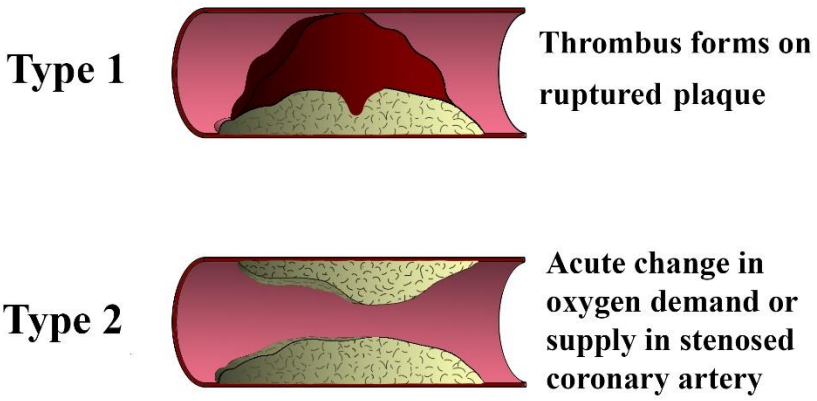


Figure 1 Pathogenesis of the most common types of acute myocardial infarction.

Type 1 myocardial infarction is defined as ischemia-related myocardial cell death caused by a thrombus closing the vascular lumen, usually caused by atherosclerotic plaque rupture. Type 2 myocardial infarction is defined as ischemia-related myocardial cell death due to a mismatch of oxygen demand and supply, not caused by a thrombus. Reasons for Type 2 myocardial infarction include arterial dissection, acute bleeding or tachycardia, often accompanied by coronary artery disease.

Type 3 myocardial infarction is a category for patients who die so early after symptom onset, that myocardial necrosis or ischaemia is not yet detectable but myocardial infarction is clinically

suspected. In the event of acute ischaemia associated with percutaneous coronary intervention, the infarction is categorized as Type 4, while acute ischaemia associated with coronary artery bypass grafting is categorized as a Type 5 myocardial infarction.[10] In principle, any condition that leads to an acute imbalance between oxygen demand and supply in the myocardium can cause myocardial infarction.

Coronary arteries[11]

The heart muscle is supplied with blood and nutrients by two main arteries. The left and right coronary artery, which both originate from the ascending aorta immediately distal to the aortic valve leaflets. The left coronary artery (LCA) runs in between the pulmonary trunk and the left atrial auricle and divides into the left anterior descending (LAD) and left circumflex artery (LCX). The LAD then runs towards the apex in between the left and right ventricular borders and mainly perfuses the anterior and anteroseptal segments of the left ventricle.

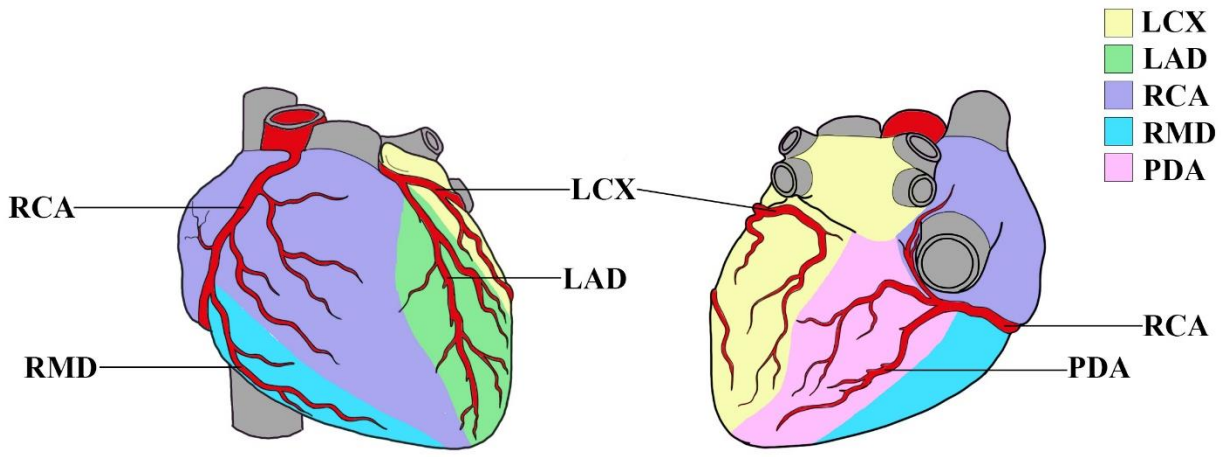


Figure modified from AMBOSS GmbH, Berlin und Köln, Germany[1].

Figure 2 Pathway and associated supply regions of the coronary arteries.

The colored areas mark the wall segments supplied by the respective coronary branches. While the left coronary artery with its two main branches LCX and LAD supplies the left ventricle with oxygen and nutrition, the right ventricle is supplied mainly by the right coronary artery and its branches.

Abbreviation index: LXC = left circumflex artery; LAD = left anterior descending; RCA = right coronary artery; RMD = ramus marginalis dexter; PDA = posterior descending artery

The LCX runs around the base of the left ventricle to the lateral wall and then towards the apex. It provides blood for the anterolateral and inferolateral segments of the left ventricle. The right coronary artery (RCA) runs around the base of the right ventricle providing branches for the right ventricle, right atrium and sinoatrial node. The first major branch of RCA is the Ramus marginalis dexter (RMD). It supplies blood to the lateral wall of the right ventricle. The posterior descending artery (PDA) runs between the ventricles at the backside of the heart. Extending to the apex, the PDA provides blood for the inferior and inferoseptal segments of the left ventricle (*Figure 2*). It is important to note that there is a number of collateral pathways, especially from the LAD to the PDA.

Significant anatomic variation exists in the coronary anatomy, and especially in the artery from which the PDA originates. This has led to a division into three main types of coronary perfusion. The anatomy described above defines the right-dominant type of myocardial perfusion, which is the most common anatomical variant with over 82% prevalence in the general population. In about 12% of individuals, the coronary circulation is left- dominant, with the PDA branching from the LCX. In about 6 percent of individuals the PDA is supplied by both RCA and LCX (co-dominant type)[12].

Left and right ventricular infarction

Depending on which coronary artery is occluded, different segments of the myocardial tissue will be cut off from oxygen supply, resulting in distinct infarction areas (*Figure 2*). It has been shown that myocardial infarction does not occur equally frequent in all areas of the myocardium. The majority of occlusions occur in either the LAD or RCA with a higher chance in the proximal thirds of these vessels[13]. Both vessels are important for the perfusion of the left ventricle, mainly the anterior, inferior and septal segments. In the less frequent case of LCX occlusion, the left ventricle and especially the lateral wall is also affected. Thus, occlusions in any of the three main coronary arteries almost always result in left ventricular infarction and dysfunction.

The right ventricle on the other hand is mainly perfused by the marginal branches of the right coronary artery[14]. Ischaemia or infarction of the right ventricular myocardium therefore mainly occurs, if the site of occlusion is located proximal to the origin of the major marginal branches[15]. While isolated right ventricular infarction is rare[16], two thirds of inferior or anterior left ventricular infarctions are accompanied by right ventricular infarction[15]. Furthermore, the function of the right ventricle may be impaired even in isolated left ventricular infarction due to the functional

interdependency between the two ventricles: The activity of the left ventricle contributes about 68% of the right ventricular systolic pressure and 80% of pulmonary flow[17]. This is due to the fact that the right ventricular free wall comprises mainly transverse muscle fibers, while the interventricular septum consists of oblique muscle fibers, which are at a mechanical advantage[18]. These septal fibers are shared between both ventricles and play an important role in right ventricular contractility[19].

Compared to the left ventricle, the right ventricular muscle tissue shows important differences in its resistance to ischemia. During systole, the right ventricle has to build up much lower pressures to sustain pulmonary circulation. In patients with normal pulmonary blood pressure, these pressures typically do not exceed 30 mmHg. While the high pressures that are generated by the left ventricular myocardium during contraction lead to compression of the perforating coronary vessels in systole, the same is not true for the right ventricle. Thus perfusion can take place throughout the whole cardiac cycle, compared to the left myocardium which is perfused almost exclusively in diastole[20]. Due to this fact, the right ventricle has longer lasting reserves even in reduced diastole duration resulting from tachycardia. Requiring lower contractility to sustain circulation, the right ventricular myocardium is significantly lower in mass compared to the left ventricle. This leads to lesser oxygen demand and therefore higher tolerance to decreasing oxygen supply[21–23].Finally, there is an extensive system of collateral vessels running from the left to the right coronary artery. This may be one of the reasons, why right ventricular function is often restored a few months after right ventricular infarction[23,24].

Anatomy of the right ventricle[11]

The right ventricle roughly approximates the shape of a trigonal pyramid, with the base being orientated towards the right atrium and pulmonary truncus and the tip towards the cardiac apex. The anterior wall (*Facies sternocostalis*) faces towards the inner side of the sternum and costae, the medial wall forms the interventricular septum and the posterior wall lies on top of the diaphragm (*Facies diaphragmatica*) (*Figure 3*).

Blood reaches the right ventricle through the tricuspid valve in the base. The posterior and anterior wall as well as the apical parts of the interventricular septum are part of the right ventricular inflow tract, presenting trabeculation on the inner wall. The outflow tract consists mainly of the basal portion of the interventricular septum and anterior wall. In the outflow tract, the inner wall is not

trabeculated but has a smooth surface. Here, the blood leaves the right ventricle through the pulmonary valve to continue its way through the pulmonary artery towards the lungs.

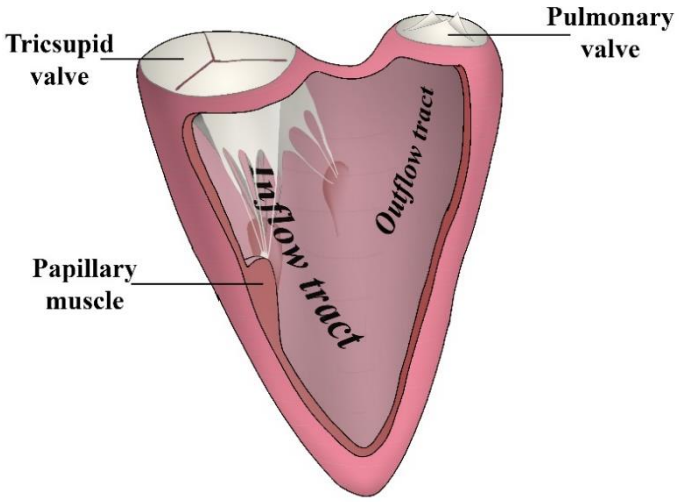


Figure 3 Model of the right ventricle

The three conical muscle streams of the papillary muscles protrude into the lumen of the right ventricle. The Chordae tendineae stretch between the papillary muscles and tricuspid valve leaflets. They prevent prolapsing of the valve leaflets into the right atrium during systole.

The cardiac wall cross-section can be divided into three distinct layers: The epicardium is the inner or visceral lamina of the pericardium. It encompasses the second layer, the myocardium. The bigger coronary vessels and large parts of the electrical conduction system of the heart are situated between these two layers. The myocardium is the thickest layer of the ventricular walls. It consists of muscle fibres responsible for the contraction of the chambers. Fibre-layers with different orientation can be distinguished in the myocardium: While the left ventricular myocardium consists of three fibre layers, the right ventricular myocardium is lacking the middle fibre layer. The subepicardial layer of the right ventricular myocardium mainly consists of circumferentially orientated fibres, while the subendocardial layer mainly consists of longitudinal fibres. The myocardium is perforated by arterioles and capillaries running from the epicardial coronary vessels towards the endocardium, the innermost layer, which coats the lumen of the ventricles. In addition to blood vessels, the endocardium also contains nerves and fibres of the electrical conduction system[11].

Risk factors

Various factors have been identified that increase the risk of acute myocardial infarction. The INTERHEART study, a standardized case-control study conducted in 52 countries worldwide identified nine major risk factors for acute myocardial infarction. According to the findings of this study, the highest risk is associated with cigarette smoking, raised apolipoprotein levels, history of hypertension, diabetes. All of these factors have been shown to be independent of sex and age[25]. They are influenceable and therefore an important target for the primary prevention of AMI. The PROCAM study, another large prospective cohort study, identified independent risk factors for the occurrence of myocardial infarction[26]. Based on these risk factors, the PROCAM health test was designed to assess the individual risk for the occurrence of a myocardial infarction within the next 10 years. The test includes the factors sex, age, diabetes mellitus, nicotine abuse, systolic blood pressure, current antihypertensive therapy and family history in the risk calculation[27].

Clinical presentation

The leading symptom of CAD is stable angina pectoris, which is defined as retrosternal chest pain that increases with physical or mental stress and is relieved by rest or the administration of nitroglycerine. In contrast, an acute myocardial infarction presents as unstable angina pectoris. This means the chest pain lasts for more than 20 minutes and is mostly irresponsive to nitroglycerine. Typically, the pain radiates to the shoulders, arms, neck, jaw and/or upper abdomen and is associated with the feeling of anxiety or agitation. In addition, the vegetative nervous system is activated, which leads to nausea, vomiting and diaphoresis[28–30].

However, up to a third of the patients with myocardial infarction, present less specific symptoms. These patients typically do not complain about severe chest pain, but about less specific symptoms such as abdominal pain, nausea or restlessness. Patients with atypical symptoms are often diabetics or elderly people. In addition, women with acute myocardial infarction often show less specific symptoms. Due to the unspecific clinical features, these patients are at a higher risk of being misjudged in the emergency department. They tend to present later and less frequently receive early reperfusion therapy[31–33].

Initial diagnosis of right ventricular infarction can be difficult due to a number of clinical characteristics: Often patients with right ventricular infarction do not show specific symptoms that distinguish them from patients without right ventricular infarction. Only 25% of the patients with

right ventricular involvement develop hemodynamic manifestation on presentation[34,35]. When present, the hemodynamic triad of hypotension, elevated jugular venous pressure and clear lungs[14,36], is a sensitive sign for right ventricular infarction. Additional signs including Kussmaul's sign, pulsus paradoxus or tricuspid regurgitation murmur may be observed[14].

Diagnosis

Acute myocardial infarction can be categorized as ST-segment elevation myocardial infarction (STEMI) and Non-ST-segment elevation myocardial infarction (NSTEMI). This distinction is made on the basis of the occurrence of ST segment elevations in the electrocardiogram (ECG). ST-segment elevations are a sign of disturbed excitation propagation in the myocardium. It is typically an expression of transmural myocardial necrosis, however their absence does not rule out acute myocardial infarction all together. Endocardial infarction and smaller infarction areas can be present without specific ECG-findings, which is why the clinical presentation and cardiac biomarkers play an equally important role in the diagnosis of acute myocardial infarction.

If AMI is suspected, a resting 12-lead ECG should be performed as soon as possible after first medical contact. For the diagnosis of STEMI at least two contiguous leads must show significant ST-segment elevation. The threshold of significance depends on the patients sex, age and the ECG lead[37]. For accurate detection of right ventricular infarction it is recommended to also look for ST-segment elevation in right precordial leads[38]. Several factors can hinder the diagnosis of STEMI via ECG: In early stages, ST-segment elevation may not yet be present, in which case hyper-acute T-waves can be an early indicator of STEMI. In patients with left bundle branch block (LBBB), STEMI cannot be ruled out by definition. Especially patients with new or previously unknown LBBB should be treated like STEMI-patients[37].

In addition to the ECG, a blood sample is acquired. The most relevant parameters are the myocardial biomarkers troponin, creatine kinase (CK) and muscle-brain type creatine kinase (CK- B), which are released into the bloodstream when cardiomyocytes are damaged due to ischaemia. Elevated biomarkers allow the diagnosis of NSTEMI when ST-segment elevation in the ECG is absent. Due to the release kinetics, elevation of these biomarkers may not be recorded in the initial blood sample. In this case, an additional blood test, usually three hours after the first sample, may be required[39].

Therapy

Reperfusion is the number one priority in the therapy of STEMI. Better availability of reperfusion therapy either by primary percutaneous intervention (PCI) or antithrombotic therapy (AT) has led to a significant decrease in mortality in patients presenting with STEMI in recent years[40]. Today the gold standard for reperfusion is the percutaneous coronary intervention. Overall patients receiving PCI show lower in-hospital mortality than patients receiving AT[4]. During the procedure, the site of acute vessel occlusion is visualized with a radiopaque medium, which is applied into the coronary arteries via catheter. Next, a coronary catheter is introduced into the culprit vessel and a balloon covered with a metal mesh (stent) is placed into the site of occlusion. The balloon is then inflated, extending the stent into the coronary artery walls. The stent is often covered with an antirestenotic drug (drug eluting stent, DES) to further prevent restenosis. In areas where PCI is not feasible within two hours of first medical contact, fibrinolysis is a viable therapeutic option[37]. Emergent coronary artery bypass graft surgery can be performed, especially when PCI failed, or mechanical infarction-related complications are present[37].

The primary reperfusion therapy is followed by a complex drug therapy, which is individually tailored to the lifestyle and the prevalence of risk factors of the patient. Every patient should take aspirin to inhibit platelet aggregation for the rest of their life. Depending on the chosen intervention procedure, a second antiplatelet inhibitor can be given for a limited time. Other groups of drugs that patients with myocardial infarction frequently receive are beta blockers, statins, calcium antagonists and aldosterone receptor antagonists[37].

Prognosis

As stated above, ischemic heart disease, including acute myocardial infarction remains one of the major causes of death worldwide. The extensive availability of reperfusion therapy through coronary intervention, faster detection of acute myocardial infarction as well as faster forwarding to specialized centers, but also the improvement of drug and non-drug prevention have led to a steady decrease in 30-day mortality over the past 30 years[41–44]. However, the short term mortality of patients presenting with STEMI remains high, with 30-day mortality ranging from 4,4 - 11,4% [40,44–46] and in-hospital mortality ranging from 3 - 12% [47].

Long-term outcome after STEMI has also improved significantly over the past 30 years with reduction in one-year mortality[45] and lesser rates of myocardial reinfarction after six months[48]. In

the HORIZONS-AMI trial a relatively recent study from 2011, the three-year mortality of STEMI patients who underwent primary PCI was approximately 6 - 8%[49]. Especially drug prevention of further cardiovascular events, in particular through dual antiplatelet therapy, e.g. with the admission of ADP-receptor-antagonists, could significantly reduce mortality over three years follow-up[50].

Despite the remarkable medical progress in the treatment of acute myocardial infarction, the disease is accompanied by significant consequences for the further life of those affected. In the course of their lives, survivors of a heart attack have a considerably increased risk of suffering further cardiovascular events. Above all, the risk of recurrent myocardial infarction, heart failure, cardiac arrhythmia, stroke, but also general mortality is increased. An exact risk stratification should be done on the individual level, using available scores like the TIMI risk score[51] or the GRACE risk model[52,53]. Nevertheless, general statements can be made about the risk distribution of certain subsequent events.

After acute myocardial infarction, the risk of sudden cardiac death, usually caused by ventricular tachycardia, is increased, especially in patients with left ventricular dysfunction or heart failure[54]. Furthermore, the risk of stroke, reinfarction and subsequent need for revascularization, but also major bleeding is elevated at least within the first three years after STEMI[55].

Right ventricular involvement

In recent years, various studies have shown that the prognosis after myocardial infarction depends largely on the involvement of the right ventricle: Patients with inferior myocardial infarction and right ventricular involvement have a higher mortality and a higher rate of serious arrhythmic complications and cardiogenic shock, compared to those without right ventricular involvement[56]. With the steadily increasing availability of PCI, the prognosis of right ventricular infarction is improving. In most cases, right ventricular performance recovers after reperfusion[57]. However, patients with persistent right ventricular dysfunction are at a distinct prognostic disadvantage[58]. The unfavorable prognosis of right ventricular dysfunction also seems to apply to anterior myocardial infarction, with higher rates of cardiogenic shock, reinfarction and mortality[59].

Early identification of STEMI patients, who are at a higher risk of adverse cardiac events is of great importance. In clinical practice, echocardiographic imaging is usually used for this purpose.

1.2 Echocardiography

Echocardiography is a noninvasive imaging procedure, which allows quantitative and qualitative analysis of cardiac anatomy and function. In echocardiographic imaging, a probe containing piezo-crystals is used to emit sound waves in the ultrasonic range of typically 1 to 20 megahertz. Placed on the skin, these sound waves penetrate the body and are reflected and scattered at surfaces with different acoustic impedance. The reflected waves can then be detected by the ultrasound probe which transmits the signal to an image processor, where a two-dimensional sectional image is calculated from the data in real-time[60].

Echocardiographic ultrasound imaging is commonly used for the quantitative assessment of cardiac dimensions and qualitative assessment of systolic and diastolic function in a number of heart conditions, including acute myocardial infarction. It is safe, non-invasive, easy and fast to acquire, low-priced and widely available in the clinical setting. For this reason, the European Society of Cardiology recommends echocardiography as the first line imaging modality for the assessment of testing left and right ventricular function, mechanical complications and thrombus detection in patients with acute ST-segment elevation infarction, before discharge[37].

Left ventricular function

In the past, the focus of the echocardiographic post-infarction assessment has been laid on the left ventricle, due to its important role for the systemic circulation. Multiple studies show the importance of the echocardiographic assessment of the left ventricular function for prognosis and risk stratification[61,62]. Moller et al. showed that left ventricular ejection fraction, wall motion score index, mitral filling patterns and Tei index obtained by transthoracic echocardiography are important prognostic markers for all-cause mortality in post-AMI patients[63] . Not only systolic but also diastolic function plays an important role for risk stratification of these patients. A restrictive filling pattern of the left ventricle has been shown to be an independent predictor of cardiovascular mortality[64,65].

Right ventricular function

In recent years, the focus of the echocardiographic examination has been extended gradually towards a more comprehensive assessment, not only of the left, but also of the right ventricle. Several studies have shown that right ventricular function is also a relevant prognostic parameter.

An association was found between impaired right ventricular function and poor short- and long-term outcome in patients who underwent percutaneous coronary intervention after acute STEMI[59,66,67]. These results illustrate the importance of an effective and comprehensive echocardiographic assessment of the right ventricular function.

The echocardiographic evaluation of the right ventricle comprises the parameters: RV fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE), tricuspid annular plane systolic longitudinal velocity (TAPSV) by tissue Doppler imaging (TDI) and right-sided index of myocardial performance (RIMP) as well as several dimensional measurements[68]. There are a large number of studies that evaluated these parameters, however, not all of them are routinely used in clinical practice. In a recent online survey with 1150 professional participants from 109 countries, 23% stated that they assessed right ventricular function in clinical routine by eye-balling alone, while around two thirds of the participants additionally used TAPSE[69]. Apart from that, all of the parameters mentioned above have their individual limitations. TAPSE is probably the easiest to obtain parameter to assess right ventricular systolic function and has a very low inter-observer variability. It is a one-dimensional measurement, used to quantify the mobility of the basal segment of the right ventricular free wall, which reflects the longitudinal displacement of the right ventricle[70]. By focusing on only a single point of measurement, however, TAPSE neglects most of the complex geometry of the right ventricle, thus possibly ignoring contributing factors of right ventricular systolic function, such as inward contraction and ventricular interdependence[71].

The tricuspid annular systolic longitudinal velocity, measured by TDI, faces the same limitations: In contrast to TAPSE, it is not the spatial extension of the tricuspid annulus that is measured but its peak velocity during systole[70]. Like TAPSE, it is angle and load dependent and also uses only a small portion of the right ventricle to assume global systolic function. Despite their good correlation with right ventricular ejection fraction (RVEF) derived by cardiac magnetic resonance imaging (CMR)[72], these methods may fail to detect regional dysfunction, especially in case of infarction in other right ventricular segments.

RVFAC is a measure of the percentage difference of the right ventricular area in systole compared to diastole. It overcomes part of the limitations of the one-dimensional measurements by requiring a two-dimensional plane for its assessment, making it angle independent and allowing for integration of radial right ventricular contraction into the calculation of right ventricular systolic function. However, to measure RVFAC, the right ventricular area must be traced manually in

systole and diastole, excluding any trabeculation and thus making image quality an important factor for correct measurements[73].

The Right Ventricular Index of Myocardial Performance (RIMP, also referred to as Tei index) is the ratio between the isovolumetric contraction and relaxation times and the ejection time of the right ventricle. It is an important predictive measure for a number of cardiac conditions including moderate chronic heart failure (NYHA II), pulmonary hypertension and patients undergoing coronary artery bypass graft surgery[74–76]. Its assessment is also rather complex: Multiple beats have to be acquired and similar R-R intervals are needed for correct measurement. The accuracy of RIMP is also affected by elevated right atrial pressures and atrial fibrillation making it less than ideal for the routine evaluation in all patients[68].

Speckle-tracking derived strain and strain rate

Strain and strain rate are additional parameters for the assessment of the ventricular function. Strain reflects the fractional change in myocardial tissue deformation. It is a dimensionless parameter and is reported as a positive or negative percentage change from the original dimension[70] (see formular below). Strain rate is a measure for tissue deformation or strain happening per one second (first derivative of strain). Both strain and strain rate can be acquired using either tissue Doppler (TDI) or speckle-tracking imaging. For several years, TDI was the only available method to quantify these parameters. Its limitations, including angle dependency, poor signal-to-noise ratio and load dependency[77] may however account for the limited day-to-day clinical use.

$$Strain = \frac{\Delta Length}{Original\ length}\%$$

Speckle-tracking echocardiography (STE) is a relatively new method to quantify strain and strain rate of the myocardial tissue. Static B-scan ultrasound imaging creates a unique pattern of bright spots or speckles in the myocardial tissue[78]. These natural acoustic markers are created by backscattered signals from structures in the myocardium, which are smaller than a wavelength[70]. The motion of these speckles correlates with small displacement tissue deformation[79], and can be tracked automatically when a user-defined region of interest (ROI) is defined. Strain and strain rate derived by STE show concordance to tissue displacement derived by TDI and CMR[80]. STE

makes the strain measurement angle independent and more reproducible[68]. Another advantage over TDI is the ability to perform the analysis after image acquisition. The technique was validated against sonomicrometry and MRI tagging as reference methods[81,82]. STE derived strain has been widely used in recent years to detect myocardial dysfunction in a number of cardiovascular diseases.

Left ventricular STE derived strain showed high sensitivity in terms of detecting left ventricular impairment in post-AMI patients compared to conventional parameters such as LVEF[83]. Park et al. showed that strain derived by STE was an independent predictor for left ventricular remodeling after acute myocardial infarction[84]. In patients with aortic stenosis, left ventricular global longitudinal strain is an independent predictor of all-cause mortality[85] and may provide additional value in the selection of patients, who profit from aortic valve replacement[86]. Left ventricular STE derived strain may provide a useful tool in the differential diagnosis of cardiac amyloidosis and hypertrophic cardiomyopathy[87,88]. Recently, Medvedofsky et al. found that right ventricular longitudinal free wall strain was associated with all-cause mortality at one year after a transcatheter aortic valve replacement[89]. In patients with pulmonary artery hypertension, right ventricular strain was predictive of future right-sided heart failure as well as mortality[90]. Few studies have focused on evaluating right ventricular strain in patients with acute myocardial infarction. Among them, Antoni et al. found that right ventricular strain independently predicted mortality, reinfarction and rehospitalization for hear failure[91] in patients with AMI. Park et al. found comparable results for patients with inferior myocardial infarction. Some studies showed significant correlation of right ventricular STE derived strain with RVEF by CMR[72,92], but data on the prognostic value of this new method is still scarce.

The assessment of left ventricular strain parameters derived by STE found its way into the echocardiography guidelines of the American Society of Echocardiography and European Association of Cardiovascular Imaging[93,94]. In contrast, the assessment of right ventricular function using STE derived strain is not mentioned at all in the American guideline, whereas the European guideline refers to its possible prognostic value in just one sentence. As of now, the usefulness of an implementation into the routine echocardiographic assessment, especially in patients with acute myocardial infarction, remains unclear.

1.3 Hypothesis

Despite all medical advances, acute coronary syndrome, and with it, acute ST-segment elevation myocardial infarction, remains a major cause of death in the western civilization, to this day. Postinterventional echocardiographic evaluation of systolic and diastolic cardiac function is an important diagnostic tool for risk stratification in patients who suffered acute myocardial infarction. While there is a large body of evidence indicating the importance of the evaluation of left ventricular function, only in recent years has right ventricular function been recognized as an important predictor for short- and long-term outcomes in patients with acute myocardial infarction. There are a number of well-known parameters for the echocardiographic evaluation of right ventricular function. However, they all have their own limitations, due to the complex shape and physiology of the right ventricle. Speckle-tracking echocardiography derived right ventricular strain is a relatively new and possibly superior method for the quantitative assessment of cardiac chamber functionality. While it is commonly and effectively used for the assessment of the left ventricular systolic function, few studies investigated the value of STE for right ventricular strain evaluation.

The aim of this study is to assess the prognostic value of right ventricular strain and strain rate derived by speckle-tracking echocardiography in patients with acute ST-segment elevation myocardial infarction who underwent percutaneous coronary intervention.

2 Methods

2.1 Study design

This study is a cohort study in which we retrospectively analyzed echocardiographic data for their prognostic relevance. The data are taken from the echo archives of the Benjamin Franklin Hospital (CBF) in Berlin. Included were patients who were admitted in the emergency department at Benjamin Franklin Hospital, Berlin, with the diagnosis of acute transmural myocardial infarction (STEMI). After the admission diagnosis was established, all patients were treated according to the current European guidelines for the management of patients with acute myocardial infarction[37]. The culprit vessel was identified and revascularized using percutaneous coronary intervention and

thrombus extraction, if applicable. During the hospitalization period, all patients received transthoracic echocardiography (TTE) to assess the cardiac function after revascularization.

For this study, the archived echo images were analyzed retrospectively. Central to our study was the calculation of right ventricular strain and strain rate by speckle-tracking echocardiography. After a follow-up period of circa 2 years, the patients were reached by telephone and asked to answer a questionnaire, regarding a number of outcome parameters.

2.2 Cohort selection and description

We included patients who were admitted with a diagnosis STEMI and received primary PCI between January 2015 and January 2016. No restrictions were made regarding the age and gender of the subjects for inclusion in our study. All patients included in this study received a post-acquisition TTE during hospitalization. Patients with poor image quality in TTE were excluded. Also excluded were patients in whom the right ventricle was completely or partially cut off in apical four-chamber view, as this does not allow the calculation of right ventricular global longitudinal strain and strain rate. A total of 99 patients were included in the further data analysis (*Figure 4*).

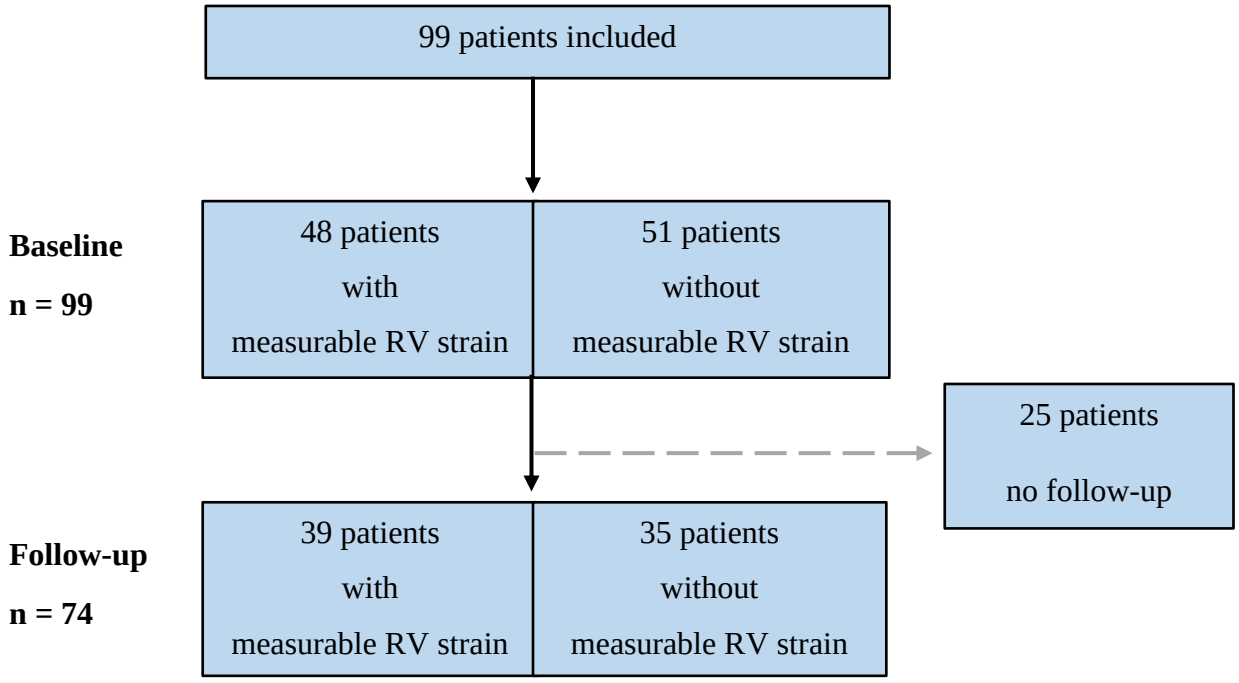


Figure 4 Flowchart of the study population.

99 patients were initially included in our study. 74 patients were reached for a follow-up questionnaire. STE derived right ventricular strain was measurable in 39 out of these patients.

Abbreviation index: STE = speckle-tracking echocardiography; RV = right ventricle

2.3 Course of treatment

At the initial presentation, a trained physician in the emergency department examined all patients. If acute myocardial infarction was suspected, continuous ECG-monitoring was established. The patients received a 12-lead electrocardiogram (ECG) and a blood sample for the measurement of cardiac biomarkers including troponine T, creatine kinase (CK) and myocardium-specific creatine kinase (CK-MB) was obtained. If there was evidence of significant ST-segment elevations in two contiguous leads or previously undetected left bundle branch block in the ECG, the patient was admitted for primary PCI according to the current guidelines. After visualizing the site of occlusion, balloon angioplasty was performed, followed by coronary stenting if feasible. All coronary interventions were performed at CBF by trained specialists.

2.4 Echocardiographic assessment

During their stay in hospital, all patients included in our study underwent two-dimensional transthoracic echocardiographic assessment (TTE) after primary PCI, to evaluate left and right ventricular function and regional wall motion. All echocardiograms were obtained by experienced investigators using the commercially available ultrasound diagnostic systems Vivid models E7 and E9 by General Electric Medical Systems, Horton, Norway. Three or more cardiac cycles were stored in cine loop format for offline evaluation. This routine TTE is referred to as baseline echocardiogram in the following text.

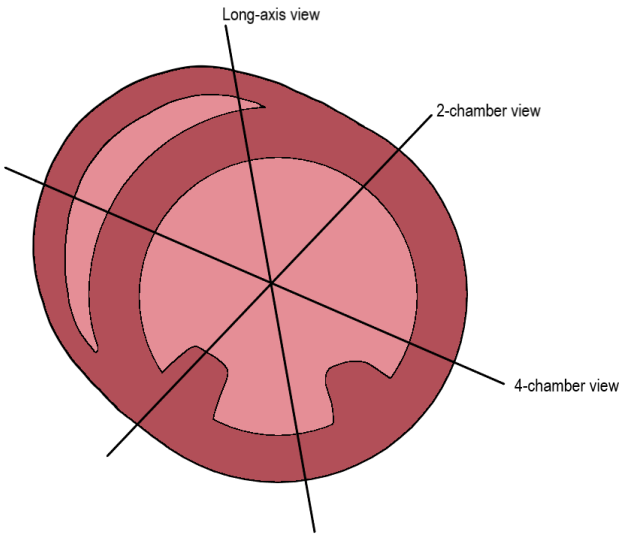
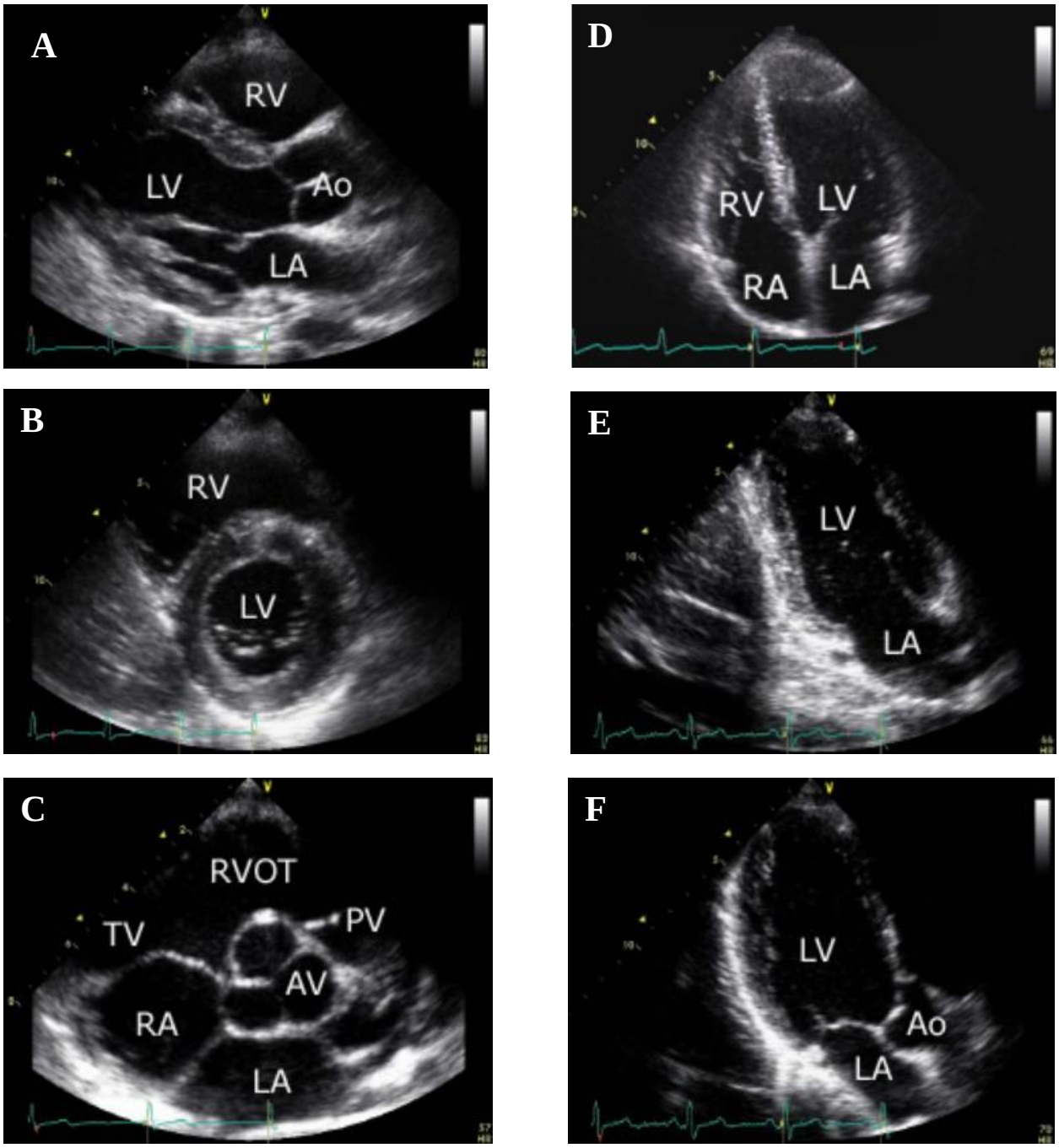


Figure 5 Different views in the apical window through a schematic axial cross-section.

The black lines indicate the orientation of the apical long-axis-, 2-chamber- and 4-chamber views, which can be achieved, by rotating the transducer in 60° intervals.

For TTE imaging of the cardiac structures, the following standard transthoracic views were obtained and archived (

Figure 6): For the *parasternal long axis view* the transducer was placed parasternal in the third or fourth left intercostal space, rotating it to present a bisection along the aortic and mitral valve and left ventricular apex. The *parasternal short axis views* were obtained by rotating the transducer 90° clockwise from the long axis view position. From there, the transducer was tilted to show the aortic valve-, mitral-, papillary- and apical planes.
For the apical window, the transducer was positioned above the apex of the heart. From there, *apical long-axis view as well as 2-, and 3-chamber view* can be obtained by rotating the transducer in 60° intervals according to *Figure 5.* The *Apical five-chamber plane* is obtained by positioning the transducer in four-chamber view and then tilting the transducer ventrally until the left-ventricular outflow tract is visible as the fifth chamber.



https://echobasics.de/tte.html, accessed on March 02, 2020

Figure 6 Standard planes in the transthoracic echocardiogram[95].

A) parasternal long axis view; B) parasternal short axis view, mitral valve plane; C) parasternal short axis view, aortic valve plane; D) apical four chamber view; E) apical two chamber view; F) apical three chamber view

Abbreviation index: LV = left ventricle; RV = right ventricle; Ao = aorta; LA = left atrium; RA = right atrium; RVOT = right ventricular outflow tract; TV = tricuspid valve; PV = pulmonary valve; AV = aortic valve

In addition to images of the standard planes, images of PW and CW Doppler measurements as well as color-coded tissue- and flow Doppler images were archived. Using these images, the following parameters were measured again for this study, in all subjects.

Left ventricular internal diameter end diastole (LVIDd) and left ventricular internal diameter end systole (LVIDs):

The internal diameter of the left ventricle was measured in the parasternal long axis view at the end of contraction and relaxation phase. The diameter was measured between the endocardial borders of the posterior and septal walls at the level of the opened mitral valve leaflets.

Interventricular septal end diastole (IVSd):

The interventricular septal was measured in the parasternal long axis view at the end of diastole. The measurement was performed from the left ventricular to the right ventricular septal endocardium between the medial and basal septal segments.

Left ventricular posterior wall end diastole (LVPWd):

In the parasternal long axis view as well, the posterior wall thickness was assessed between the medial and basal posterior wall segments at the end of diastole.

In the case of suboptimal image quality, the aforementioned dimensions were assessed by using M-Mode and placing a doppler signal on the level of the opened mitral valve leaflets in parasternal long axis view. This method was only used when the image quality did not allow exact identification of the endocardial borders in the regular view as it is more susceptible to angular displacements of the ultrasonic probe.

Left ventricular mass (LVM)

The left ventricular mass was calculated by inserting LVIDd, LVPWd and LVSd into the Devereux formula[96]:

$$\boldsymbol{LVM = 0.8\,x\,(1.04\,x\,[(LVIDd + LVPWd + LVSd)^3 - LVIDd^3]) + 0.6}$$

Diameter of the left ventricular outflow tract (LVOT):

In the parasternal long axis view, the largest diameter of the LVOT was measured between the aortic valve leaflets.

Left ventricular ejection fraction (LVEF):

The left ventricular ejection fraction is defined as the percentage of end diastolic left ventricular blood volume, ejected in each systole. It was calculated using the modified Simpson's rule (method of disks). The endocardial border was traced in both apical four- and two-chamber view at the end of systole as well as diastole. By dividing the left ventricular cavity into cross sectional disks, the software can then calculate the volume of each disc, by assuming an elliptical shape for each one. All volumes are added up, to get an estimate of both the end-diastolic and end-systolic left ventricular volume. The modified Simpson method uses a biplane approach by taking two planes into the calculation, to get a more precise estimate of the left ventricular ejection fraction.

Left atrial systolic volume (LAsV) and right atrial systolic volume (RAsV):

The volume of the left and right atrium was measured in the end-ventricular-systole using a biplane area-length method: The area was calculated in the apical two and four-chamber view by tracing the endocardial borders of the left and right atrium. The software also measures the length from a line across the mitral valve hinge points to the back wall of the atrium. An estimate of the volume is then created using these parameters.

Mitral inflow velocities (E-wave, A-wave and E/A-ratio):

The left ventricular diastolic filling velocities was measured by placing a pulsed-wave Doppler probe in the mitral valve aperture in apical four-chamber view. Two flow-curves can be seen in diastole: The early-diastolic E-wave is created through relaxation of the left-ventricular myocardium. In late-diastole the contraction of the atrial myocardium creates another smaller-flow curve (A-wave). Peak-flow was measured for both waves and a ratio between the two was created (E/A-ratio).

Mitral annular velocity (E'-wave, E/E'-ratio):

The velocity of the mitral annulus was measured by using tissue doppler imaging and placing a pulsed-wave doppler over the lateral and septal mitral annulus. Two waves can usually be seen, which correspond to the early-diastolic ventricular relaxation (E'-wave) and late-diastolic atrial contraction (A'-wave). Peak-velocity of the E'-wave was measured for the lateral and septal mitral annulus. An average between the two was created and a ratio between E-wave and the averaged E'-waves was calculated (E/E'-ratio).

Left ventricular outflow tract velocity time integral (LVOT-VTI):

By placing a PW-Doppler probe into the left ventricular outflow tract in apical five-chamber view, a curve can be displayed in systole representing the moving blood volume. The outline of this curve was then traced and the area under the curve was calculated, to get the velocity time integral (VTI) of the left ventricular outflow tract.

Tricuspid annular plane systolic excursion (TAPSE):

In apical four chamber view the M-Mode Doppler was placed into the lateral annulus of the mitral valve to display its time-dependent longitudinal movement through the cardiac cycle.

Mitral and tricuspid regurgitation (MR and TR):

Mitral and tricuspid regurgitation was identified using color flow Doppler in apical four-chamber view. When a regurgitation jet could be seen originating from either mitral or tricuspid orifice, the severity of valvular regurgitation was estimated by measuring the Vena contracta, according to the current recommendations of the European Society of Cardiology. The Vena contracta was measured in apical four-chamber and apical two-chamber view with an adapted Nyquist limit of 40-70 cm/s. With a vena contracta diameter <3 mm, MR was considered mild, <7 intermediate and ≥7 severe[97].

Estimated systolic pulmonary artery pressure (PASP):

The systolic pulmonary artery pressure was estimated by assessing the peak velocity of the tricuspid regurgitation jet in systole (Vmax). This is done by placing a continuous wave doppler probe between the tricuspid valve leaflets in apical four-chamber view. By inserting Vmax into the formula below, the right ventricular systolic pressure was calculated. Then an estimated right atrial pressure of 5 mmHg was added to calculate PASP[70].

$$PASP = (Vmax^2 \times 4) + 5\ mmHg$$

Left ventricular global longitudinal strain (LV-GLS):

We measured left ventricular strain and strain rate at an offline workstation using the built in Q-Analysis 2DStrain tool in EchoPAC software version 113 by General Electric Healthcare, Horten, Norway. All measurements were taken in apical four-, three- and two-chamber view, in a single cardiac cycle, with at least 60 frames per second. To get a reference point for the cardiac cycle, the software uses the time of aortic valve closure. If the software was unable to automatically find the frame, it was manually selected by the observer. The region of interest (ROI) was placed manually in end-systole, by tracing the endocardial borders of the left ventricle. In addition to the built-in tracking control, the observer also verified optimal tracking of the ROI. Peak systolic strain values were used in this study to assess the longitudinal strain of all six ventricle segments visible in apical four-, three, and two-chamber view. The values of the segments were averaged to calculate the global longitudinal strain of the left ventricle.

Right ventricular global longitudinal strain (RV-GLS) and free wall strain (RV-FWS):

The right ventricular global longitudinal strain and free wall strain were both measured in apical four-chamber view. At the time of this study, the software EchoPAC does not provide a dedicated tool to analyze right ventricular 2D strain by speckle tracking echocardiography. For this reason, the algorithm for the left ventricular strain measurement was used. Minor changes have been made to the default configuration to enable the most accurate tracking possible. First, the region of interest was mirrored vertically so that its septal segment labeling corresponded to the ventricular septum and the lateral segments were placed over the free wall of the right ventricle. Second, the width of the ROI was adjusted to fit the narrower wall of the right ventricle. In addition, the endocardial algorithm was used for right ventricular strain measurement. Besides the automatic

quality control by the software, the tracking of each segment was also checked by the examiner. Particular attention was paid to correct tracking of the basal lateral segment, as this is where tracking problems occurred most frequently (*Figure 7*).

For the measurement of RV-GLS the mean value for all six segments was calculated, while for RV-FWS we calculated the mean of only the three lateral segments representing the right ventricular lateral wall. Because of the shortening of muscle fibers during systole, peak systolic strain values are preceded by a negative sign, where more negative values reflect a greater deformation (contraction) of the myocardium and zero means no deformation at all. This means that higher values are to be interpreted as worse systolic function.

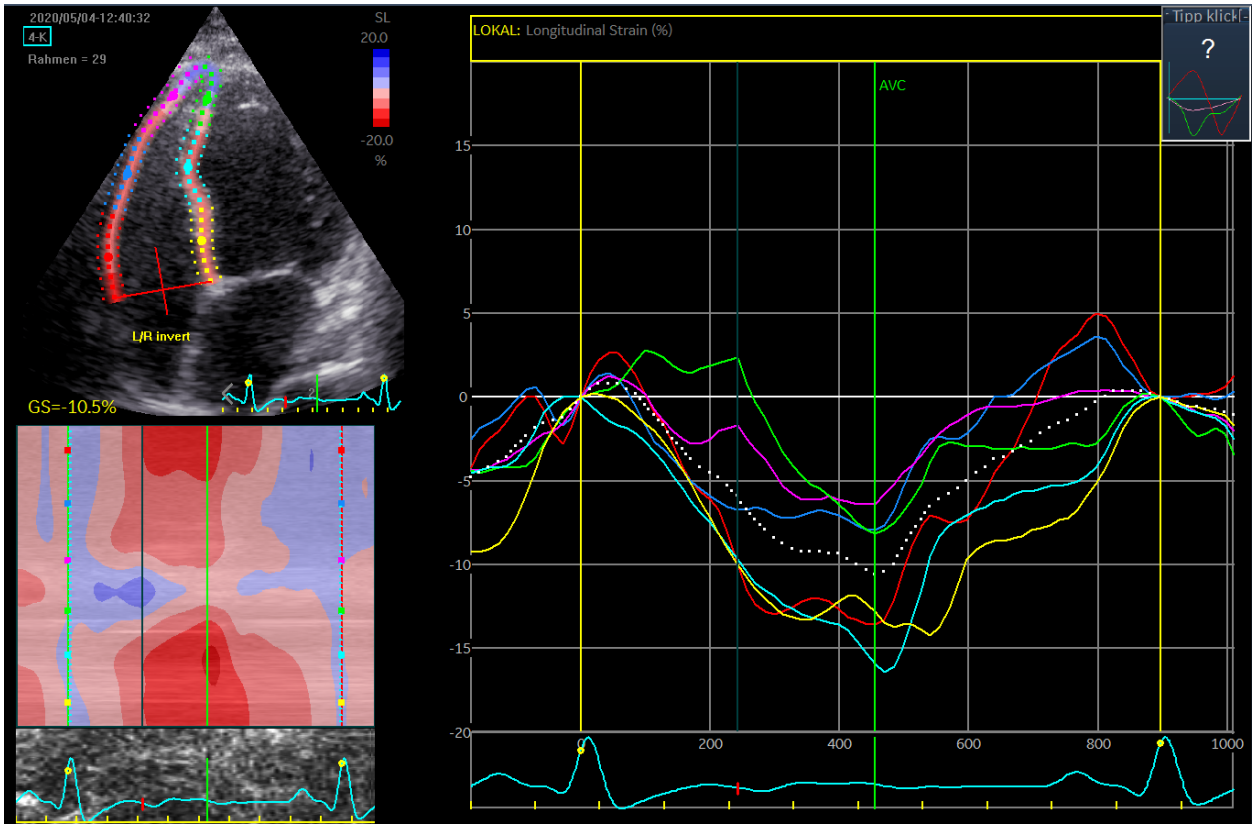


Figure 7 Right ventricular strain and strain rate measurements in EchoPAC Version 203.

The region of interest (ROI) is placed manually in end-systole along the right ventricular myocardial wall. In each of the six segments the software tracks the speckle displacement throughout systole and outputs a time graph. The peak systolic strain is reported as a negative value for each segment. Global longitudinal right ventricular strain is calculated by averaging all six segments while right ventricular free wall strain is calculated by averaging only the three lateral segments.

Right ventricular peak systolic strain rate (RV-SSR):

For the measurement of the right ventricular strain rate the same precautions were taken as for the measurement of the right ventricular strain. In addition to the percentage spatial deformation, the software also outputs its first derivative, i.e. the rate of deformation. For further data analysis, the peak velocity reached in systole was used. Since Strain is output as a negative value, Strain rate is also a negative velocity.

Ideally, right ventricular strain and strain rate measured by STE should be assessed in an apical four-chamber view, which is optimized for the right ventricle. For this, starting from the regular four-chamber view, the transducer is tilted medially until the right ventricle is visible in the center of the image. Only regular four-chamber view images were available for this study. Due to the fact that in some of the archived echo images in the apical four-chamber view the free wall of the right ventricle was cut off or covered by a rib due to sound cancellation, it was not possible to evaluate the strain and strain rate in some patients. In total, right ventricular global longitudinal strain was measurable in 48 patients.

2.5 Follow-up

After a follow-up phase of 25 months on average, the patients were contacted again by phone, and asked to participate in a survey regarding several outcome parameters. Out of the 99 patients initially included in this study, 74 were followed up by this telephone questionnaire. The following outcome parameters were obtained from these telephone interviews: 1. number of heart related hospitalizations during the follow-up period; 2. cause of these hospitalizations; 3. number of PCIs performed after the initial hospitalization; 4. number of myocardial infarctions after the initial hospitalization; 5. number of strokes during the follow-up period; 6. NYHA Classification; 7. LVEF, measured on an echocardiogram performed during the follow-up period at our hospital, and 8. death by any cause during follow-up. Furthermore, all patients were asked to rate their subjective quality of life at the time of the survey, compared to the months before the initial myocardial infarction on a scale from 1 = considerably worse to 5 = considerably better. Initial RV-GLS data was available in 39 of the patients we interviewed for a follow-up.

2.6 Statistical Analysis

For statistical data analysis, we used IBM SPSS Statistics version 24.0.0.0 64 bit for Windows. A p-value below 0.05 was considered statistically significant for all statistical analysis. All variables were tested for normal distribution using the Shapiro-Wilk-Test. Normally distributed variables are expressed as means ± 1 standard deviation, while non-normally distributed variables are expressed as median followed by the interquartile range in brackets. The Chi-square test was used to compare frequencies. In the case of violation of the requirements of the Chi^2-Test, the Fisher exact Test was used instead. The t-test for independent samples was used for comparing means in parametric data. For non-parametric data, we used the Mann-Whitney-U-Test. Correlations between continuous variables were analyzed using the Pearson correlation coefficient. Ordinal and nominal variables, like the number of rehospitalizations during follow-up or all-cause mortality, were analyzed for correlations using Spearman's correlation coefficient.

First, the subgroup of patients with measurable strain parameters (n = 48) was compared with the rest of the cohort to determine whether the two groups differed significantly in their baseline characteristics.

The whole cohort was then examined for correlations of individual measurements of the baseline echocardiogram. Especially RV-GLS, RV-FWS and RV-SSR were analyzed for correlations with TAPSE but also with the left ventricular function parameters LVEF and LV-GLS. Using the cut-off values for LVEF, TAPSE and pulmonary artery pressure known from the literature, subgroup analyses were performed to see if the strain values in these groups differed significantly. We also formed subgroups according to the respective occluded coronary artery. Within these groups the parameters LVEF, LV-GLS, TAPSE, RV-GLS, RV-FWS and RV-SSR were examined for significant differences.

In the next step, subgroups were built regarding the outcome parameters death, rehospitalization due to any cause, due to acute decompensated heart insufficiency and due to acute coronary syndrome, NYHA stage and impaired LVEF during follow-up echocardiogram. These subgroups were compared for differences in any of the left and right ventricular function parameters.

Since, on the one hand, no generally valid cut-off values for right ventricular strain and strain rate have been established so far and, on the other hand, the algorithms for calculation differ between software manufacturers, separate cut-off values were defined for this study. For RV-GLS and RV-FWS cut-offs were defined, using Receiver Operator Characteristics Curves. Our primary endpoint, two-year mortality was chosen as the reference for selecting a cut-off. The optimal cut-

off for RV-GLS was chosen at -12,99 with a sensitivity of 0,857 and 1-specificity of 0,094 and then rounded to -13. For RV-FWS we found an optimal cut-off at -18,85 with a sensitivity of 0,857 and a 1-specificity of 0,156, which was then rounded to -19. For both RV-GLS and RV-FWS values higher or similar to the cut-offs were considered abnormal in all subsequent tests.

In consensus with the American Society of Echocardiography and the European Association of Cardiovascular Imaging, a TAPSE of 17 mm or below was considered abnormal for our statistical analysis[98].

The cut-off value for LV-GLS we used is derived from the JUSTICE study, a study with 333 healthy volunteers, in which left ventricular global longitudinal strain measurements were performed with Vivid E7 and E9 devices and GE's EchoPAC software. The average LV-GLS of these healthy subjects was -21,3[99]. We added twice the standard deviation of 2,1 to get a cut-off for LV-GLS at -17, rounded, that excludes 95% of the healthy population. It should be noted that the European Association of Cardiovascular Imaging (EACVI) currently recommends a cut-off of -20. However, the consensus document points out the heterogeneity of the standard values documented so far[94].

Table 1 Cut-off values used for the statistical analysis of echocardiographic RV parameters.
For TAPSE we used a cut-off at 17 mm, and for LV-GLS a cut-off of -17 based on the JUSTICE study. The cut-offs for RV-GLS and RV-FWS were chosen based on ROC curves.

Parameter	Cut-off
TAPSE	<= 17 mm
RV-GLS	>= -13
RV-FWS	>= -19
LVEF	< 50%
LV-GLS	> -17

Abbreviation index: TAPSE = tricuspid annular plane systolic excursion; RV-GLS = right ventricular global longitudinal strain; RV-FWS = right ventricular free wall strain; LVEF = left ventricular ejection fraction; LV-GLS = left ventricular global longitudinal strain

Multivariate analysis was used to identify independent predictors for two-year all-cause mortality and perceived heart related health status after 2-years. Due to the small number of cases, especially in deceased patients, the Firth penalized logistic regression model[100] was used instead of a conventional logistic regression to calculate odds ratios for the predictors Age, Sex, LVEF, TAPSE and RV-GLS. The same model was used to estimate the odds ratios for exceeding the previously defined cut-off values for LVEF, TAPSE and RV-GLS.

3 Results

3.1 Population characteristics

Out of the 99 patients included in this study, 71,7% were male. The average age was 60 (± 9,6) years for men and 71 (± 13,6) years for women. PCI was conducted in the right coronary artery in 40,4% of the cases. 45,5% of the myocardial infarctions were assigned each to the ICD-categories anterior (I21.0) and posterior (I21.1) infarction. A Killip score of 1 was assigned most often, with 93,9% of the patients being scored 2 or lower. The median of the measured troponin T and creatine kinase peak values was 556 ng/l and 1679 U/l, respectively. The prevalence of major cardiovascular risk factors at the time of admission was as followed: 88,9% of the patients had elevated hyperlipidaemia, 78,8% had arterial hypertonia, 50,5% reported regular cigarette smoking or smoking history. 25,3% of the patients were diagnosed with diabetes mellitus and 17,2% had positive family history for cardiovascular diseases. The prevalence of previously diagnosed coronary artery disease was 17,2% in the study population, as was the prevalence of previously diagnosed atrial fibrillation. 14,1% had a pulmonary condition at the time of admission and a total of 9,1% of the patients were diagnosed with chronic kidney disease Stage 1 to 3, prior to the admission. 3% had an implantable cardioverter-defibrillator or cardiac pacemaker at the time of infarction.

3.2 Baseline echocardiogram

The echocardiographic assessment was conducted on average for 3,6 days after the PCI. The mean LVEF was 53,7% (± 10,34%), Mean LV-GLS was -12,90 (± 4,72). The mean for TAPSE was 22,64 mm (± 4,23 mm) and for RV-GLS and RV-FWS the mean was -18,09 (± 6,08) and -21,95 (± 7,99) respectively. The mean right ventricular peak systolic strain rate (RV-SSR) was -1,18/s (± 0,31) in the cohort. The mean estimated systolic pulmonary artery pressure was 30,38 (± 10,16) mmHg. Mitral or tricuspid regurgitation was seen in more than 50% of cases in this cohort (*Table 2*).

Additional parameters from the baseline echocardiogram can be found in the addendum (*Table 10*).

Table 2 Baseline characteristics of the study population.
The table shows the age and gender distribution as well as the percentage frequencies of different baseline parameters. In brackets is the standard deviation for mean values and 1st and 3rd quartiles for medians.

			All patients n = 99	
Gender in %	Male Female		71,7 28,3	
Age in years as mean (± SD)	Male Female		60 (± 9,6) 71 (± 13,6)	
ICD-Code in %	I21.0 (anterior) I21.1 (posterior) I21.2 (other) I21.3 (undefined)		45,5 45,5 7 2	
Cardiovascular Risk Factors in %	Dyslipidaemia Arterial hypertension Nicotine abuse Diabetes mellitus Positive family history		88,9 78,8 50,5 25,3 17,2	
Killip Classification in %	I II III IV		77,8 16,2 3 3	
Premorbidities in %	Coronary artery disease Atrial fibrillation ICD/pacemaker Pulmonary disease Chronic Kidney disease	 St. 1 St. 2 St. 3	17,2 17,2 3 14,1 2 2 5,1	
Biomarker peaks as median (1st and 3rd quartiles)	Troponin T (hs) in ng/l Creatine kinase in U/l CK-MB in U/l		556 1679 176	(51,5; 2386,0) (561; 3127) (65; 310)
Echocardiographic assessment as mean (± SD)	LVEF in % TAPSE in mm LV-GLS RV-GLS RV-FWS RV-SSR in units/s PASP in mmHg MR in % TR in % 	 Grade I Grade II Grade III Grade I Grade II Grade III	53,73 22,64 -12,90 -18,09 -21,95 -1,18 30,38 55,6 13,1 3,0 55,6 3,0 5,1	(± 10,34) [n = 99] (± 4,23) [n = 95] (± 4,72) [n = 86] (± 6,08) [n = 48] (± 7,99) [n = 48] (± 0,31) [n = 48] (± 10,16) [n = 64]

Abbreviation index: ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; LV-GLS = left ventricular global longitudinal strain; RV-GLS = right ventricular global longitudinal strain; RV-FWS = right ventricular free wall strain; RV-SSR = right ventricular peak systolic strain rate; PASP = estimated systolic pulmonary artery pressure; MR = mitral regurgitation, TR = tricuspid regurgitation; SD = standard deviation

Table 3 Comparability of the subgroup with measurable RV-GLS.

In this table, the subgroup of patients with measurable strain data (n = 48) is compared with the rest of the cohort. There are no significant differences in baseline characteristics between the two groups, suggesting that both groups are a sample from the same population.

			Strain data available (n = 48)	**Strain data missing (n = 51)**	**Significance**
Gender in %	Male		72,9	70,6	p = 0,797
	Female		27,1	29,4	
Age in years as mean (± SD)			62,14 (± 11,68)	64,37 (± 12,12)	p = 0,355
ICD-Code in %	I21.0 (anterior)		56,3	35,3	p = 0,087
	I21.1 (posterior)		33,3	56,9	
	I21.2 (other)		8,3	5,9	
	I21.3 (undefined)		2,1	2,0	
Cardiovascular Risk Factors in %	Dyslipidaemia		85,4	92,2	p = 0,286
	Arterial hypertension		72,9	84,3	p = 0,166
	Nicotine abuse		60,4	41,2	p = 0,056
	Diabetes mellitus		25,0	25,5	p = 0,955
	Postitive family history		16,7	17,6	p = 0,897
Killip Classification in %	I		85,4	70,6	p = 0,157
	II		8,3	23,5	
	III		4,2	2,0	
	IV		2,1	3,9	
Premorbidities in %	Coronary artery disease		16,7	17,6	p = 0,897
	Atrial fibrillation		16,7	17,6	p = 0,897
	ICD/pacemaker		2,1	3,9	p = 0,594
	Pulmonary disease		8,3	19,6	p = 0,108
	Chronic kidney disease	St. 1	0	3,9	p = 0,838
		St. 2	2,1	2,0	
		St. 3	4,3	5,9	
Biomarker peaks as median (1st and 3rd quartiles)	Troponin T in ng/l		556 (89,0; 2517)	529,50 (28; 2321)	p = 0,599
	Creatine kinase in U/l		1992 (503,25; 4123,75)	1231 (637; 3001)	p = 0,334
	CK-MB in U/l		191 (79,5; 376,25)	151 (63; 276)	p = 0,155
Echocardiographic assessment as mean (± SD)	LVEF in %		52,65 (± 10,42)	54,75 (± 10,27)	p = 0,315
	TAPSE in mm		22,02 (± 4,55)	23,20 (± 3,88)	p = 0,176
	LV-GLS		-12,12 (± 4,80)	-13,69 (± 4,56)	p = 0,123
	RV-GLS		-18,09 (± 6,08)	no data	no data
	RV-FWS		-21,95 (± 7,99)	no data	no data
	RV-SSR in units/s		-1,18 (± 0,31)	no data	no data
	PASP in mmHg		30,18 (± 10,07)	30,61 (± 10,44)	p = 0,867
	MR in %	Grade I	60,4	51,0	p = 0,746
		Grade II	10,4	15,7	
		Grade III	2,1	3,9	
	TR in %	Grade I	58,3	52,9	p = 0,822
		Grade II	4,2	2,0	
		Grade III	4,2	5,9	

Abbreviation index: ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; LV-GLS = left ventricular global longitudinal strain; RV-GLS = right ventricular global longitudinal strain; RV-FWS = right ventricular free wall strain; RV-SSR = right ventricular peak systolic strain rate; PASP = estimated systolic pulmonary artery pressure; MR = mitral regurgitation, TR = tricuspid regurgitation; SD = standard deviation

STE derived strain measurements were available in 48 patients. There were no significant differences in baseline characteristics when comparing the subset of patients with available strain data with the rest of the cohort. The greatest difference between the two groups was in relation to nicotine abuse (60,4% vs. 41,2%), although the difference was not significant (p = 0,056) (*Table 3*).

3.3 Interdependence of right and left ventricular function

RV-GLS and RV-FWS showed high correlation (p < 0,001; r = 0,857). There was a significant correlation between TAPSE and RV-GLS (p = 0,015, r = -0,361) as well as TAPSE and RV-FWS (p = 0,012, r = -0,370). RV strain measurements also correlated with the two parameters LVEF and LV-GLS, demonstrating worse right ventricular systolic function in the case of left ventricular systolic impairment. The correlation between RV-GLS and LVEF was significant (p = 0,001) with a Pearson's r of -0,478, as was the correlation of RV-GLS and LV-GLS (p = < 0,001, r = 0,543). The correlation of RV-FWS with LVEF (p = 0,020, r = -0,334) and LV-GLS (p = 0,006, r = 0,414) was also significant but weaker (*Figure 8*). RV-SSR correlated with right ventricular global longitudinal and free wall strain, but showed no correlation with any other echocardiographic parameter at baseline.

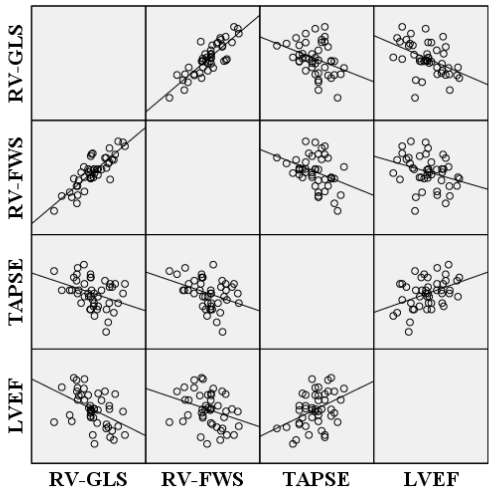


Figure 8 Scatterplot-Matrix of right and left ventricular systolic function parameters.

The correlation of the two established parameters LVEF and TAPSE with the strain measurements of the right ventricle can be seen. Due to the fact that a higher myocardial deformation and therefore better systolic function is represented as a more negative strain value, the TAPSE and LVEF are negatively correlated to the strain measurements.

Abbreviation index: RV-GLS = right ventricular global systolic function; RV-FWS = right ventricular free wall strain; TAPSE = tricuspid annular plane systolic excursion; LVEF = left ventricular ejection fraction

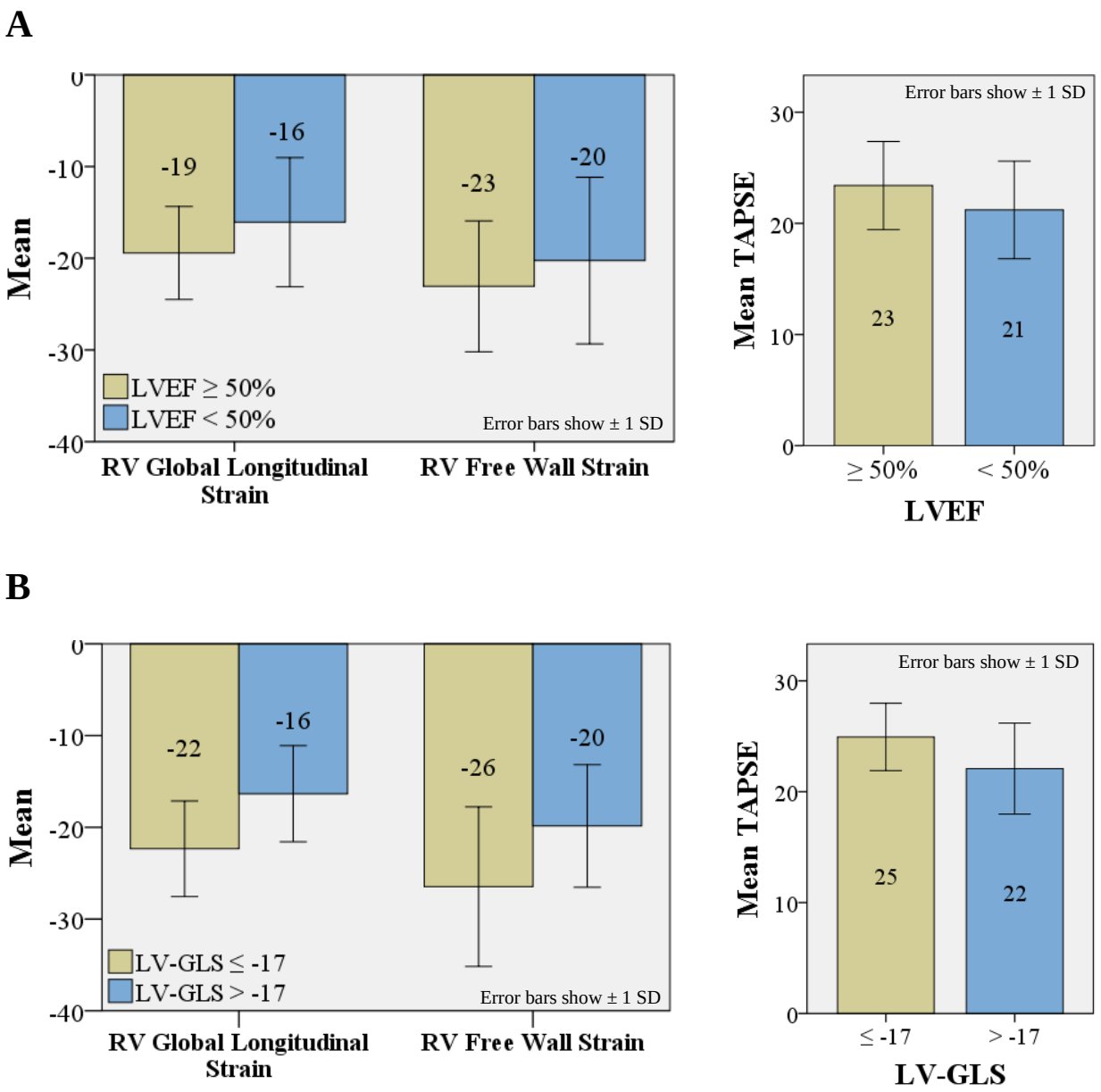


Figure 9 RV-GLS, RV-FWS and TAPSE in patients with normal vs. impaired LVEF (A) and LV-GLS (B).

A) TAPSE was significantly lower in patients with an LVEF below 50% (21,21 mm ± 4,39 mm) compared to patients with normal LVEF (23,40 mm ± 3,97 mm). RVGLS- and RV-FWS were higher in patients with impaired LVEF, however the difference was not statistically significant. B) Patients with impaired left ventricular global longitudinal strain had significantly lower TAPSE (22,09 mm ± 4,10 mm vs. 24,94 mm ± 3,04 mm), significantly higher RV-GLS (-16,35 ± 5,24 vs. -22,33 ± 5,21) and significantly higher RV-FWS (-19,85 ± 6,68 vs. -26,48 ± 8,70).

Abbreviation index: LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion, LV-GLS = left ventricular global longitudinal strain

68,7% of the patients in this study had an impaired LV-GLS of above -17. Among them, the right ventricular global longitudinal and free wall strain were also significantly higher and TAPSE was significantly lower, compared to patients with normal LV-GLS. RV-GLS was on average at -22,33 ± 5,21 in the latter, compared to -16,35 ± 5,24 in the subgroup with impaired left ventricular strain (p = 0,006). RV-FWS in patients with normal LV-GLS was -26,48 ± 8,70, versus -19,85 ± 6,68 (p = 0,021), and TAPSE averaged at 24,94 mm ± 3,04 mm versus 22,09 mm ± 4,10 mm (p = 0,007). Again, there was no significant difference in right ventricular strain rate when comparing patients with normal and impaired LV-GLS (1,23/s ± 0,26/s vs. 1,14/s ± 0,33/s, p = 0,474) (*Figure 9B*).

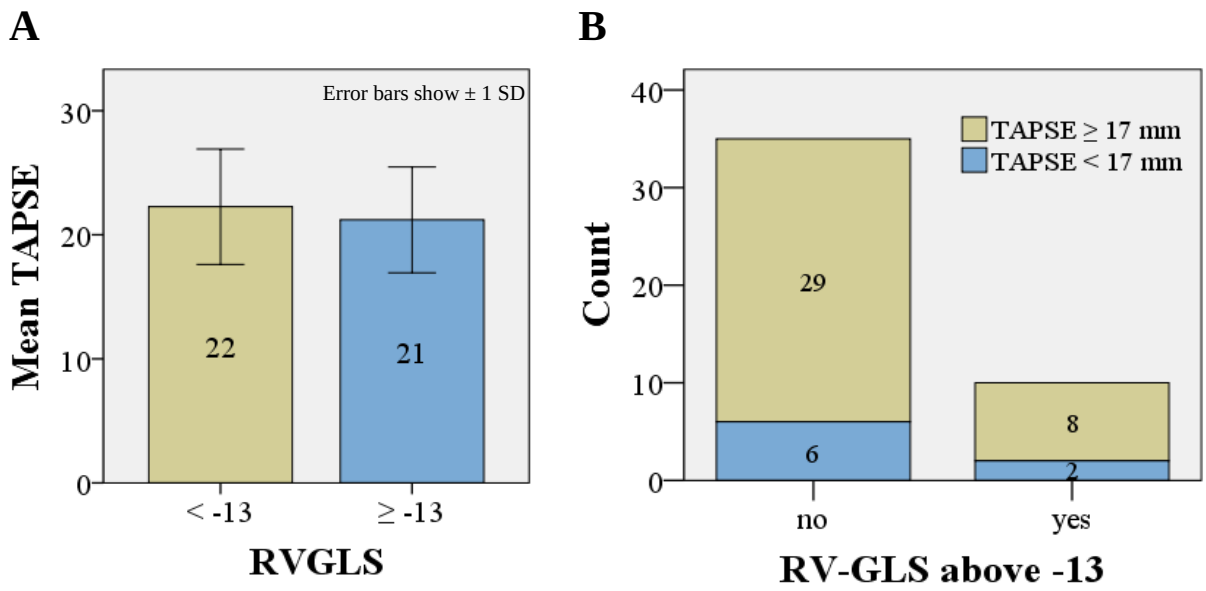


Figure 10 TAPSE in patients with normal and impaired RV-GLS.

(A) There is no significant difference in TAPSE between the patients with a right ventricular strain above and below a cut-off of -13. (B) TAPSE is normal in 80% of the patients with impaired RV strain.

Abbreviation index: TAPSE = tricuspid annular plane systolic excursion; RV-GLS = right ventricular global longitudinal strain

Interestingly, we saw no difference in TAPSE, when comparing patients with an RV-GLS above and below our cut-off of -13 (21,20 mm ± 4,26 mm vs. 22,26 mm ± 4,66 mm, p = 0,523). Only 20% of patients with an impaired RV-GLS, had a TAPSE below 17 mm (*Figure 10*).

The estimated systolic pulmonary artery pressure was higher on average in patients with impaired RV-GLS (38,94 mmHg ± 14,31 mmHg vs. 28,37 mmHg ± 8,16 mmHg), although the difference was not statistically significant (p = 0,197).

3.4 LCA vs. RCA

Between patients with occlusion of the left vs. right coronary artery there were no significant differences in right ventricular function parameters TAPSE, RV-GLS and RV-FWS, however the left ventricular function varied significantly in the two groups. LVEF was on average 6,67 percent lower in patients with occlusion of the LCA compared to patients with occlusion of the RCA (p = 0,001). LV-GLS was on average 3,02 points higher in these patients (p = 0,003) (*Table 4*).

Table 4. Functional parameters depending on the culprit vessel.

LVEF and LV-GLS are significantly different in patients with LCA/LCX occlusion compared to RCA occlusion. No differences can be seen regarding the right ventricular functional parameters TAPSE; RV-GLS and RV-FWS.

	LCA	**RCA**	**Significance**
LVEF in % (n = 99)	51,04 (± 10,46)	57,71 (± 8,88)	p = 0,001
LV-GLS (n = 86)	-11,75 (± 4,39)	-14,76 (± 4,71)	p = 0,003
TAPSE in mm (n = 95)	22,43 (± 4,07)	22,95 (± 4,48)	p = 0,558
RV-GLS (n = 48)	-18,33 (± 6,41)	-17,52 (± 5,38)	p = 0,680
RV-FWS (n = 48)	-22,81 (± 8,13)	-19,86 (± 7,52)	p = 0,248
RV-SSR in units/S (n = 48)	-1,22 (± 0,32)	-1,09 (± 0,30)	p = 0,210

Abbreviation index: LVEF = left ventricular ejection fraction; LV-GLS = left ventricular global longitudinal strain; TAPSE = tricuspid annular plane systolic excursion; RV-GLS = right ventricular global longitudinal strain, RV-FWS = right ventricular free wall strain; RV-SSR = right ventricular peak systolic strain rate; LCA = left coronary artery; RCA = right coronary artery

3.5 Two-year follow-up

Out of the 74 patients we interviewed, seven died (9.5%) in the follow-up period. Right ventricular strain was significantly higher in this group (-10.19 ± 2.89), compared to the patients who survived (-20.27 ± 5.32, p < 0.001). Unsurprisingly, RV-FWS showed similar results, with a mean of -15,30 ± 5,78 in the patients who died vs. -24,48 (± 7,70) in the patients who survived (p = 0,004). As in the previous tests, there was no significant difference in strain rate between the survivors and the patients who died (-1,24/s ± 0,28/s vs. -1,05/s ± 0,40/s, p = 0,268). TAPSE was lower in patients who died in the follow-up period, although the difference was not significant (19.00 ± 6.84 mm vs. 23.34 ± 3.99 mm, p = 0,183) (*Table 5*). TAPSE and right ventricular strain parameters did not differ significantly between patients who had been hospitalized for any heart

related cause during the follow-up period. There was however a significantly higher initial RV-GLS in patients who had one or more hospitalization due to acute decompensated heart failure (n = 3) in the follo-up period (-10,28 ± 3,53 vs. -20,33 ± 5,46, p = 0,021). TAPSE was lower in these patients (19,00 mm ±8,49 mm vs. 23,38 mm ± 4,19 mm) however the difference was not statistically significant (p = 0,598). With regard to acute coronary syndromes that occurred after the initial myocardial infarction, we could not detect any differences in the initial echocardiogram. There was a trend towards lower initial TAPSE measurements, in patients with higher reported NYHA stage in the follow-up interview (*Figure 11*). Patients reporting a NYHA class of II or above in the interview had significantly lower TAPSE in the initial echocardiogram (21,91 ± 3,60 vs. 24,38 ± 4,14, p = 0,022). RV-GLS was higher in patient reporting NYHA II or above (-19,11 ± 4,63 vs. -21,30 ± 5,44) though the difference was not significant. TAPSE did not correlate with any of the outcome parameters examined in the follow-up interview except for NYHA Classification.

Table 5 Comparison of the baseline characteristics in the survivors and deceased.

			Survivors	Deceased	Significance
Gender in %	Male		68,7	57,1	p = 0,675
	Female		31,3	42,9	
Age in years as mean (± SD)			63,05 (± 11,12)	75,40 (± 8,25)	p = 0,006*
ICD-Code in %	I21.0 (anterior)		41,8	57,1	p = 0,441
	I21.1 (posterior)		49,2	28,6	
	I21.2 (other)		7,5	14,3	
	I21.3 (undefined)		1,5	0	
Cardiovascular Risk Factors in %	Dyslipidaemia		94,0	71,4	p = 0,096
	Arterial hypertension		79,1	71,4	p = 0,640
	Nicotine abuse		52,2	28,6	p = 0,430
	Diabetes mellitus		25,4	28,6	p = 1,000
	Postitive family history		20,9	0	p = 0,334
Killip Classification in %	I		85,1	57,1	p = 0,028*
	II		13,4	14,3	
	III		1,5	14,3	
	IV		0	14,3	
Premorbidities in %	Coronary artery disease		16,4	42,9	p = 0,120
	Atrial fibrillation		14,9	14,3	p = 1,000
	ICD/pacemaker		1,4	14,3	p = 0,181
	Pulmonary disease		13,4	57,1	p = 0,016*
	Chronic kidney disease	St. 1	1,5	1,4	p = 0,414
		St. 2	2,7	2,7	
		St. 3	3,0	4,1	
Biomarker peaks as median (1st and 3rd quartiles)	Troponin T in ng/l		351 (50,25; 1578,50)	2889 (167; 7514)	p = 0,033*
	Creatine kinase in U/l		1261 (492; 3090)	2359 (317; 4721)	p = 0,536
	CK-MB in U/l		152 (63; 276)	295 ; 556)	p = 0,341
Echocardiographic assessment as mean (± SD)	LVEF in %		56,31 (± 10,33)	42,22 (± 9,65)	p = 0,001**
	TAPSE in mm		23,34 (± 3,99)	19,00 (± 6,84)	p = 0,183
	LV-GLS		-13,97 (± 4,95)	-7,72 (± 2,71)	p = 0,004*
	RV-GLS		-20,27 (± 5,32)	-10,19 (± 2,89)	p < 0,001**
	RV-FWS		-24,48 (± 7,70)	-15,30 (± 5,78)	p = 0,004*
	RV-SSR in units/s		-1,24 (± 0,28)	-1,05 (± 0,40)	p = 0,268
	PASP in mmHg		29,35 (± 9,28)	34,49 (± 13,21)	p = 0,394
	MR in %	Grade I	55,2	42,9	p = 0,136
		Grade II	13,4	28,6	
		Grade III	1,5	14,3	
	TR in %	Grade I	59,7	42,9	p = 0,013*
		Grade II	1,5	28,6	
		Grade III	3,0	14,3	

Abbreviation index: ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; LV-GLS = left ventricular global longitudinal strain; RV-GLS = right ventricular global longitudinal strain; RV-FWS = right ventricular free wall strain; RV-SSR = right ventricular peak systolic strain rate; PASP = estimated systolic pulmonary artery pressure; MR = mitral regurgitation, TR = tricuspid regurgitation; SD = standard deviation

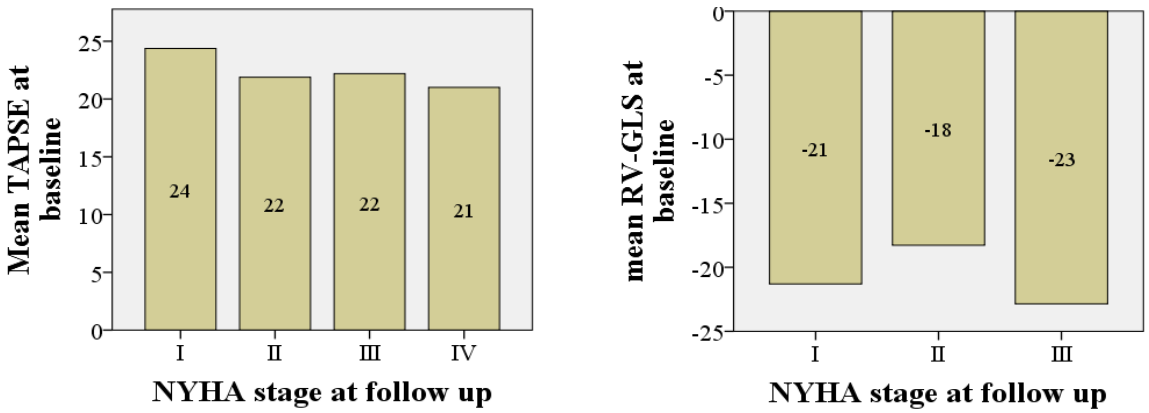


Figure 11 Initial right ventricular function in the echocardiogram in relation to the NYHA stages reported after follow-up.

Patient who reported more exertional dyspnea in the follow-up interview also had lower TAPSE levels in the initial echocardiogram. The difference in mean TAPSE was significant when comparing patients in NYHA stage I to NYHA stages II to IV. RV-GLS did not show a similar trend.

Abbreviation index: TAPSE = tricuspid annular plane systolic excursion; RV-GLS = right ventricular global longitudinal strain; NYHA = New York Heart Association stage

3.6 Correlation of RV strain with different outcomes

For RV-GLS, we saw significant correlations with death during follow-up ($p < 0{,}001$, $r = 0{,}606$), as well as with LVEF measured in a later echocardiographic assessment ($p = 0{,}013$, $r = -0{,}646$). RV-FWS also showed a significant correlation with death during follow-up ($p = 0{,}06$, $r = 0{,}433$) and follow-up LVEF ($p = 0{,}03$, $r = -0{,}580$), though with a lower coefficient, indicating a weaker correlation (*Figure 12*).

Both right ventricular strain measurements did not correlate with reported NYHA stages at follow-up. The peak systolic strain rate of the right ventricle did not correlate with any of the outcome parameters.

The baseline LVEF showed significant correlations with death during follow-up ($p = 0{,}001$, $r = -0{,}363$) and LVEF obtained in a follow up echocardiogram ($p < 0{,}001$, $r = 0{,}666$). Similar correlations could be seen between LV-GLS and death during follow-up ($p = 0{,}002$, $r = 0{,}378$), as well as follow-up LVEF ($p < 0{,}001$, $r = -0{,}631$).

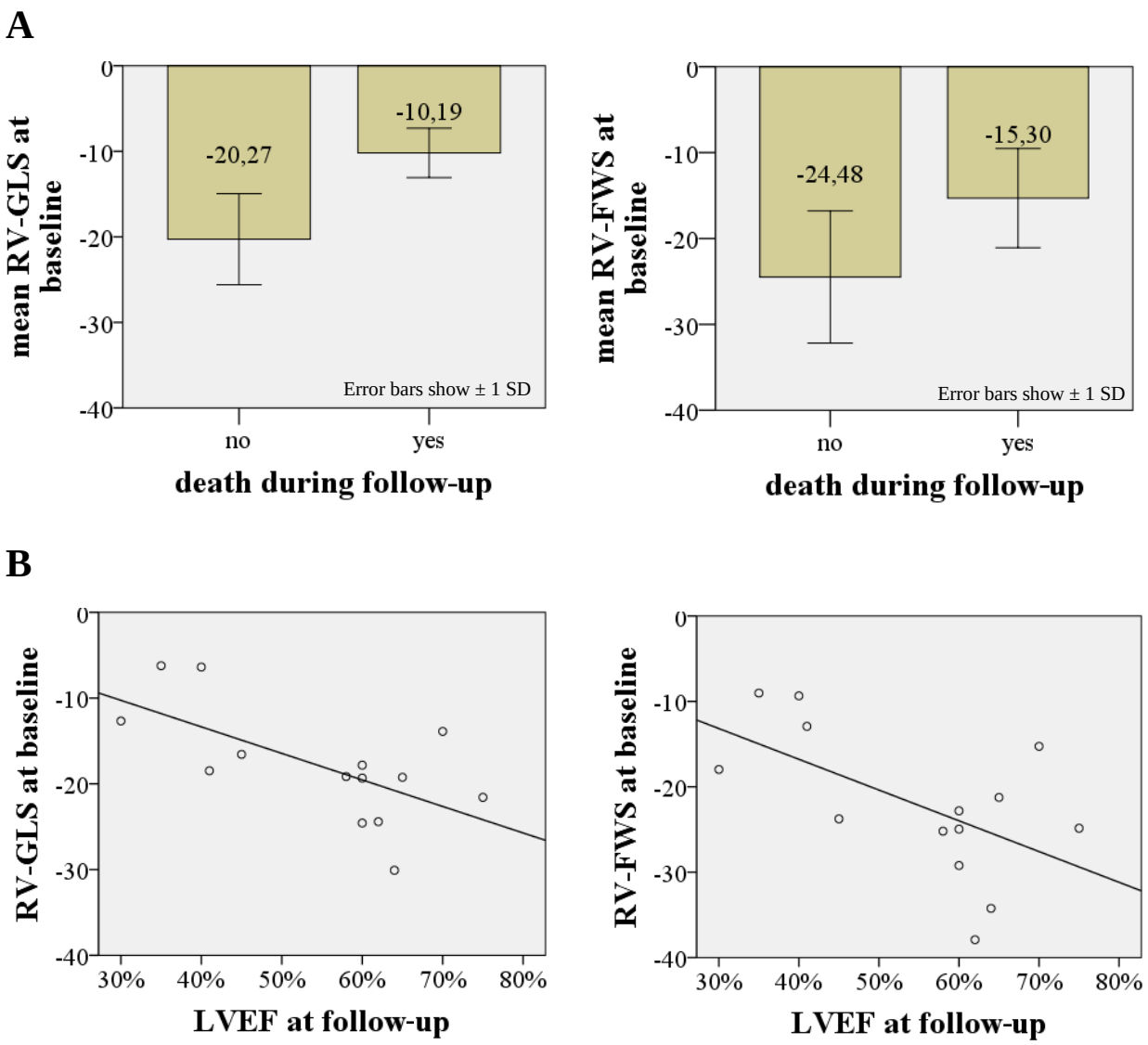


Figure 12 Relation between initial right ventricular global longitudinal- (A) and free wall strain measurements (B) with occurrence of death during follow-up and LVEF in a follow-up examination.

There was a significant correlation between RV-GLS and death during follow up ($p < 0,001$, $r = 0,606$). On average, patients who died during the follow-up period had higher initial RV-GLS (-10,19 ± 2,89) than patients who survived (-20,27 ± 5,82). The same is true for RV-FWS (-15,30 ± 5,78 vs. -24,48 ± 7,70), although the correlation was less pronounced ($p = 0,06$, $r = 0,433$). (B) Both strain measurements also showed a negative correlation with LVEF assessed during a follow-up echocardiogram. The correlation was more pronounced for RV-GLS ($p = 0,013$, $r = -0,646$) compared to RV-FWS ($p = 0,03$, $R = -0,580$).

Abbreviation index: RV-GLS = right ventricular global longitudinal strain; SD = standard deviation; LVEF = left ventricular ejection fraction; RV-FWS = right ventricular free wall strain

3.7 RV strain correlates with perceived health status

Of all ventricular function parameters in the baseline echocardiogram, only RV-GLS and RV-FWS showed a significant correlation with the subjectively perceived state of well-being. RV-GLS and RV-FWS both were positively correlated with subjective well-being meaning higher initial strain measurements (read worse right ventricular function) were associated with an improvement in the subjectively perceived state of health compared to the months before the initial myocardial infarction (*Figure 13*). RV-GLS showed a stronger correlation (Spearmans ρ = 0,471, p = 0,008) than RV-FWS (Spearmans ρ = 0,361, p = 0,047).

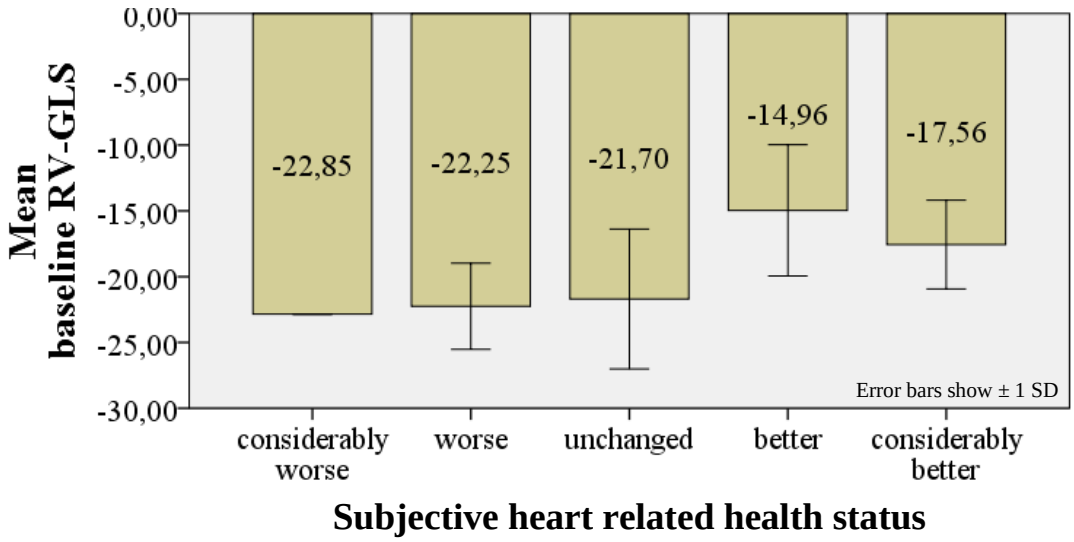


Figure 13 Association between baseline RV-GLS and the subjective heart related health status reported by the participants when compared to the months before the initial myocardial infarction.

The worse the right ventricular function immediately after the infarction was, the more positively patients describe the course of subjectively perceived health. Especially patients who describe their health status as better or considerably better had high initial right ventricular strain values.

Abbreviation index: RV-GLS = right ventricular global longitudinal strain

Patients who assessed their health status as better or significantly better compared to the time before the infarction had a significantly higher RV-GLS and therefore more impaired right ventricular in the first echocardiogram after the myocardial infarction (-15,70 ± 4,48 vs. -21,93 ± 4,57, p = 0,003) (*Figure 14*). The most effective cut-off for RV-GLS to predict an improvement in subjective health status is at -18,34 with a sensitivity of 71,4 and a specificity of 83,3 (*Figure 15*). A logistic regression analysis shows that the Odds ratio for an improvement in

the subjectively perceived state of health is 1,38 (95%-CI 1,05 – 2,15, p = 0,034)) for each point increase in RV-GLS (*Table* 6).

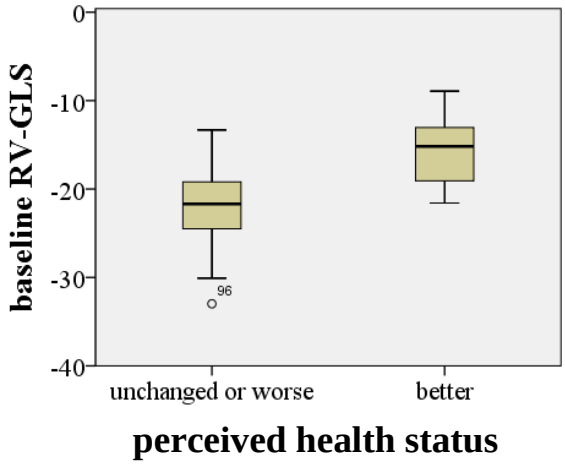


Figure 14 Comparison of RV-GLS between patients who reported worse or unchanged subjective heart related health status versus patients with improved subjective health status.

The patients who report an improvement of perceived heart related health when compared to the time before the initial infarction had a significantly higher mean initial right ventricular strain (-15,70 ± 4,48 vs. -21,93 ± 4,57, p = 0,003).

Abbreviation index: RV-GLS = right ventricular global longitudinal strain

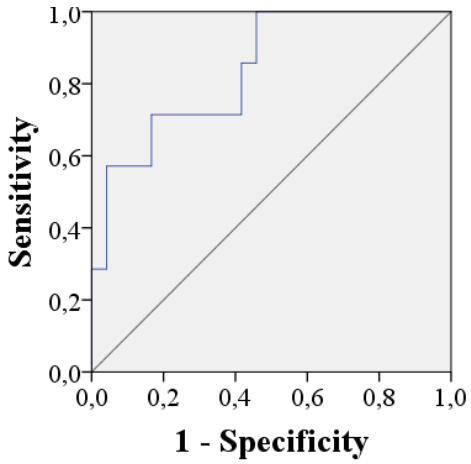


Figure 15 ROC curve of RV-GLS for the prediction of a perceived health improvement two years after myocardial infarction compared to the months before the infarction.

A RV-GLS of rounded -18 had a sensitivity of ca. 71% and a specificity of ca. 83% for the prediction of an improvement in perceived health.

Abbreviation index: RV-GLS = right ventricular global longitudinal strain

Table 6 Logistic regression for the endpoint subjective heart related health status.

An increase in RV-GLS by one point raises the chance of feeling subjectively better two years after a myocardial infarction compared to the months before the infarction by 1,38 times. Shown are the odds ratios for subjectively improvement of the heart related health-status compared to the months before the myocardial infarction in relation to male sex, age, RV-GLS, TAPSE and LVEF.

	OR	95%-CI		Significance
Gender Male	0,96	0,11	16,49	0,973
Age	0,94	0,80	1,04	0,245
RV-GLS	1,38	1,05	2,15	0,016*
TAPSE	0,98	0,72	1,28	0,899
LVEF	1,08	0,95	1,25	0,233

Abbreviation index: RV-GLS = right ventricular global longitudinal strain; TAPSE = tricuspid annular plane systolic excursion; LVEF = left ventricular ejection fraction; OR = odds ratio; CI = confidence interval

3.8 Predictive value of RV strain and TAPSE

Both RV-GLS and RV-FWS were effective at predicting death after two years. For our primary endpoint, a cut-off of -13 was identified for RV-GLS with a sensitivity of 86% and specificity of 91% for predicting all-cause mortality after 2 years. The optimal cut-off for RV-FWS was -19 with a sensitivity of 86% and a specificity of 83%. TAPSE was unable to predict all-cause death during the follow-up period better than chance. In our data, it achieved a sensitivity of 50% with a specificity of less than 10% at a cut-off of 17 mm (*Figure 16*).

For the prediction of an impaired left ventricular ejection fraction in a follow-up echocardiogram, a cut-off of -17 was found for RV-GLS with a sensitivity of 80% and a specificity of 89%. TAPSE showed no correlation with later LVEF measurements and therefore was not useful in predicting impaired left ventricular function during the follow-up. At the cut-off of 17 mm the specificity was under 10%.

Eleven out of the 48 patients, or 22,9% with measurable RV-GLS, had a value above the cut-off, while 16 out of 48, or 33,3%, had an RV-FWS value above the cut-off. Only 11 out of 95, or 11,6%, had an impaired TAPSE.

Patients with RV-GLS of -13 or above had a significantly higher chance of dying during the follow- up period, with a mortality of 66,7% vs. 3,3% in the group with initial RV-GLS below -13. For RV-FWS, a value of -19 or above yielded a mortality rate of 54,5% vs. 3,6% in patients with values below -19. Out of the patients with an impaired TAPSE (< 17 mm), 37,8% died during the follow-up period. The mortality rate of patients with normal TAPSE was at 4,8%.

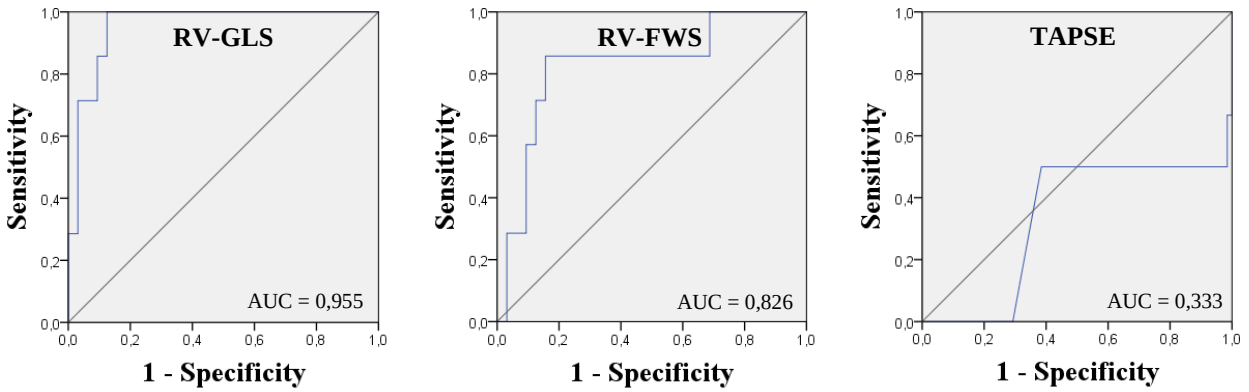


Figure 16 ROC curves of RV strain and TAPSE for the prediction of all-cause mortality after 2 years follow-up.
RV-GLS is a strong predictor of mortality, with an optimal cut-off at -13 (sensitivity 86%, specificity 91%). RV-FWS is also effective at prediction death after two years at a cut-off of -19 (sensitivity 86%, specificity 83%). In contrast, TAPSE could not predict mortality better than chance with an AUC of < 0,5. At a cut-off of 17 mm, it reaches a sensitivity of 50% with a specificity of < 10%.

Abbreviation index: RV-GLS = right ventricular global longitudinal strain; RV-FWS = right ventricular free wall strain; TAPSE = tricuspid annular plane systolic excursion; AUC = area under the curve

Multivariate analysis shows that RV-GLS but not TAPSE or LVEF is an independent predictor of death during the follow-up period of two years. An increase in RV-GLS by 1 point yielded a 1,36-fold increased risk of dying (OR 1,36, 95%-CI 1,01 – 2,50, p = 0,043). In our data, TAPSE had very poor predictive value with an OR of 1,00 and a p-value of 0,997 (*Table 7*).
Having an RV-GLS of > -13 is associated with a 24,66-fold increased risk of death during follow-up, but with a large confidence interval ranging from 1,78 to 3391,41 (p = 0,017). A TAPSE of < 17 mm elevated the risk by roughly eight times, though this was not statistically significant (p = 0,195) (*Table 8*).

Table 7 RV-GLS is an independent predictor for death during the two-year follow-up.
An increase in RV-GLS by one point is associated with a 1,36-fold increased risk of dying. Shown are the odds ratios for the endpoint death in relation to the measured RV parameters.

	OR	95%-CI		Significance
Male Gender	0,91	0,05	56,54	0,945
Age	1,05	0,97	1,18	0,229
RV-GLS	1,36	1,01	2,50	0,043*
LVEF	0,96	0,80	1,11	0,559
TAPSE	1,00	0,72	1,40	0,997

Abbreviation index: RV-GLS = right ventricular global longitudinal strain; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; OR = odds ratio; CI = confidence interval

Table 8 An RV-GLS of > -13 is associated with a substantial risk-increase of dying during the two-year follow-up.

In comparison, a TAPSE of < 17 mm did not reach statistical significance in predicting death during follow-up.

	OR	95%-CI		Significance
Male Gender	1,58	0,13	86,23	0,724
Age	1,04	0,97	1,20	0,268
RV-GLS > -13	24,66	1,78	3391,41	0,017*
TAPSE < 17 mm	8,07	0,33	1248,88	0,195
LVEF < 50%	3,03	0,31	53,25	0,339

Abbreviation index: RV-GLS = right ventricular global longitudinal strain; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; OR = odds ratio; CI = confidence interval

Table 9 Multivariate analysis of RV-FWS adjusted to age, sex TAPSE and LVEF.

An increase of RV-FWS by one point is associated with a 1,12-fold increased risk of dying during follow-up. RV-FWS did however not reach statistical significance with a 95%-CI of 0,96-1,49.

	OR	95%-CI		Significance
Male Gender	0,82	0,05	49,68	0,891
Age	1,08	1,00	1,27	0,058
RV-FWS	1,12	0,96	1,49	0,162
TAPSE	1,07	0,82	1,46	0,617
LVEF	0,92	0,78	1,03	0,158

Abbreviation index: RV-FWS = right ventricular free wall strain; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; OR = odds ratio; CI = confidence interval

4 Discussion

4.1 Why we consider the right ventricle

After Isaac Starr had shown in 1943, that on the basis of experimental animal studies, the destruction of the right ventricle was associated with minimal changes in the central venous pressure[101], the idea of clinically relevant right ventricular infarction was neglected for decades. It was not until the 1970s that Cohn et al. suggested that right ventricular dysfunction could be a clinical entity, independent of the left ventricle and associated with a specific clinical syndrome[102]. Nevertheless, scientific research on right ventricular infarction only slowly gained momentum in the following years. In a 1985 myocardial scintigraphy study, Shah et al. showed that not only was the number of myocardial infarctions with right ventricular involvement underestimated, but that this right ventricular involvement was also associated with an increased rate of complications[103].

In the following years, there was increasing evidence that right ventricular infarction is associated with a worse prognosis[104] and, like left ventricular infarction, benefits from thrombolytic therapy[105]. However, the question of how to detect right ventricular dysfunction quickly and reliably remained unsolved for a long time. In his editorial published in 1995, Oldershaw discusses the difficulties of assessing right ventricular function, especially since techniques for assessing the left ventricle were often not transferable to the right ventricle[106]. In the 2000s, echocardiography has become increasingly important for a fast assessment of right ventricular function. Several studies now show that right ventricular systolic function is an important predictor for long-term outcomes like death, heart failure and even stroke[59,67,107,108], but also affects the short-term prognosis independent of left ventricular function[109].

4.2 How we used to assess right ventricular function

In 2010, the American and Canadian societies as well as the European Association of Echocardiography recommended the following echo parameters for the assessment of right ventricular systolic function: RIMP, RVFAC, TAPSE and TAPSV[73,110]. Ten years later, Jones et al. have again summarized the state of the art for the echocardiographic assessment of the right ventricle. The result: Essentially, the same parameters for the evaluation of the right heart are still being used as in 2010, while new parameters such as 2D strain and strain rate now show great promise[111].

What procedures are actually routinely used in everyday practice? A recent survey with 1150 echocardiographers from 109 countries asked this precise question and found that the possibilities for a comprehensive assessment of the right ventricle are generally not fully utilized. More than two thirds of the participants only used TAPSE plus eyeballing for the evaluation of RV systolic function. Less than one third additionally included TAPSV into the routine evaluation. 23% neglected any other method than eyeballing in their everyday routine. Newer parameters like right ventricular 2D STE strain were commonly used only in 3% of the participants. The authors conclude that although advanced parameters were shown to be highly accurate, only very few echocardiographers actually use them in their clinical routine[69]. Why is this problematic?

4.3 Why the established parameters have limitations

When Zornoff et al. showed the prognostic value of RVFAC in patients with myocardial infarction in 2002, he specifically pointed out the limitations of this method, arguing that RVFAC may not adequately reflect the complex geometry of the right ventricle[107]. The most commonly used RV parameter, namely TAPSE, faces even more limitations being one-dimensional and therefore angle dependent. It may fail to accurately represent right ventricular function and could be heavily influenced by overall heart motion[112]. Another study showed poor correlation between TAPSE and CMR derived right ventricular ejection fraction[113]. RIMP on the other hand, is dependent on the pressure of the right atrium and yields falsely low values in the case of elevated right atrial pressure[68].

4.4 What we can expect from STE derived RV strain

Cardiovascular magnetic resonance imaging can be considered the gold standard for assessing ventricular function[114]. STE derived RV strain showed the strongest correlations with CMR derived RVEF out of all common echo parameters, both in a mixed cohort[72] and in patients with heart failure[115]. Especially in patients where TAPSE did not accurately reflect the RVEF, STE derived strain provided significant added value, most likely due to the inclusion of the apical RV segments[72]. Especially in myocardial infarction where regional dysfunction is prevalent, it seems logical to include all segments of the right ventricle in the measurement. In fact, compared to TAPSE, TAPSV, RIMP and RVFAC, STE derived global longitudinal strain most closely correlated with RVEF by CMR in patients with first STEMI and was the best echocardiographic predictor of right ventricular dysfunction[116].

STE derived two-dimensional strain has already been evaluated for its diagnostic and prognostic value in a number of conditions[117]. It was shown in patients with chronic CAD that right ventricular free wall strain is an independent predictor of cardiovascular mortality and hemodynamically unstable ventricular arrhythmia even in patients with normal left ventricular function[118]. In patients with pulmonary arterial hypertension it was shown that STE derived global longitudinal RV strain showed superior correlation with the functional status assessed by six-minute walking distance compared to conventional parameters[119].

The superiority of 2D strain measurements was also apparent in patients with acute myocardial infarction. In a study by Antoni et al. RV-FWS and RVFAC were independent predictors of major adverse cardiac events, while TAPSE failed to add any incremental prognostic value[91].

4.5 What our results show

Population characteristics

Almost three quarters of the participants in our study were male. Women were on average 11 years older than the male participants at the time of the myocardial infarction. The gender and age distribution in our cohort thus corresponds to the epidemiological data on myocardial infarction in Germany[120]. The two most prevalent risk factors were dyslipidemia and arterial hypertension. About 17% of the patients included had previously diagnosed CAD.

Baseline echocardiogram

While the average LVEF in the cohort was borderline normal at 53%, the average LV-GLS was -12 and therefore impaired in our study population. TAPSE was on average normal at 22 mm. RV-GLS was on average at -18 while RV-FWS averaged at -22. The peak systolic RV strain rate was -1,18 on average.

Although the data on reference ranges for 2-dimensional STE derived RV strain is scarce, a few studies have proposed reference values derived from the general population without cardiovascular conditions. In a meta-analysis, an RV-FWS of -27 ± 2 was seen in a total of 552 healthy subjects[121]. Another study with 493 healthy participants found an average RV-FWS of -26,4 ± 4,2 and an average RV-GLS of -21,5 ± 3,2. The average peak systolic strain rate was reported at -1,4 ± 0,3[122]. A third study with 276 healthy participants reported an average RV-FWS of -30,5 ± 3,9 with a limit of normality at -23,3 and an average RV-GLS of -25,8 ± 3,0 with a limit of normality at -20,2[123]. In all three studies, the 2D strain evaluations were performed in EchoPAC software by General Electric Healthcare, Horten, Norway, which we also used in this study. This is important to mention, because the algorithms for the strain calculation are not standardized and therefore different measurements are obtained from different manufacturers.

The EACVI as of now only recommends a cut-off value for RV-FWS. According to their latest recommendation, a value above -23 should be considered abnormal[94]. The average values for RV-GLS (-18,09 ± 6,08), RV-FWS (-21,95 ± 7,99), RV-SSR (-1,18 ± 0,31) measured in our study cohort are all above the published reference ranges. Just as left ventricular strain reveals a dysfunction, which we are unable to measure with LVEF, right ventricular strain reveals right ventricular dysfunction, where TAPSE still reports normal values. Carluccio et al. underlined this, by showing that right ventricular strain provides incremental prognostic value in patients with heart failure with reduced ejection fraction (HFrEF) and normal TAPSE[124].

For the assessment of right ventricular 2-dimensional speckle-tracking strain, the EACVI recommends a right-heart-optimized 4-chamber view. Since such image data were not available for this study, the right ventricle including the free wall was not completely visible in some patients. Accordingly, only 48 of the 99 patients included in this study had usable 2-dimensional strain data. For this reason, we compared the subgroup with measurable RV strain with the rest of the study cohort. There were no statistically significant differences in any of the baseline characteristics. Therefore, we assumed that both subgroups were from the same general population for further data analysis.

Interdependence of right and left ventricular function

Our study shows a significant but not very strong correlation of TAPSE with RV-GLS (p = 0,015, r = -0,361) and RV-FWS (p = 0,012, r = -0,370). This finding is in line with a number of studies that have previously reported a generally good correlation of these parameters[125–127]. The correlation seems to be stronger in healthy subjects compared to patients with regional dysfunction[125], as is present in myocardial infarction. This can be attributed to the lack of inclusion of the apical RV segments when assessing TAPSE[72] and could explain the relatively weak correlation we found in our study.

Right ventricular function, measured by RV-GLS, RV-FWS and TAPSE, was closely correlated with left ventricular function (both with LVEF and LV-GLS). Since in RV-GLS the interventricular septum is included in the ROI, a correlation with left ventricular function, especially with LV-GLS, seems obvious. However, it is interesting to note that there is also a significant correlation between left ventricular function and TAPSE as well as RV-FWS. Patients with impaired LVEF (< 50%) had a significantly lower TAPSE (21,21 mm ± 4,39 mm vs. 23,40 mm ± 3,97 mm, p = 0,015), and also higher RV-GLS and RV-FWS (although not statistically significant). When comparing patients with normal and impaired LV-GLS, all three RV parameters (TAPSE, RV-GLS and RV-FWS) were significantly impaired. In our opinion, this underlines the dependence of right ventricular systolic function on the left ventricular function.

We divided the cohort into two groups according to the measured RV-GLS at a cut-off of -13. We found that the average TAPSE in these two groups was almost equal (21,20 mm ± 4,26 mm vs. 22,26 mm ± 4,66 mm, p = 0,523). Only 20% of the patients with an impaired RV-GLS also had an impaired TAPSE. While a low systolic excursion of the tricuspid annulus is associated with a higher strain (lower absolute value), not every impaired strain measurement is accompanied by a

low TAPSE. Here we can see two advantages of the assessment of right ventricular strain compared to the one-dimensional TAPSE: Firstly, it allows a much more subtle gradation of right ventricular function than TAPSE. While in the latter only gradations in millimeter steps are possible and practical, the quantitative computer-assisted speckle-tracking method allows an exact gradation of myocardial deformation to several decimal places. Secondly, this can be done across all segments of the right ventricle, so that regional dysfunctions that do not influence TAPSE can be visible in 2-dimensional STE derived strain measurements.

LCA vs. RCA

Contrary to our first expectation, right ventricular function did not differ in RCA occlusion compared to LCA occlusion. This could be due to the fact that mainly RCA occlusions, which are located proximal to the right ventricular branches, lead to relevant right ventricular ischemia[24,128]. Furthermore, isolated right ventricular infarction is rare and often accompanied by left ventricular infarction[15]. At the same time, left ventricular dysfunction, as would be expected with LCA occlusion, also leads to right ventricular impairment. These two mechanisms may lead to an equalization of right and left ventricular function between the two groups with RCA or LCA occlusion.

Left ventricular systolic function was significantly reduced in patients with LCA occlusion compared to RCA occlusion. This underlines the importance of the two left coronary artery branches LAD and RCX for the supply of the left ventricle. Even if parts of the left ventricle are supplied via the right coronary artery, left ventricular systolic function depends highly on the status of the left coronary artery. Recently Backhaus et al. showed in a large CMR study, that left ventricular infarction size and impairment was the largest in LAD occlusions, while RCA occlusions led to the smallest infarction size and lowest ventricular impairment[129].

Two-year follow-up

The two-year mortality in our study cohort of STEMI patients after percutaneous coronary intervention was 9.5%. The mortality of STEMI patients with primary PCI is currently reported in the literature to be about 10% within the first three years[49,130,131].

In the initial echocardiogram, the deceased patients had significantly impaired right ventricular strain (both global and free wall strain) compared to the survivors. For TAPSE no statistically

significant differences between the two groups could be detected. RV-GLS and RV-FWS showed significant correlation with death during the follow-up period. No such correlation could be seen for TAPSE. In fact, the only outcome parameter TAPSE correlated significantly with, was the NYHA stage at the time of the follow-up questionnaire. Lower initial TAPSE was associated with a higher NYHA stage after two-years. This is in line with previous findings on the correlation of TAPSE and follow-up NYHA stage[132].

RV strain correlates with perceived health status

The question in our interview regarding the subjectively perceived state of health revealed unexpected results. On average, patients with initially worse right ventricular strain stated in the follow-up questionnaire, that their health status had improved compared to the weeks before the initial myocardial infarction. A cut-off for RV-GLS at -18 was predictive of an improvement in perceived health status with a sensitivity of 71% and a specificity of 83%. Furthermore, every point increase in RV-GLS was associated with a 1,38-fold increased chance in reporting an improvement in perceived health status compared to the weeks before the initial myocardial infarction.

We see two possible reasons for this result: On the one hand, the right ventricle has a considerable potential for regeneration of its systolic function. This has been observed especially in right ventricular infarction. In one study, the authors saw an improvement of right ventricular ejection fraction measured by radionuclide ventriculography of almost 50% within four years[133]. Another study reported comparable improvements after only ten days[134]. In a third study, RV wall motion abnormalities persisted in only 18% of the patients with myocardial infarction and right ventricular dysfunction six weeks after hospital discharge[135].

On the other hand, the average right ventricular global and free wall strain among the deceased patients was significantly higher than among the survivors. These patients fall off the grid in the evaluation, as they did not take part in the follow-up questionnaire, therefore shifting the results in the direction of an improvement. It can thus be stated, that survivors with initially poor right ventricular function speak on average of an improvement in subjectively perceived quality of life. However, a general deduction of this improvement from the initial right ventricular strain measurement would be deceptive as can be seen in the following paragraph.

Predictive value of RV strain and TAPSE

The main finding of this study is that two-dimensional speckle-tracking derived right ventricular strain and especially RV-GLS is an independent predictor of all-cause mortality within 2 years. It performs better than TAPSE at predicting this outcome. A cut-off for RV-GLS at -13 reached a sensitivity of 86% and a specificity of 91% for the prediction of death during the first two years after myocardial infarction. Two thirds of the patients with an RV-GLS above -13 died during the follow-up, while the mortality in the group with an RV-GLS below -13 was only 3,3%. Multivariate analysis adjusted to Age, Sex, TAPSE and LVEF identified RV-GLS as an independent predictor of death during the follow-up. Every point increase in RV-GLS was associated with a 1,36-fold increased risk of dying. Having an impaired RV-GLS (above -13) was associated with a roughly 25 times higher risk of dying during follow-up compared to not having an impaired RV-GLS. Our results confirm the previously published work on this topic. In a similarly designed study with patients with inferior myocardial infarction, Park et al. showed that RV-GLS holds an additional predictive value over TAPSE, RVFAC and LVEF for the prediction of major adverse cardiac events over a follow-up of 54 months. The authors identified a cut-off at -15,5 to separate patients at a significantly lower 5-year survival rate. In contrast to our work, Park et al. used a different software by Siemens to analyze the right ventricular strain[127], which makes a direct comparison of RV-GLS between the two studies impossible.

For RV-FWS a cut-off at -19 also had a sensitivity of 86% but slightly lower specificity at 83% for the prediction of death during follow-up. Here we saw a mortality of 54,7% in patients with impaired RV-FWS vs. only 3,9% in patients with an RV-FWS below -19. In a multivariate logistic regression analysis, RV-FWS did not reach statistical significance as an independent predictor for death during the follow-up period ($p = 0,162$) with an odds ratio of 1,12 and a 95%-CI of 0,96 – 1,49. In a small cohort of 44 patients with first acute STEMI, Zamfir et al. identified RV-FWS as a predictor for major cardiovascular events during hospitalization[66]. Risum et al. found that RV-FWS was independently associated with the occurrence of ventricular arrhythmias and sudden cardiac death, and performed superior to TAPSE[136]. Kanar et al. found that RV-FWS is an independent predictor of 30-day all-cause mortality in patients with inferior myocardial infarction. A cut-off at -14 predicted the endpoint with a sensitivity of 88.9% and a specificity of 62.5%[137]. In a large study by Antoni et al., a cut-off of -22.1 was identified for RV-FWS for the prediction of a composite endpoint including rehospitalization, reinfarction and death. Exceeding the cut-off was associated with a more than twofold increased risk of reaching the endpoint. In the study, 23% of the patients with impaired RV-FWS reached the composite endpoint within four years while

only 7% of patients with normal RV-FWS reached the composite endpoint. The study also found that, in contrast to RV-FWS, TAPSE did not predict the endpoint after adjustment for other variables that predicted adverse outcome[91]. The study by Antoni et al. is one of the first and probably the largest study to date on the prognostic significance of right ventricular strain in acute myocardial infarction. However, in the study, the free wall strain was calculated as the average of the three lateral segments without including the septum in the ROI. This could lead to lower feasibility and reproducibility and is discussed in 4.6.

In our study, TAPSE was not able to predict the primary endpoint better than chance with an area under the curve of only 0,333. At 17 mm the specificity for the prediction of death during follow-up was under 10%. The mortality in patients with an impaired TAPSE was 37,8% while 4,8% of the patients with normal TAPSE died during follow-up. This is where our results differ from the work on TAPSE published so far. Awad et al. very recently underlined the role of TAPSE as an independent predictor of major cardiovascular events within the first 30 days after a STEMI[138]. The use of TAPSE for the identification of patients with right ventricular infarction and increased risk for poor prognosis has been demonstrated in many previous studies[66,139,140]. We believe that our contradictory results for TAPSE are due to the low number of cases, resulting in too little ability to show a predictive effect of TAPSE. Accordingly, these results should only be interpreted in the context of the significantly better performance of RV-GLS and RV-FWS, and should by no means be considered in isolation.

A word on strain rate

In this study, no prognostic value was shown for right ventricular peak systolic strain rate measured by speckle-tracking echocardiography in patients with acute STEMI. There was no correlation between RV-SSR and any of the investigated outcome parameters. Furthermore, the only parameters in the baseline echocardiogram that correlated with RV-SSR were RV-GLS and RV-FWS. RV-SSR was not significantly lower in patients with impaired TAPSE, neither was the difference significant in patients with left ventricular dysfunction. So far, the literature on the STE derived right ventricular strain rate is rather scarce. In patients with left ventricular assistant device (LVAD) implantation, STE derived right ventricular strain rate was identified as a predictor of postoperative right ventricular dysfunction[141]. Another study reported a significantly decreased strain rate in patients with systemic lupus erythematodes and pulmonary hypertension[142]. To our

knowledge, this is the first study that analyzed the prognostic role or right ventricular peak systolic strain rate in patients with acute myocardial infarction

4.6 RV-GLS or RV-FWS?

The term right ventricular global longitudinal strain is not uniformly used in the literature. While some studies include all six segments of the right ventricle, i.e. three segments of the lateral wall and three septal segments, other studies only use the mean value of the three lateral segments to report global longitudinal strain. The majority of studies in recent years worked with right ventricular free wall strain. One of the reasons for this is that the interventricular septum is usually attributed to left ventricular function and is included in some left ventricular parameters such as LV strain. Some authors therefore suspect a distortion of right ventricular function by left ventricular influence. Currently RV-FWS is the default parameter for reporting right ventricular two-dimensional strain[143], mainly due to the more extensive literature[94,98]. However, for the calculation of the RV-FWS it is still advantageous to include the interventricular septum in the ROI, as this increases the feasibility and reproducibility of the average strain of the three lateral segments, as two recent studies show[123,144]. In addition, another study concluded that the measurement of RV-GLS, i.e. including and averaging all six right ventricular segments, produced lower intra- observer, test–retest, and inter-observer absolute difference compared to RV-FWS[145].

The results of our study demonstrate a general advantage of RV-GLS over RV-FWS in the prediction of death during a two-year follow-up after STEMI. RV-GLS showed a stronger correlation with death during follow-up and had a higher specificity and larger AUC for the prediction of death during follow-up compared to RV-FWS. Our results show that RV-GLS remained an independent predictor of death even when LVEF was included into the multivariate analysis. Thus, the prognostic relevance of 6-segment RV-GLS, with included septum, cannot be explained by left ventricular function alone.

4.7 Limitations

Due to the small case number of 99 patients, the results of this study can only reflect trends. Especially since only seven patients died during the follow-up, the statistical analysis of these rare events is difficult. For this reason, our results should be viewed with some caution. For example, no prognostic value could be seen for TAPSE in our data, despite the large body of evidence supporting this parameter. Nevertheless, we consider our results, which are statistically significant

despite the small number of cases, to be robust, especially since only statistical models applicable to the small number of cases were used.

For this study, the health status of patients prior to myocardial infarction was not assessed. The cardiovascular risk profile was obtained when the patients were admitted. However, it is not always known whether a cardiac condition pre-existed prior to myocardial infarction, possibly influencing the prognosis of these patients.

Our methodology of strain measurement should also be mentioned. All right ventricular strain measurements were performed in an apical four-chamber view not specifically adapted for the right ventricle. The EACVI currently recommends a RV-focused apical four chamber view for optimal visualization of the right ventricle[143]. While only standard apical four-chamber view images were available for this study, only data with complete visualization of the right ventricle were included in the RV strain calculations.

Furthermore, there are first indications that the right ventricular strain measurement in several planes is more effective than the measurement in a single plane[146]. However, the implementation of these models is also associated with a considerable additional effort in the collection of the strain values and should therefore in our opinion not be used in routine investigations at the present time.

4.8 Conclusion

To our knowledge, this is the first study evaluating the prognostic value of two-dimensional RV STE derived strain vs. TAPSE in patients with STEMI and primary PCI on GE ultrasound machines and software. Our study shows that right ventricular strain (especially RV-GLS), albeit not strain rate, is correlated with death during a two-year follow-up. A RV-GLS of -13 and a RV-FWS of -19 show high sensitivity and specificity in detecting patients at risk of dying within the first two years. An increase of one point in RV-GLS is associated with a 1,36x increased risk of dying. Having a RV-GLS above -13 severely increases the risk of dying (25x). TAPSE was not effective at predicting death during follow-up. Impaired right ventricular strain was also predictive of improved subjective health-status in the survivors after a two-year follow-up. Right ventricular STE derived strain shows superior prognostic value compared to TAPSE and should be implemented in echocardiographic routine evaluation of patients with STEMI.

Addendum

Table 10 Additional parameters from the baseline echocardiogram.

Parameter	Mean ± SD	n
LVIDd in mm	48,8 ± 7,7	98
LVSd in mm	11,2 ± 4,0	99
LVPWd in mm	11,4 ± 4,2	98
LVM in g	208,41 ± 67,94	97
LVIDs in mm	36,4 ± 0,83	99
E in m/s	0,77 ± 0,21	98
A in m/s	0,71 ± 0,25	97
E/A-ratio	1,23 ± 0,67	96
E' in m/s	0,09 ± 0,07	70
E/E'-ratio	9,73 ± 3,35	70
LVOT in mm	20,1 ± 2,8	96
LVOT VTI in cm	19,68 ± 4,75	88
RVOT in mm	26,4 ± 3,9	31
LAsV in mL	50,85 ± 21,10	99
RAsV in mL	40,10 ± 22,75	88

Abbreviation index: LVIDd = left ventricular internal diameter end-diastole; LVSd = left ventricular septum diameter end-diastole; LVPWd = left ventricular posterior wall diameter end-diastole; LVM = left ventricular mass; LVIDs = left ventricular internal diameter end-systole; E = early mitral inflow velocity; A = atrial mitral inflow velocity; E' = early mitral annular velocity; LVOT = left ventricular outflow tract diameter; RVOT = right ventricular outflow tract diameter; VTI = velocity time integral; LAsV = left atrial volume end-systole; RAsV = right atrial volume end-systole; SD = standard deviation

Verlaufsfragebogen

Patientennummer: _____

☐ Patient verstorben am: _____

1. Waren Sie seit dem Ereignis erneut wegen Erkrankungen des Herzens in stationärer Behandlung?
    a. Anzahl der stationären Behandlungen
    b. Diagnosen

2. Wurden seit dem Ereignis weitere perkutane Koronarinterventionen durchgeführt?

3. Haben Sie seit dem Ereignis einen weiteren Herzinfarkt erlitten?

4. Haben Sie seit dem Ereignis einen Schlaganfall erlitten?

5. Sind Sie Träger eines Herzschrittmachers oder implantierbaren Defibrillators?

6. Leiden Sie an Herzrhythmusstörungen?
    a. Welcher Art?

7. Sind Sie dauerhaft in ambulanter kardiologischer Behandlung?
    a. Adresse des niedergelassenen Kardiologen
    b. Wurde im Verlauf eine weitere Echokardiografie durchgeführt?
        i. Datum der aktuellsten echokardiographischen Untersuchung
        ii. Aktuelle LVEF

8. Ab welchem Belastungsgrad setzt bei ihnen Luftnot ein? NYHA-Klassifikation!

9. Wie ist Ihr subjektiver Zustand im Vergleich zu den letzten Monaten vor dem Infarkt?

Deutlich schlechter	schlechter	unverändert	besser	deutlich besser

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Eidesstattliche Versicherung

„Ich, Fabian Opahle versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Speckle-tracking derived strain imaging and its use in evaluating right ventricular function in patients with ST-segmental elevation infarction. A new prognostic tool?; Strain imaging mittels Speckle-tracking Echokardiografie und seine Verwendung zur Beurteilung der rechtsventrikulären Funktion bei Patienten mit ST-Strecken-Hebungsinfarkt. Ein neues Prognoseinstrument? selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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