Diagnostic and Prognostic Use of Myocardial Strain in Patients with Acute Myocardial Infarction

Thesis

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Contents

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List of Papers

I   Sjoli B, Orn S, Grenne B, Ihlen H, Edvardsen T, Brunvand H. Diagnostic capability and reproducibility of strain by Doppler and by speckle tracking in patients with acute myocardial infarction. JACC Cardiovasc Imaging 2009; 2:24-33.

II   Sjoli B, Orn S, Grenne B, Vartdal T, Smiseth OA, Edvardsen T, Brunvand H. Comparison of left ventricular ejection fraction and left ventricular global strain as determinants of infarct size in patients with acute myocardial infarction. J.Am.Soc.Echocardiogr 2009; 22:1232-1238.

III   Sjoli B, Grenne B, Smiseth OA, Edvardsen T, Brunvand H. The advantage of global strain compared to left ventricular ejection fraction to predict outcome after acute myocardial infarction. Echocardiography 2011; 28:556-563.

Abbreviations

AVC = Aortic Valve Closure

AMI = Acute Myocardial Infarction

ceCMR = Contrast-enhanced Cardiac Magnetic Resonance

ECG = Electrocardiogram

LV = Left Ventricle/Ventricular

LVEDV = Left Ventricular End Diastolic Volume

LVEF = Left Ventricular Ejection Fraction

LVESV = Left Ventricular End Systolic Volume

PET = Positron Emission Tomography

PCI = Percutaneous Coronary Intervention

ROC = Receiver Operating Characteristics

SPECT = Single Photon Emission Computed Tomography

STEMI = ST-segment Elevation Myocardial Infarction

SD = Standard Deviation

TDI = Tissue Doppler (velocity) Imaging

WMS(I) = Wall Motion Score (Index)

Introduction

Background

Coronary heart disease is a major cause of death and disability in developed countries.[1] Morbidity and mortality following acute myocardial infarction (AMI) are closely related to infarct size and location.[2-4] Reperfusion therapy by thrombolysis or primary percutaneous coronary intervention (PCI) salvages viable myocardium and preserves left ventricular (LV) function by reduction of LV infarct size.[5] Evaluation of the degree of myocardial injury as a result of myocardial necrosis in the acute phase of ST-segment elevation myocardial infarction (STEMI) may be of clinical importance to guide further revascularization and add important diagnostic and prognostic information in these patients. The goal of risk stratification after AMI is to identify patients whose outcomes can be improved through specific medical interventions.[6] Contrast-enhanced cardiac magnetic resonance (ceCMR) is considered as the gold standard for assessment of final LV infarct size.[3,7] However, these examinations are time-consuming, expensive and not readily available in the emergency room. Echocardiographic techniques are easily accessible and may be used as bedside tools to study regional and global function in AMI. Left ventricular ejection fraction (LVEF) measured by echocardiography during initial hospitalization is a well-established marker of LV global function and predicts short- and long-term morbidity and mortality in patients with AMI.[8] Direct visualization of wall motion in myocardial segments may describe both regional and LV global function, but is observer dependent and subject to significant variability.[9] Measurement of myocardial deformation by strain has emerged as a promising tool to evaluate normal and ischemic myocardium in order to evaluate regional and LV global function. Global strain based on tissue Doppler imaging has been shown to correlate well with LV infarct size as measured by ceCMR.[10] In this study global strain had a better correlation with LV infarct size as compared to LVEF and may challenge LVEF as a parameter of LV injury in patients with AMI. However, a challenge with strain measurements has been the lack of uniformity in the way strain is measured. Strain has been presented as peak systolic strain, end systolic strain and peak negative

strain, and it is unclear which of these strain measurements should be preferred. In addition, strain may be measured by speckle tracking and the relationship between different strain methods and LV infarct size needs to be further explored. We therefore sought to clarify the diagnostic capability and reproducibility of strain by Doppler and by speckle tracking to predict final LV infarct size. Furthermore, we investigated whether global strain could predict clinical events as compared to LVEF.

Myocardial Infarct Sizing

In animal and post-mortem studies, LV infarct size can be verified by histopathology. The most widely and precise used technique for measurement of LV infarct size in experimental models is staining by triphenyl tetrazolium chloride (TTC).[11] In clinical studies, there are several techniques available for the evaluation of LV infarct size after AMI. Electrocardiogram (ECG) is available in the acute phase and is easily repeatable. Electrical properties are different in normal and infarcted myocardium, and infarct sizing can be assessed using Selvester QRS Scoring System.[12] However, the ECG has limited ability to resolve small differences in LV infarct size. ST-segment elevation score has demonstrated only modest correlation to LV infarct size.[13] Biochemical infarct sizing is based on the correlation between the amount of damaged myocardium and release to the blood pool of specific markers of cardiac necrosis. Peak values correlate to LV infarct size, but the accuracy depends on correct timing of the blood sampling in relation to the ischemic event.[2] Measurement of troponin T after 72 hours is closely related to LV infarct size, but limits its use in the acute phase of AMI.[14,15]

A number of imaging techniques are potentially available for the measurement of LV infarct size and have been evaluated and compared to TTC staining with good results. Retention of radioactive tracers in viable myocytes are utilised in single photon emission computed tomography (SPECT). The final perfusion defect can be used to measure LV infarct size. There is a close association between LV infarct size measured by SPECT imaging and measurements that have been traditionally used to assess LV infarct size in clinical medicine, including LVEF, end-systolic volume, regional wall motion, enzyme release and resting thallium-201 myocardial perfusion imaging.[2] Positron emission tomography (PET) is based on visualization of viable non-infarcted myocardium due to

preserved glucose metabolism. Infarcted myocardium measured by ceCMR, is visualized due to retention of contrast agent in the infarcted tissue (Figure 1). LV infarct size is precisely measured by ceCMR which also predicts recovery of function after revascularization and after AMI.[2] In addition, ceCMR provides information on the surrounding anatomy and the spatial resolution of ceCMR is superior to that of SPECT and PET. CeCMR is therefore the most widely used technique to measure LV infarct size in clinical studies. However, these techniques are not readily available bedside and their use therefore limited. Thus, there is a need for improved bedside tools to increase the precision of predicting LV infarct size. Echocardiography may be one such method.
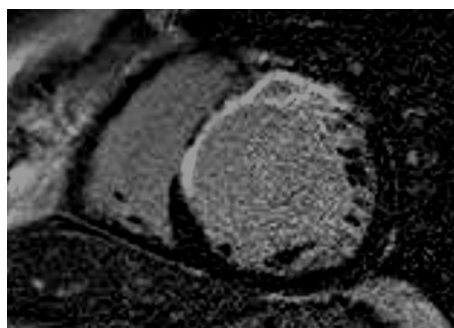
Figure 1: Scar visualization by contrast-enhanced cardiac magnetic resonance (ceCMR). Hyperenhanced area shows the scar in an anterior and septal myocardial infarction.

LV Function and Prognosis after Acute Myocardial Infarction

The benefit of echocardiography has been demonstrated in establishing the diagnosis, location and extent of myocardial infarction. In particular, echocardiography is useful for assessment of prognosis and risk stratification.[16] The echocardiographic scanners are widely distributed mainly due to its low cost and safe bedside modality.

LV systolic function is most commonly assessed by echocardiographic LVEF and is an important predictor of outcome.[17,18] LVEF guides further treatment after primary reperfusion is established.[19,20] This method is calculated as a relative volume reduction during systole and is suitable for normally shaped left ventricles. However, the measurement of LVEF presents a number of challenges related to image quality, assumptions of LV geometry and expertise.[21] Ischemic injuries of the LV are regional, and LVEF does not provide information on segmental LV function. In addition, LVEF by echocardiography is limited by high observer variability and poor agreement with reference methods mainly because of load dependency and technical challenges.[22-24] In some studies wall motion

score index has been shown superior to LVEF in predicting outcome after AMI.[25-27] An advantage of wall motion evaluation is determination of regional function in myocardial segments and may be accurate when the observer is experienced. Visual assessment has, however, limited ability to detect more subtle changes in function and more objective and reliable approaches are thus needed for an accurate description of LV injury in patients with AMI.

Myocardial strain by Doppler has been shown superior to wall motion score index and post-systolic shortening in the diagnosis of myocardial ischemia and the detection of viable myocardium.[28-30] Strain determines regional myocardial function and can be measured by Doppler or speckle tracking. Both methods have been validated against sonomicrometry in experimental studies of acute myocardial ischemia,[31,32] and by different cardiac magnetic resonance techniques in patients with ischemic heart disease,[30,33-35] and are prominent tools in the evaluation of myocardial injury.[36,37] Strain represents fractional or percentage change of tissue length and is expressed as a dimensionless unit either as percent shortening or lengthening. Lagrangian strain is tissue elongation relative to length at end diastole and is commonly used, but Eulerian strain (the instantaneous length) is also used. A positive strain value represents lengthening as a result of myocardial injury, whereas a negative value represents shortening as a result of active contraction. Determination of lengthening or hampered shortening may be used to predict degree of injury as a result of ischemia and necrosis.

The two strain methods are based on different principles and can potentially give different results. Strain by Doppler is limited to the measurement of movement parallel to the ultrasound beam. The method is time-consuming and requires specific imaging protocols. Strain by speckle tracking may be measured independently of angle and measures regional deformation in circumferential and longitudinal directions of the LV (Figure 2a and b). Such measurements may add important information in the separation of subendocardial from transmural necrosis. This method is based on natural acoustic markers (speckles) in gray-scale images. Dedicated software identifies the speckle patterns, and the strain curves reflect the average value of all the acoustic markers in each segment.
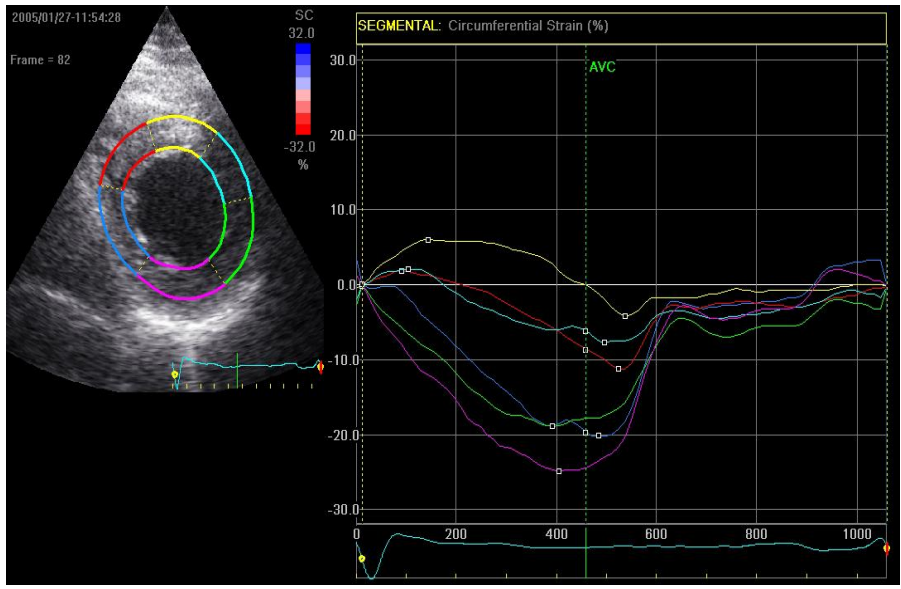
Figure 2a: *Circumferential strain by speckle tracking from parasternal short-axis view from a patient with acute anterior myocardial infarction. Myocardial strain curves illustrate systolic lengthening and reduced shortening in the anterior myocardial wall (red, yellow and light blue curves).*
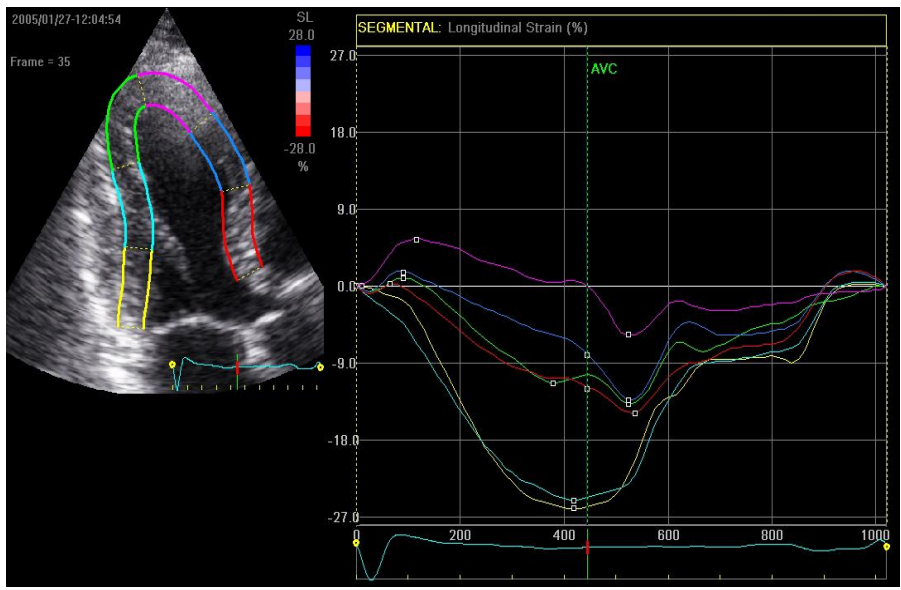
Figure 2b: *Longitudinal strain by speckle tracking from apical long-axis view from a patient with acute anterior and septal myocardial infarction. Myocardial strain curves correspond to the segments from the apical long-axis view. The apical and septal segments show reduced systolic strain values.*

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Determination of deformation has been expressed as peak systolic, end systolic or peak negative strain.[10,38] Thus, there is no consensus on which part of the strain curve best reflects actual deformation. It is therefore of interest to identify the preferred determination of strain. Furthermore, it is not clear whether strain by Doppler or strain by speckle tracking should be preferred in patients with acute STEMI to estimate final LV infarct size.

Global strain by both Doppler and speckle tracking has been shown to be an improved method for evaluation of LV function and injury compared with two-dimensional LVEF by echocardiography.[10,21,39] Recently, Stanton and co-workers[21] demonstrated that global strain may predict all-cause mortality with improved quality compared to LVEF in an unselected patient population. However, global strain and LVEF by echocardiography has not been compared directly in patients with AMI with a focus on prediction of LV infarct size, clinical cardiac outcome and reproducibility. The present thesis aimed to investigate these issues.

Aims of the Thesis

General Aim:

To investigate the ability of strain to predict myocardial necrosis, LV function and clinical cardiac outcome in patients with acute STEMI.

Specific Aims:

I. To investigate whether strain by Doppler or by speckle tracking should be preferred in acute STEMI to predict final LV infarct size measured by ceCMR and to study at which time during the cardiac cycle strain should be measured (Paper I).

II. To determine the relationship between segmental infarct size and segmental strain in anterior and inferior myocardial infarction and the ability of strain to separate subendocardial from transmural necrosis (Paper I).

III. To determine at which time during initial hospitalization global strain should be measured for the optimal prediction of final LV infarct size in patients with AMI (Paper II).

IV. To compare the ability of global strain and LVEF to predict LV infarct size and cardiac events in patients with acute STEMI (Paper II and III).

Patient Population

The thesis is based on data from a prospective study of 77 consecutive patients (age 64 ± 12 years, 18 women) with first time acute STEMI treated with thrombolysis (Table 1). Patients were examined with echocardiography within 3.5 hours after treatment with thrombolysis and either at discharge or the first visit after discharge. No patients were excluded due to poor image quality. Twenty-nine patients were studied in all three papers. The third paper reports on all the patients. The first paper included 36 patients with both tissue Doppler and gray-scale images. In paper Π, 39 patients were examined by ceCMR between 6 and 23 months after discharge. Coronary angiography was performed 31 ± 46 hours after thrombolysis. None of the patients had significant valve disease, arrhythmia or history of myocardial infarction.

Parameters	Results
Age (years)	64 ± 12
Male sex	59 (77%)
Diabetes	6 (8%)
Hypertension	26 (34%)
Smoking status	39 (51%)
Anterior infarction	35 (46%)
Inferior infarction	42 (54%)
Time of ischemia (minutes)	177 ± 141
Systolic BP (mmHg)	139 ± 26
Heart rate (per minute)	74 ± 19

Table 1: Clinical characteristics of the patients during acute STEMI (n = 77). Values are numbers (percent) or mean ± SD, BP = Blood Pressure, STEMI = ST-segment elevation myocardial infarction, Time of Ischemia = Time from symptom onset to start thrombolysis.

Methods

Echocardiography

Examinations were performed with a digital ultrasonic device system (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). The patients were examined in left supine position using the parasternal short-axis at the papillary muscle level and apical 4-chamber, 2-chamber and long-axis views of LV. Great care was taken to obtain high-quality echocardiographic recordings of all LV walls. Three consecutive cardiac cycles were stored during breath-hold. All recordings were stored digitally. In all patients, tissue Doppler images (TDI) were obtained with a frame rate of 152 ± 8 frames/s. Gray-scale images were obtained with a frame rate of 76 ± 2 frames/s in paper I and 67 ± 15 frames/s in paper II. Patients were examined in the acute phase 2 hours after admission and at discharge or the first visit after discharge (10 ± 5 days).

Image Analysis

Exploration time was measured to determine the time needed to perform the analyses of global peak systolic strain by speckle tracking (paper II), global peak negative strain by Doppler (paper III) and to assess LVEF (paper II and III).

Strain

Echocardiographic recordings were analyzed with Echopac (GE Vingmed Ultrasound, Horten, Norway). A 16-segment LV model was obtained from the apical 4-chamber, 2-chamber and long-axis recordings. In addition, in the first paper, 6 segments were analyzed from parasternal short-axis gray-scale recordings.[40] Peak systolic strain was defined as the peak positive or peak negative strain value during systole. End systolic strain was defined as the magnitude of deformation at the time of aortic valve closure (AVC) in the apical long-axis view, and peak negative strain was the maximum negative strain value during systole or early diastole (Figure 3). Post-systolic shortening was calculated as the difference between deformation after AVC and end systolic strain. In addition, strain values from 16 apical segments of the LV were averaged to assess global strain.
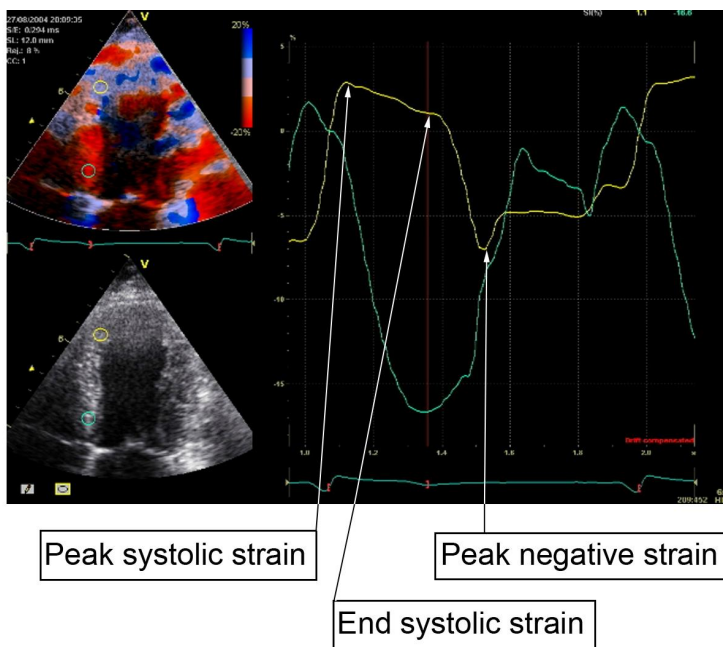
Figure 3: *Representative strain curve from apical 4-chamber view with electrocardiogram from a segment with transmural infarction illustrated by Doppler, showing measurements of peak systolic, end systolic and peak negative strain. The differences between peak systolic strain, end systolic strain and peak negative strain as seen in segments with large infarcts where there is systolic bulging and post-systolic shortening. This pathologic strain curve (yellow) is compared with a normal strain curve (green).*

The different segmental longitudinal strain assessments (peak systolic, end systolic and peak negative strain by Doppler and by speckle tracking) were compared with the corresponding segmental infarct size measured by ceCMR.

Strain by Doppler

Three myocardial longitudinal strain curves were obtained in the basal part of each segment from the TDI recordings, using a region of interest of 6 x 6 mm, which was set as a default. Measurements were obtained from one of three consecutive cardiac cycles.

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The velocity signal was optimized, including avoidance of reverberation artefacts, and the region of interest was tracked frame by frame. Segments that were poorly visualized, with aliasing on tissue velocity, or with insonation angle > 30°, were excluded. Global strain was calculated as an average of strains from 16 LV segments.

Strain by Doppler was used in Paper I and Paper III. Since this strain method was the only commercially available method at the start of inclusion in our study, we analyzed global peak negative strain, as previously reported by Vartdal et al.[10] Global strain by Doppler was compared to LVEF to predict outcome in the whole study group in paper III.

Strain by Speckle Tracking

The new two-dimensional strain software identified the endocardial border, and myocardial motion was automatically tracked in each gray-scale imaging view. Segmental longitudinal and circumferential strain curves reflected the average strain value of all the acoustic markers within each segment. In segments with poor tracking, the observer readjusted the endocardial trace line until a better tracking score was achieved. If this was not possible, the segment was excluded.

Strain by speckle tracking was used in Paper I and II. Peak systolic strain by speckle tracking was assessed in Paper II due to the conclusion from Paper I. From the 16-segment LV model, territorial peak systolic strain was defined as an average of segmental strains based on the perfusion areas of the 3 major coronary arteries.[40,41] The angiographic culprit lesion was used to guide the culprit territorial peak systolic strain. Global strain was calculated as an average of strains from 16 LV segments. In addition, time to peak strain was measured from the aortic valve opening to peak negative strain.

Left Ventricular Ejection Fraction

LVEF by echocardiography was assessed by the modified biplane Simpson's method from apical 4- and 2-chamber gray-scale recordings. End-diastole was defined as the frame closest to the R-wave, and end-systole was defined as the minimal cavity area just before mitral valve opening. According to the recommendations of the American Society of Echocardiography, the inner contour of the LV cavity was manually traced, leaving the papillary muscles and trabeculations within the cavity.[42]

In paper I, LVEF was reported for description of the patient population. In

paper II and III, LVEF was compared to global strain as a major part of the study.

Wall Motion Score and Wall Motion Score Index

An experienced observer, blinded for patient information, assessed visually wall motion score (WMS) in a 16-segment model according to the American Society of Echocardiography criteria.[43] The observer evaluated image quality and segments were discarded if the quality was found insufficient for analysis. Wall motion score index (WMSI) was calculated by dividing the total score by the number of segments analyzable. WMS was related to segmental infarct size by ceCMR in paper II. WMSI was compared to LVEF and global strain as predictors of outcome in paper III.

Contrast-enhanced Cardiac Magnetic Resonance

CMR is regarded the gold standard for cardiac deformation and scar imaging due to its high spatial resolution, excellent reproducibility and ability to visualize even small subendocardial infarctions. ceCMR was therefore chosen as the reference method for measurements of LV infarct size in paper I and II. This is an expensive and time-consuming examination, and the method is sensitive to motion artefacts caused by breathing, irregular heart rhythm, tremor or restlessness. Care was taken to inform and calm the patients and to appropriately instruct patients during sequences requiring breath-hold.

Patients were scanned in a supine position by a 1.5-T whole-body scanner (Intera R 10.3 Philips Medical Systems, Best, the Netherlands) using a dedicated cardiac coil. The images were ECG-gated and obtained during breath-hold. Myocardial mass was obtained by a steady-state free precession technique (balanced fast field echo) covering the LV with 10 to 14 contiguous slices (8-mm thickness, 2-mm gap). Late-enhancement images were acquired 10 to 15 min after administration of 0.25 mmol/kg of a gadolinium-based contrast agent, using an inversion-recovery-prepared T1-weighted gradient-echo sequence covering LV with 10 to 14 contiguous slices (10-mm thickness, 0-mm gap). Inversion time was individually adapted aiming to null normal myocardium (typically 200-300ms). To aid the assessment of apical portions of the ventricle, six images were recorded with 30º separation through the long axis of the LV. Similar density (1.05 g/cm) was assumed

for both hyperenhanced and non-hyperenhanced myocardium.

Post-processing was performed with the View Forum Software (Philips Medical Systems) by one observer blinded for patient information. LV mass and volumes (LV end-diastolic volume [LVEDV] and LV end-systolic volume [LVESV]) were determined using short-axis volumetry. LVEF by ceCMR was calculated as (LVEDV-LVESV) / LVEDV and used in paper II. For the segmental assessment of the LV, a 16 segment model was used.[40] LV infarct size was expressed as percentage of late enhanced area of total myocardium for each LV segment, and the segments were divided into three groups on the basis of the extent of myocardial infarction (no infarction, 1% to 50% necrosis of the segment, and 51% to 100% necrosis of the segment). The total LV infarct size was reported as the percentage of total LV mass. To investigate the ability of global strain and LVEF to diagnose large infarctions, the patients were divided into groups depending on the LV infarct size (small infarctions < 20% LV infarct size and large infarctions > 20% LV infarct size).

Feasibility

All patients included had sufficient image quality for analysis of strain by Doppler.

Some segments were not possible to analyze. Summarizing the results from all the patients, the feasibility of strain by Doppler was 96% (1188 of 1232 segments) in the acute phase of AMI and 95% (1079 of 1136 segments) after ten days. Gray-scale images were not initially systematically obtained since strain by Doppler was the only commercially available method at the start of inclusion. In paper I, the feasibility of longitudinal strain by speckle tracking was 93% (538 of 576 segments) in the acute phase and 91% after ten days. In the short axis, the feasibility of circumferential strain by speckle tracking was 90% (194 of 216 segments) and 84%, respectively. Infarct size was analyzed in all (624) LV segments by ceCMR in paper Π.

Reproducibility

Strain and LVEF were determined by two independent observers blinded for the others results. In paper I, strain by Doppler and by speckle tracking was analyzed in 20 randomly selected patients by two independent observers.
In paper II, LVEF and 320 segments of strain by speckle tracking was analyzed in 20 randomly selected patients by two independent observers. In paper III, we used the results of LVEF from paper II and two

independent observers analyzed the corresponding 20 patients by strain by Doppler.

Follow-up

Clinical endpoints were registered as significant cardiac first time events and reported in paper III. Endpoints were defined as cardiac death, re-infarction and hospitalization for heart failure, unstable angina or life threatening arrhythmia as previously described by Galasko et al.[26] Planned procedures such as revascularization of a non-culprit coronary artery were not considered as a cardiac event. Re-infarction was defined based on established criteria for the diagnosis of AMI. Heart failure was defined as new onset or worsening of clinical heart failure. Unstable angina was defined as new clinical unstable angina pectoris according to Braunwald's criteria.

Statistical Methods

Data were presented as mean values with standard deviations (SD). In paper I and II, the paired nominal data were evaluated by McNemar tests calculated by exact methods and segment-wise analyses were uncorrected. Paired Student t tests were used to compare the changes from the acute phase

to ten days in LVEF and global strain. Independent samples t tests were used to compare anterior and inferior infarctions (paper III). The segmental infarct size by ceCMR was compared with the corresponding segmental strain values and wall motion scores using analysis of variance with the post hoc Scheffe test.

Receiver operating characteristic (ROC) curves were constructed, and areas under the curves were measured to determine cut-off values for optimal sensitivity and specificity for segmental and global peak systolic strain and LVEF to diagnose large infarcts as defined. Due to the prognostic value of infarct size, segmental cut-offs were set to identify transmural necrosis (infarct size > 50%) in paper I and global cut-offs were set to identify large LV infarctions (infarct size > 20%) in paper I and II. In paper III, ROC curve was constructed to determine cut-off value of LVEF for optimal prediction of outcome. ROC curves for LVEF and global strain were compared according to the method described by Hanley and McNeil [44] using dedicated software (Medcalc v.10.4, Mariakerke, Belgium).

The correlation between each LV parameter and total LV infarct size or LVEF measured by ceCMR was analyzed by linear

regression. Linear regression was also used to calculate the value of global strain which corresponds to LVEF 44% (Y (global strain) = B0 (-7.547) + B1 (-0.184) x X (LVEF)). The correlation coefficient between LVEF and global strain was calculated in the acute phase and after ten days in all patients as well as separate for patients with anterior and inferior infarctions (paper III). In paper I, multivariate regression analyses were performed to compare segmental or global strain and to find the best time during the cardiac cycle for estimating final LV infarct size. In paper II, multivariate regression analyses were performed for global strain and LVEF in the acute phase and after revascularization to test which of the parameters were best in predicting LV

infarct size. Multivariate logistic regression analyses were used to assess the prognostic impact of global strain, LVEF and WMSI in paper III.

Event free survival was analyzed by means of Kaplan-Meier survival curves, and the differences between groups were assessed by log-rank tests (paper III). Reproducibility was calculated as intraclass correlation coefficient. $P < 0.05$ was considered statistically significant with the exception of logistic regression analyses where $p < 0.10$ was considered significant.

Summary of Results

Paper I

Diagnostic Capability and Reproducibility of Strain by Doppler and by Speckle Tracking in Patients with Acute Myocardial Infarction

In 36 patients with STEMI, we investigated the ability of strain by Doppler and by speckle tracking echocardiography assessed in the acute phase to diagnose LV infarct size measured by ceCMR and studied at which time during the cardiac cycle strain should be measured. The different segmental longitudinal strain assessments (peak systolic, end systolic and peak negative strain) separated significantly ($p < 0.0001$) between the different levels of infarct transmurality regardless of method, with better reproducibility for strain by speckle tracking. Segmental circumferential strain separated subendocardial from transmural necrosis better than longitudinal strain. With a cut-off value of -13.3% for segmental circumferential strain, sensitivity was 80% and specificity was 74% for prediction of transmural infarction. When using a multivariate regression analysis, segmental peak systolic strain by speckle tracking correlated significantly with segmental

infarct size measured by ceCMR in the acute phase ($p < 0.0001$). Global strain showed a good correlation with LV infarct size, with the best correlation for global peak systolic strain by speckle tracking ($\beta = 0.76$, $p < 0.0001$). The reproducibility was ranked as excellent for both global strain by Doppler and strain by speckle tracking. Inter-observer variability, expressed by intraclass correlation coefficients, for global peak systolic strain by Doppler and by speckle tracking was 0.89 and 0.85, respectively.

Paper II

Comparison of Left Ventricular Ejection Fraction and Left Ventricular Global Strain as Determinants of Infarct Size in Patients with Acute Myocardial Infarction

This paper compared LVEF and global peak systolic strain by speckle tracking as predictors of final LV infarct size measured by ceCMR in 39 patients with STEMI treated with thrombolysis. Measurements were assessed in the acute phase and after revascularization (10 ± 5 days after admittance). Global strain and LVEF by

echocardiography correlated well in the acute phase (r = -0.74, p < 0.0001) and even better after revascularization (r = -0.88, p < 0.0001). Segmental analyses showed that both strain and wall motion score could differentiate subendocardial from transmural scar measured by ceCMR. The correlation between culprit territorial strain and infarct size was better after revascularization (r = 0.70, p < 0.0001) than in the acute phase (r = 0.65, p < 0.0001). In the acute phase, global strain correlated better with final LV infarct size than LVEF (r = 0.62, p < 0.0001 and r = -0.51, p = 0.009, respectively). After revascularization, the correlation with LV infarct size improved for both global strain and LVEF (r = 0.76, p < 0.0001 and r = -0.74, p < 0.0001, respectively). In multivariate regression analyses, global strain was significant in predicting final LV infarct size measured by ceCMR both in the acute phase and after revascularization, while LVEF was not significant.

For global strain after revascularization a cut-off value of -15.0% had a sensitivity of 90% and a specificity of 86% to identify myocardial infarcts larger than 20%. For LVEF after revascularization a cut-off value of 52% had a sensitivity of 90% and a specificity of 69% to identify myocardial infarcts larger than 20%. Global strain

should preferably be measured after revascularization for optimal prediction of LV infarct size.

Inter-observer variability, expressed by intraclass correlation coefficients, for global strain and LVEF was 0.91 and 0.72, respectively.

Paper III

The Advantage of Global Strain compared to Left Ventricular Ejection Fraction to predict Outcome after Acute Myocardial Infarction

In this study we compared the ability of global strain and LVEF to predict outcome after AMI. LV function was measured using peak negative strain by Doppler and LVEF in 77 patients. Measurements were performed at admission and after 10 ± 5 days. Outcome was measured as the combined endpoint of cardiac death, re-infarction and hospitalization for heart failure, unstable angina or life threatening arrhythmia. The patients were followed for 3.29 ± 1.59 years (range 0-5.22 years) and 17 cardiac events were registered. The cut-off value of LVEF was 44% for optimal prediction of outcome. LVEF ≤ 44% versus > 44% and the corresponding global strain value ≥ -15.6% versus < -15.6% was used to predict cumulative event free survival. Both

methods significantly predicted cardiac combined events at admittance and after ten days with no difference. After ten days, however, global strain remained the only significant predictor of outcome in a multivariate logistic regression model ($p < 0.0001$, odds ratio 1.79). Global strain and LVEF were more impaired in anterior than inferior infarction both in the acute phase and after 10 days ($p < 0.0001$). The correlation between global strain and LVEF was highest in patients with anterior infarctions examined after 10 days. Inter-observer reproducibility measured as intraclass correlation was better for global strain than for LVEF (0.92 versus 0.71).

Discussion

This thesis demonstrates that global strain may become an improved predictor of LV infarct size and function, as well as clinical cardiac outcome in patients with acute STEMI treated with thrombolysis. Global strain measured by Doppler and speckle tracking are both excellent markers of LV infarct size. However, global strain by speckle tracking has some advantages over strain by Doppler since it separates small and large infarcts with better precision than strain by Doppler. In addition, circumferential strain by speckle tracking may be used to evaluate the extent of necrosis in myocardial segments. For optimal evaluation of LV infarct size and clinical cardiac outcome, global strain should be measured after revascularization. In the acute phase of AMI, global peak systolic strain by speckle tracking seems to be the best method for prediction of final LV infarct size.

We have also found that global strain may evaluate LV function with precision and correlates well with LVEF by both echocardiography and ceCMR. One advantage with global strain compared to LVEF in the evaluation of LV function and injury is better inter-observer reproducibility.

LVEF versus Global Strain in predicting LV Infarct Size and Clinical Cardiac Outcome

In clinical practice, LVEF by echocardiography is a well-established tool to describe LV function after AMI[8] and the prognostic importance of this method has been demonstrated in several large clinical studies.[16,18,45] However, the prognostic value after AMI has been questioned. Low LVEF may be the result of reduced contractile function due to continuing ischemia or a result of LV dilatation caused by infarct expansion and stretching of the myocardial scar. Furthermore, assessment of LVEF early after AMI can be misleading owing to the presence of myocardial stunning.[16] Finally, the measurement of LVEF has limitations due to significant variability

between observers. LVEF measures volume changes secondary to myocardial contraction and is not a direct measure of myocardial function. Therefore, it may be of great interest to measure the extent of necrosis in patients with AMI, rather than LV volume changes. Measurement of LV infarct size after AMI is an important predictor of short- and long-term morbidity and mortality.[18,46] CeCMR identifies viable myocardium and correlates inversely with recovery of contractile function.[47,48] In addition,Wu et al[49] have suggested that the measurement of LV infarct size by ceCMR is a better predictor of outcome than LVEF by ceCMR after AMI. Thus, ceCMR may measure LV infarct size with high precision because of its excellent repeatability.[50] However, ceCMR is not readily available bedside and is costly. Therefore, it is of interest to estimate LV infarct size by more available methods. Vartdal et al[10] demonstrated that global peak negative strain by Doppler could predict LV infarct size as measured by ceCMR better than LVEF by echocardiography in patients with acute anterior myocardial infarction 1.5 hours after primary PCI. We confirmed this finding in patients with both anterior and inferior STEMI by demonstrating that global strain predicted LV infarct size better than

LVEF, when using ceCMR as the reference method (Figure 4).

In the acute phase of AMI, global strain predicts LV infarct size better than LVEF. However, after revascularization, both global strain and LVEF correlated well with LV infarct size, and better than in the acute phase. This may be due to the effect of revascularization on LV ischemia, as well as reduced effect of myocardial stunning. LV function at this stage is therefore mostly affected by necrosis, and the associations between echocardiographic markers of LV function and infarct size become improved. This suggests that global strain and LVEF should preferably be measured after the patient is revascularized for optimal prediction of LV infarct size and function in AMI. However, global strain demonstrates advantages over LVEF particularly by a better ability to diagnose large infarcts. In a multivariate analysis, global strain and not LVEF was associated with LV infarct size. Additionally, global strain could predict LV infarct size both in the acute phase and after function and infarct size become improved. This suggests that global strain and LVEF should preferably be measured after the patient is revascularized for optimal prediction of LV infarct size and function in
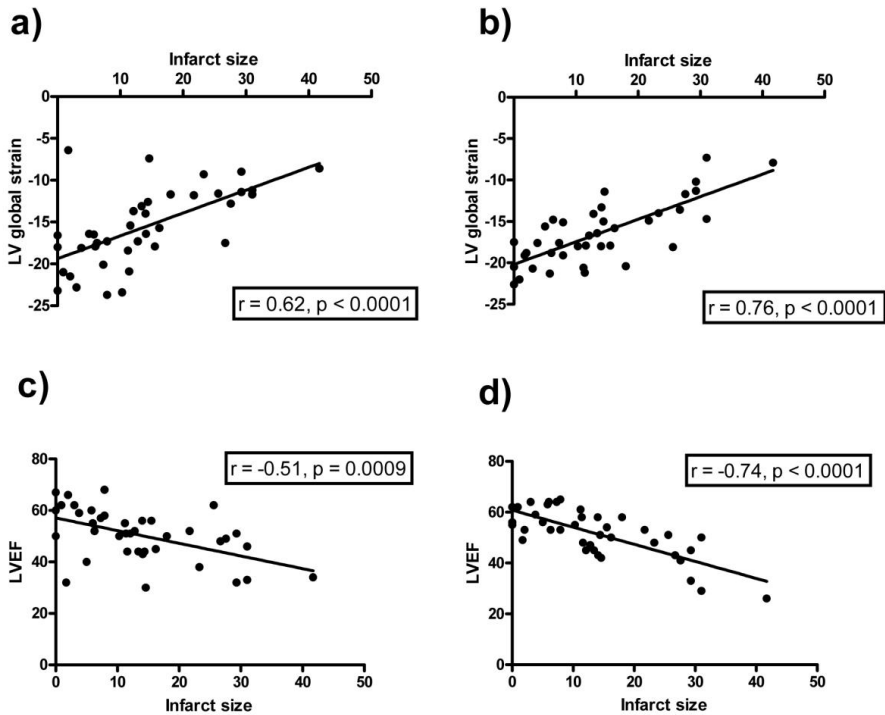
Figure 4: *Relationship between left ventricular infarct size measured by contrast-enhanced cardiac magnetic resonance (ceCMR) and global peak systolic strain by speckle tracking and left ventricular ejection fraction (LVEF) in the acute phase and after revascularization. These figures show that in the acute phase, global strain a) correlated better with LV infarct size than LVEF c). After revascularization, the correlation with LV infarct size improved for both global strain b) and LVEF d).*

AMI. However, global strain demonstrates advantages over LVEF particularly by a better ability to diagnose large infarcts. In a multivariate analysis, global strain and not LVEF was associated with LV infarct size. Additionally, global strain could predict LV infarct size both in the acute phase and after revascularization. Global strain is easy to perform, is independent of the angiographic results and takes into account strain from the whole LV. We therefore suggest that global

strain is to be preferred as a measure of LV infarct size.

In this work, we demonstrated that LVEF and global strain correlated well in the acute phase and even better after revascularization (Figure 5), but the reproducibility was better for global strain. Despite its widespread use as a parameter of LV function, the measurement of LVEF by two-dimensional echocardiography is limited by variability, particularly between observers.[51] In paper II, the reproducibility tests of global peak systolic strain by speckle tracking showed a lower inter-observer variability than LVEF by echocardiography in the acute phase. In addition, the reproducibility was better for global peak

negative strain by Doppler than LVEF, as presented in paper III.

A major limitation of LVEF by echocardiography in patients with AMI is that the biplane Simpson's method is based on an assumption of symmetric left ventricular geometry. As a consequence, the biplane Simpson's method may partly fail to measure LVEF with precision in patients with AMI. Global strain does not rely on such geometric assumptions, but rather measures regional myocardial function with precision. Thus, global strain may be performed with excellent repeatability and may be an improved parameter to predict LV function, infarct size and clinical cardiac events in the acute phase after AMI. In addition, global strain may be more sensitive
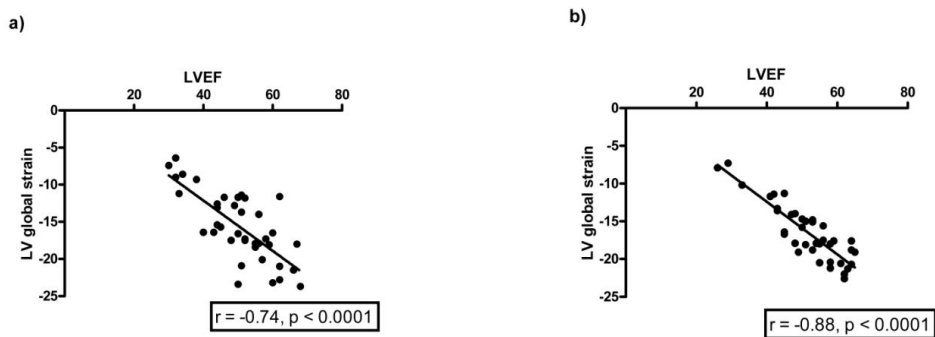
Figure 5: *Relationship between global peak systolic strain by speckle tracking and LVEF in the acute phase and after revascularization. These figures show that the correlation between global strain and LVEF was good in the acute phase a) and even better after revascularization b).*

than LVEF to changes in long-axis shortening. Finally, global strain by speckle tracking may be measured with highly comparable exploration time compared with LVEF and may be suitable in clinical practice. This is in contrast to measurement of strain by Doppler which is time-consuming.

Stanton et al[21] demonstrated that global strain was superior to LVEF and WMSI for the prediction of all-cause mortality in an unselected patient population undergoing echocardiographic examinations. We extend their findings by demonstrating prospectively that global strain by Doppler could predict clinical cardiac outcome after acute STEMI to the same extent as LVEF, but with improved reproducibility (Figure 6).
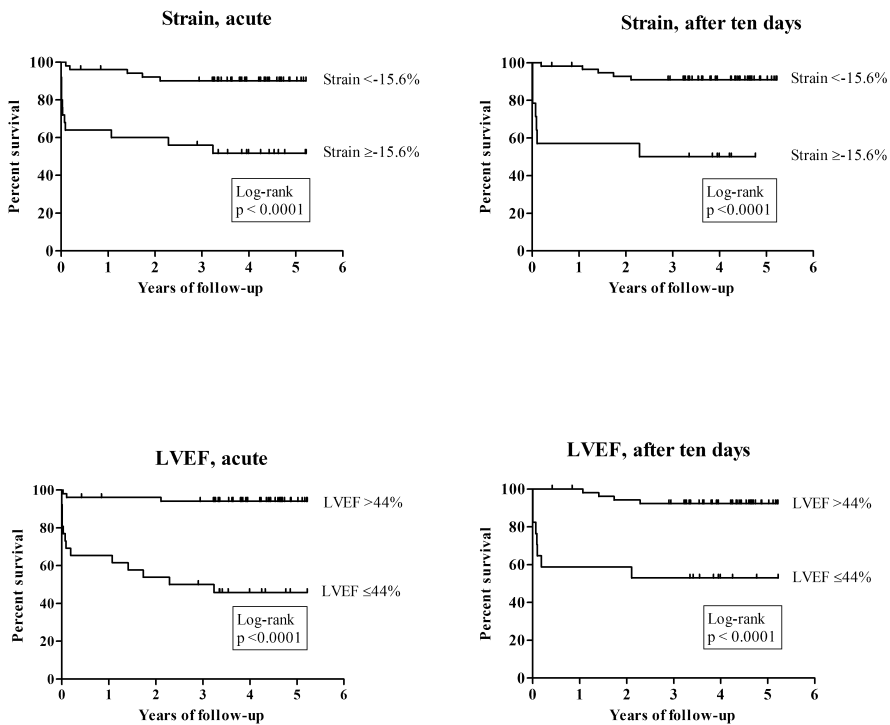
Figure 6: Kaplan-Meier event free survival curves illustrating cardiac combined event free survival for global strain ≥ -15.6 and < -15.6 and LVEF ≤ 44% and > 44% in the acute phase and after ten days in patients with acute myocardial infarction.

In addition, we showed that global strain remained the only significant predictor of clinical cardiac outcome after revascularization in patients with STEMI. The relation between global strain and LVEF was highest in patients with anterior infarcts were LV dysfunction and infarct size was most prominent and lower in patients with inferior infarcts were LV injury was less extensive. According to Stanton et al[21], global strain is better to predict outcome than LVEF particularly when LVEF is > 35 %. This finding may be due to methodological differences. In a 16 segments model, strain by Doppler may identify the most pathologic strain within one segment, whereas LVEF is performed by assessment of the relative volume reduction during systole. Thus, impairment of LVEF requires decreased function in several segments. Global strain may therefore be more sensitive than LVEF in the separation of LV injury in patients with limited myocardial scars. This may explain why LVEF was not as predictive as global strain in the multivariate model after revascularization.

In summary, we suggest that evaluation of LV injury in patients with AMI may be improved by using global strain instead ofLVEF.

Segmental Strain and Transmurality

Evaluation of myocardial segments in patients with AMI may have important clinical implications. By visual inspection it is not possible to distinguish between dysfunctional segments as a result of necrosis, ischemia or stunning. Identification of viable segments with infarct size measured by ceCMR less than 50 % in the region of the infarct-related artery may benefit from early revascularization after thrombolytic treatment. In contrast, myocardial segments with more than 50 % necrosis after AMI reduce the likelihood of improvement in contractility after revascularization. This level of necrosis is therefore considered an important threshold in order to define viability.[52] We demonstrated that peak systolic, end systolic and peak negative segmental longitudinal strain were able to discriminate normal from necrotic myocardium and differentiate subendocardial and transmural infarctions on a group level. In a study by Chan et al[36], circumferential strain was better than longitudinal strain in the differentiation of segments with subendocardial from transmural necrosis. We confirmed these findings in paper I.

The systolic phase of strain in normal myocardium is characterized by shortening, whereas the transmurally ischemic myocardium is characterized by systolic lengthening and post-systolic shortening. Longitudinal deformation mainly represents subendocardial contraction, whereas circumferential deformation mainly represents contraction of the midmyocardial and subepicardial layers. Therefore, longitudinal contraction is more sensitive to subendocardial ischemia and necrosis than circumferential contraction.[36,53] As shown in our study, longitudinal and circumferential strains were all significantly reduced in transmurally infarcted segments compared to subendocardial and non-infarcted segments. Because longitudinal strain in segments with subendocardial necrosis is more affected than circumferential strain, further deterioration of longitudinal strain is not as pronounced as for circumferential strain in segments with transmural necrosis. As a consequence, the measurement of circumferential strain separated segments with transmural necrosis from segments with subendocardial necrosis better than longitudinal strain. This is important because patients with subendocardial necrosis in the region of the infarct-related artery may

benefit from early revascularization after thrombolytic treatment.

Post-systolic shortening was introduced as a promising tool for detecting viable myocardium, but the mechanical explanation of this phenomenon has been less investigated. Skulstad et al[54] demonstrated in an animal model that post-systolic contraction occurs during both moderate ischemia when the myocardium is hypokinetic and during severe ischemia when the myocardium is dyskinetic. Lately, the measurement of post-systolic shortening has not been able to detect viable myocardium nor describe necrosis with precision in acute and chronic myocardial infarction.[29,30] We confirmed that post-systolic shortening had a poor correlation with LV infarct size. We also compared segmental longitudinal peak systolic strain by speckle tracking and wall motion score as indices of infarct transmurality assessed by ceCMR in 16 LV segments. Both methods could distinguish subendocardial from transmural necrosis, but with large standard deviations and thus limited diagnostic precision. Wall motion score has only one level for description of segmental hypokinesia and becomes less sensitive compared to strain in the determination of myocardial dysfunction. Based on these

findings, we suggest that the measurement of segmental circumferential strain may add important information in the evaluation of viable segments in patients with AMI.

We demonstrated a relatively high standard deviation for strain on a segmental level (Figure 6), and therefore it seems necessary to assess global strain for the most accurate assessment of myocardial injury in patients with AMI. Although circumferential strain was able to separate subendocardial from transmural necrosis better than longitudinal strain on a segmental level, the addition of circumferential strain in the assessment of global strain did not increase the diagnostic precision. This finding is most probably caused by improved circumferential strain values in segments without necrosis or with subendocardial necrosis compared with longitudinal strain. Circumferential strain may compensate for the reduced longitudinal strain in these segments. All three strain parameters regardless of method could assess global strain with a significant correlation to LV infarct size, but the correlation was slightly higher for strain by speckle tracking. Thus, global strain by speckle tracking separated small and large LV infarcts with better precision than strain by Doppler.
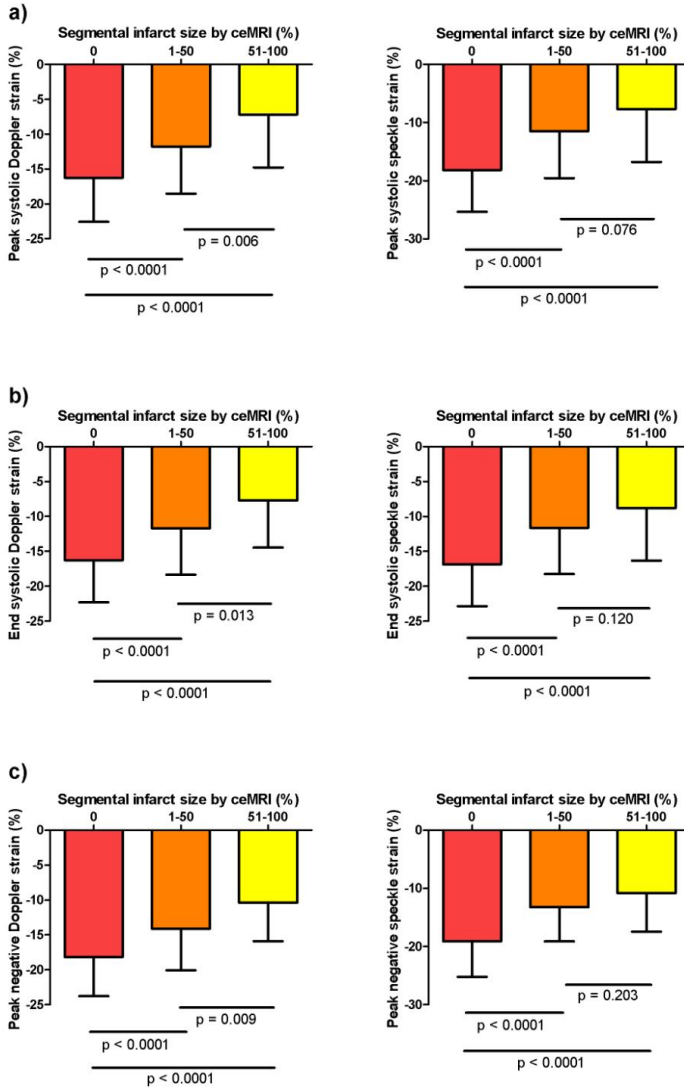
Figure 6: *This figure shows that infarct size in each segment is inversely related to a decrease in corresponding a) peak systolic, b) end systolic, and c) peak negative strain values regardless of strain method in patients with anterior myocardial infarction. 0 = no infarction; 1-50 = 1% to 50% late enhancement by ceCMR (subendocardial infarction); 51% -100% late enhancement by ceCMR (transmural infarction); ceCMR = contrast-enhanced cardiac magnetic resonance.*

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Strain by Doppler versus Strain by Speckle Tracking

The two strain methods are based on different principles and can potentially give different results. We showed that segmental longitudinal strain was able to discriminate normal from necrotic myocardium and differentiate subendocardial and transmural infarctions on a group level. These findings were regardless of whether strain was measured by Doppler or speckle tracking. However, in the study of Cho et al[34], segmental strain analysis by speckle tracking displayed superior ability to differentiate normal and dysfunctional segments when compared to strain measured by Doppler. This difference between the two strain methods may be due to the angle dependency inherent in all Doppler strain measurements. Although strain by Doppler is sufficiently robust, the application for routine clinical use must overcome several drawbacks. During acquisition, every effort should be taken to align the tissue direction parallel with the beam direction, although this is technically challenging in the apical segments. However, strain measured by speckle tracking is less angle-dependent and thus a more robust method. The second limitation is signal noise. It is important to

optimize the approach to acquisition and processing, including high frame rate. However, these measures make this technique rather time-consuming. In our studies, great care was taken to obtain high-quality recordings of all LV walls both in TDI and gray-scale images and thus angle dependency and signal noise may become minor limitations.

Strain by speckle tracking has several advantages over strain by Doppler. The acquisition is less demanding because a sector width and frame rate can be used that are more consistent with standard imaging. The method is two-dimensional in which the speckled pattern is followed frame by frame and may quantify contraction in a longitudinal, circumferential and radial direction. This speckle pattern is unique for each myocardial region and it is relatively stable throughout the cardiac cycle.[55] In addition, strain by speckle tracking allows tracking of natural acoustic speckles which are equally distributed within the whole myocardium, so that all components of deformation may be measured.[56] Strain by Doppler, on the contrary, is one-dimensional and is measured from a representative region of interest within the segment and does not reflect strain from the whole segment. This may lead to greater variability and may

explain our findings that strain by speckle tracking showed better reproducibility than strain by Doppler on a segmental level. By assessing global strain, reproducibility was strengthened for strain by Doppler and by speckle tracking with no differences between the two methods. These findings supported that global strain should be assessed to describe LV injury in AMI.

In paper I, we found that injury is separated slightly better by strain by speckle tracking in anterior than in inferior myocardial infarction. These findings may be caused by reduced lateral resolution in echocardiograms of the LV. Strain by speckle tracking may be less sensitive for diagnosing injury in the posterior myocardial circulation as shown by Hanekom et al.[56] By assessing global strain, some of these difficulties may be overcome.

Global strain by speckle tracking separated small and large LV infarcts with better precision than strain by Doppler. Some of the differences between global strain by Doppler and speckle tracking in paper I may be caused by the effect of myocardial stunning and ischemia, which was detected by strain by Doppler, but not by longitudinal strain by speckle tracking. The latter may be caused by methodological differences. Doppler strain may identify the

most pathologic strain within one segment, whereas strain by speckle tracking is based on the sum of strain values within the whole segment. Thus, values of strain by Doppler in the acute phase of AMI may be slightly lower as a consequence of myocardial stunning and ischemia, which affects the correlation between strain and final LV infarct size.

Strain by Doppler is limited to the measurement of movement parallel to the ultrasound beam, whereas strain by speckle tracking measures regional deformation in circumferential and longitudinal directions of the LV. In paper I, both longitudinal and circumferential strain was assessed by speckle tracking. Although circumferential strain was able to separate subendocardial from transmural necrosis better than longitudinal strain on a segmental level, the addition of circumferential strain in the assessment of global strain did not increase the diagnostic precision.

Our comparison between strain by Doppler and strain by speckle tracking shows that both methods work well in order to determine global strain. However, strain by speckle tracking has some advantages, particularly since circumferential strain may be determined. In addition, global strain may be determined more rapidly with speckle

tracking. Since our study was designed prior to commercial use of speckle tracking, we did not have complete data with strain by speckle tracking in the whole patient population. Paper III is therefore performed with strain by Doppler, which is as good as strain by speckle tracking in determining global strain. However, in the future, we would suggest strain to be measured by speckle tracking.

What should be measured on the Strain Curve?

Several studies have shown characteristics features of strain in ischemic myocardium. Peak systolic strain has been shown to be superior to TDI and wall motion analyses in detection of acute ischemic myocardium.[28] Vartdal et al[10] showed that global peak negative strain correlated well with final LV infarct size in patients with AMI. Sachdev et al[38] showed that decreasing peak systolic strain in chronic myocardial infarction correlated well with increasing transmurality of infarction. These studies have used different strain parameters and show the lack of consensus on whether strain should be measured as peak systolic, end systolic or peak negative strain as a diagnostic or prognostic parameter in ischemic myocardium. We found that peak systolic,

end systolic and peak negative segmental longitudinal strain were able to discriminate normal from necrotic myocardium and differentiate subendocardial and transmural infarctions on a group level. These findings were regardless of whether strain was measured by Doppler or speckle tracking. However, when using a multivariate regression analysis, segmental peak systolic strain by speckle tracking correlated significantly with segmental infarct size measured by ceCMR in the acute phase. At a global level, peak negative strain by Doppler and peak systolic strain by speckle tracking were statistically the best parameters for predicting total LV infarct size, but the correlation was slightly higher for strain by speckle tracking. Peak systolic strain was defined as the peak positive or peak negative strain value during systole and may therefore be a better parameter of systolic lengthening in a transmurally ischemic myocardium. In addition, values of strain by Doppler in the acute phase of AMI may be slightly lower s a consequence of myocardial stunning and ischemia, which affects the correlation between strain by Doppler and final LV infarct size. According to these results, we suggested that in the acute phase in patients treated with thrombolysis, global peak systolic strain by speckle tracking should be the preferred method for diagnosing the

degree of LV injury. As a consequence, in paper II, comparisons were made between global peak systolic strain by speckle tracking and LVEF by echocardiography as predictors of LV infarct size in patients with STEMI, using ceCMR as the reference method.

At the start of study inclusion, TDI was the only commercially available method. We therefore based the patient inclusion in paper III on the study by Vartdal et al.[10] However, in the future, global peak systolic strain by speckle tracking should be preferred.

Clinical Perspectives

Evaluation of the degree of myocardial injury as a result of myocardial necrosis in the acute phase of STEMI may be of clinical importance to guide further revascularization and add important diagnostic and prognostic information in these patients. The goal of risk stratification after AMI is to identify patients whose outcomes can be improved through specific medical interventions. This thesis has therefore some clinical implications. First, global strain seems to have several advantages over LVEF by echocardiography in the evaluation of LV infarct size and function in patients with AMI. Our findings suggest that global peak

systolic strain should be measured after revascularization for optimal prediction of LV infarct size and function in patients with STEMI.

Second, measurement of circumferential strain separated segments with transmural necrosis from segments with subendocardial necrosis better than longitudinal strain. This is important because patients with subendocardial necrosis in the region of the infarct-related artery may benefit from early revascularization after thrombolytic treatment.

In addition, global strain demonstrates a better inter-observer reproducibility than LVEF and may become an improved bedside tool to evaluate LV function as a prognostic marker after AMI. Echocardiography is more available at low costs compared to other advanced imaging techniques. Cardiologists who perform echocardiography can learn strain calculations easily. Our results suggest that echocardiography with strain measurements should be considered after revascularization and preferably before discharge.

Finally, global strain by speckle tracking may be measured with highly comparable exploration time compared with LVEF and may thus be suitable for clinical practice.

Limitations

We have been able to demonstrate that global strain may predict clinical outcome to the same extent as LVEF despite a limited number of patients and clinical cardiac combined events. Studies in large patient cohorts are needed to confirm these findings.

Generalizability

In the acute phase of AMI, there is a mixture of myocardial ischemia, stunning and necrosis.

However, we demonstrated that global strain assessed after revascularization was superior to LVEF in predicting LV infarct size and clinical outcome. Therefore, in patients with acute STEMI, evaluation of LV injury should preferably be performed at discharge and this finding strengthens the generalizability of this work.

Territorial strain, like other non-invasive indices of coronary artery stenosis, is based on schematic distribution territories and thus ignores the individual variation in coronary topography. According to our thesis, global strain after revascularization had a better correlation with LV infarct size and may therefore be more generalizable.

Echocardiography

Care was taken to obtain optimal image quality in this work. Therefore, a very high proportion of myocardial segments were of acceptable quality for strain analysis. The success of speckle tracking depends on the quality of gray-scale images, while TDI requires specific imaging protocols. Stationary reverberations or inadequate wall visualization results in poor tracking and unreliable strain measurements. The feasibility in this work was, however, in accordance with other studies performed with modern echocardiographic machines, harmonic frequencies and study protocols using strain by Doppler or strain by speckle tracking.[30,57]

The high proportion of analyzed segments is in our view not a limitation, but one of the strengths with this work. We demonstrated that with good image quality and standardized echocardiographic examinations, strain measurements can be performed with very low rate of discarded segments. Because only segments with visually poor tracking were discarded, time-demanding and subjective evaluation was reduced. In our view, this increases the

generalizability of the results. Also, to improve generalizability and reduce subjective evaluation, no adjustments were made to the default settings for strain analyses in Echopac except slight adjustments of the endocardial outline and width of the region of interest, if the visual tracking was poor for the analysis of strain by speckle tracking. For measurements of strain by Doppler, the velocity signal was optimized, including avoidance of reverberation artefacts. In addition, three myocardial strain curves were obtained in the basal part of each segment from the TDI recordings, using a region of interest of 6 x 6 mm, which was set as a default. The region of interest was tracked frame by frame throughout the cardiac cycle to follow the myocardial movement. Special attention was made to avoid stationary artefacts and the blood pool. Nevertheless, as with other imaging modalities, clinicians inexperienced in image acquisition and analysis would need some training for optimal performance.

In addition to image quality, tissue Doppler and speckle tracking are dependent on frame rate. High frame rates are associated with high level of noise, whereas low frame rates may cause poor tracking due to excessive frame to frame displacement of speckles.[58] For strain by Doppler a low frame rate may cause an underestimation of peak values. This was taken into account in this work by obtaining gray-scale images at frame rates between 50 and 90 frames/seconds and TDI at frame rates between 140 and 160 frames/seconds. Because strain by Doppler was the only commercially available method at the start of inclusion, sufficient gray-scale images were not obtained in the first patients included. This explains why just strain by Doppler and not strain by speckle tracking was used when studying clinical endpoints in the whole patient population.

Strain by Doppler is time-consuming. The mean time to measure global strain by Doppler was 12.0 ± 1.1 minutes, and the mean time to assess LVEF was 2.3 ± 0.3 minutes ($p < 0.0001$), whereas the mean time to assess global peak systolic strain by speckle tracking was 2.6 ± 0.4 minutes. When evaluating regional myocardial function with tissue Doppler, knowledge of the limitations of this technique is essential to ensure appropriate acquisition as well as correct post-processing since artefacts often mimic pathology. Thus, especially post-processing is time-consuming and therefore strain by speckle tracking should be used in the future in order to determine global strain.

All functional parameters of myocardial deformation, including strain, are load dependent and should be interpreted with care when there are changes in loading conditions.[32,59] The measurements in this work were performed within 3.5 hours after treatment with thrombolysis which means about 2 hours after admission and at discharge or the first visit after discharge. Although all patients were considered hemodynamically stable, potential load differences could not completely be ruled out. Most likely end diastolic pressure is higher in the acute phase of AMI than at discharge, and it is therefore reasonable to assume a higher load pressure and wall stress early after thrombolytic treatment .The load-dependency is even more complex in ischemia or myocardial infarction, where intraventricular load differences might occur with reciprocal changes in the infarcted and adjacent myocardium.[60] Load may therefore affect strain more in the acute phase than at discharge.

Strain by Doppler is measured parallel to the ultrasound beam and therefore allows assessment only in the longitudinal direction. Although strain by speckle tracking also allows assessment of radial deformation, radial strain was not a topic of this work. Radial thickening is a result of myocyte thickening and shear forces of the oblique fibers in the subendocardium,[61] whereas no myofibril deformation occurs in the radial direction. Moreover, there are technical concerns about radial strain. Recent works have demonstrated that radial strain is inferior to longitudinal and circumferential strain in identifying ischemia and necrosis.[62]

Assessment of LV function by LVEF or WMSI is well established in most echolaboratories. Strain, however, is a relatively new parameter. Although reproducibility of strain is excellent, an important limitation is the inconsistency between different hardware manufacturers due to lack of industrial standard. Consequently, the results of this work cannot routinely be transferred to other echocardiographic systems, which is a weakness with the measurement of strain as compared to LVEF and WMSI.

ceCMR

Assessment of LV infarct size was performed visually and the patients were examined with a 1.5 T scanner in paper I and II. The strength of the magnetic field influences the quality of the images.[63]

All patients were examined by ceCMR between 6 and 23 months. This wide

range for ceCMR studies was due to the administration of patients who were to be examined by ceCMR. However, none of the patients experienced re-infarction between the first event and ceCMR, which indicates that LV infarct size measures were comparable in these patients. Careful anamnesis and new ECG was therefore obtained to reduce the risk of including patients with possible re-infarctions in the statistical analysis of LV infarct size. Ripa et al[64] studied short- and long-term changes in myocardial function, morphology, edema and infarct mass after STEMI evaluated by serial ceCMR. They observed a significant decrease in infarct mass from baseline to one month and unchanged mass from one month to six months. Fieno et al[65] found that LV infarct size measured by ceCMR decreases during the first weeks or months after the acute event. The fact that the changes almost exclusively occurred within the first months after the infarction may justify the wide time interval for studying the chronic scar and final LV infarct size.

Delayed myocardial enhancement is not specific for myocardial infarction and can occur in a variety of disorders.[66] Although relatively rare, inflammatory or infectious diseases of the myocardium, cardiomyopathies, cardiac neoplasms and congenital or genetic cardiac conditions might cause delayed enhancement. In contrast to myocardial infarcts, the distribution of delayed enhancement in these conditions is often midwall and does not follow the perfusion area of a coronary artery. Therefore, critical review of the distribution of late enhancement as well as the patient's history is important during analyses.

Cross-registering identical segmental locations between the echocardiographic and CMR modalities might be a problem when comparing segments from two different imaging modalities.[67] Segments within the infarct border zone are more susceptible for this possible inaccuracy because both myocardial deformation and infarct distribution are more heterogenous in these regions. Care was taken to minimize the problem.

Statistics

Common statistical tests were used in these papers with one exception. In paper III, a statistical test described by Hanley and McNeil[44] were used to compare ROC curves for LVEF and global strain as predictors of clinical cardiac outcome. Cox regression was not used in this work because this method is a "semi-parametric" approach and no

particular type of distribution is assumed for the survival times, but a strong assumption is made that the effects of the different variables on survival are constant over time and are additive in a particular scale. There are many potential difficulties when performing Cox regression. We therefore compared the ROC curves and used multivariate logistic regression analyses to assess the prognostic impact of global strain, LVEF and WMSI.

In paper I, segmental infarct size by ceCMR was compared with the corresponding strain values for strain by Doppler and by speckle tracking by using analysis of variance with the post hoc Scheffe test. In a 16 segment model, the different segments are internally dependent and the segment-wise analyses are therefore described as uncorrected. In the same paper, multivariate regression analyses were performed to compare segmental or global strain and to find the best time during the cardiac cycle for estimating final LV infarct size. However, peak systolic, end systolic and peak negative strain are not independent parameters, but reflect different time-point on the same strain curve. Multivariate regression analyses are designed to rate predictors internally by prediction skills. Since deformation defects are a consequence of infarct size rather than the opposite, a comparison of correlation coefficients for the deformation indices with LV infarct size would be a better test as described by Cohen et al.[68]

Conclusions

General Conclusion:

Global strain is a good predictor of myocardial necrosis, LV function and clinical cardiac outcome in patients with acute STEMI.

Specific Conclusions:

I. In acute STEMI, global peak systolic strain by speckle tracking should be the preferred method for predicting final LV infarct size measured by ceCMR. Global strain by speckle tracking separated small and large LV infarcts with better precision than strain by Doppler.

II. The different segmental longitudinal strain assessments (peak systolic, end systolic and peak negative strain by Doppler and speckle tracking) separated significantly between the different levels of infarct transmurality in the whole patient group. Injury was separated slightly better by strain by speckle tracking in anterior than in inferior myocardial infarction. Circumferential strain separated subendocardial from transmural necrosis better than longitudinal strain in the acute phase in patients with STEMI.

III. Global strain should preferably be measured after revascularization for optimal prediction of final LV infarct size in patients with AMI.

IV. Global strain measured after revascularization predicts LV infarct size and cardiac events superior to LVEF in patients with acute STEMI.

Reference List

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De SG, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010;121:e46-e215.

2. Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. J Am Coll Cardiol 2004;44:1533-1542.

3. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992-2002.

4. Stone PH, Raabe DS, Jaffe AS, Gustafson N, Muller JE, Turi ZG, Rutherford JD, Poole WK, Passamani E, Willerson JT, . Prognostic significance of location and type of myocardial infarction: independent adverse outcome associated with anterior location. J Am Coll Cardiol 1988;11:453-463.

5. White HD, Van de Werf FJ. Thrombolysis for acute myocardial infarction. Circulation 1998;97:1632-1646.

6. Peterson ED, Shaw LJ, Califf RM. Risk stratification after myocardial infarction. Ann Intern Med 1997;126:561-582.

7. Shan K, Constantine G, Sivananthan M, Flamm SD. Role of cardiac magnetic resonance imaging in the assessment of myocardial viability. Circulation 2004;109:1328-1334.

8. St John SM, Pfeffer MA, Plappert T, Rouleau JL, Moye LA, Dagenais GR, Lamas GA, Klein M, Sussex B, Goldman S, . Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. Circulation 1994;89:68-75.

9. Kvitting JP, Wigstrom L, Strotmann JM, Sutherland GR. How accurate is visual assessment of synchronicity in myocardial motion? An In vitro study with computer-simulated regional delay in myocardial motion: clinical implications for rest and stress echocardiography studies. J Am Soc Echocardiogr 1999;12:698-705.

10. Vartdal T, Brunvand H, Pettersen E, Smith HJ, Lyseggen E, Helle-Valle T, Skulstad H, Ihlen H, Edvardsen T. Early prediction of infarct size by strain Doppler echocardiography after coronary reperfusion. J Am Coll Cardiol 2007;49:1715-1721.

11. Fishbein MC, Meerbaum S, Rit J, Lando U, Kanmatsuse K, Mercier JC, Corday E, Ganz W. Early phase acute myocardial infarct size quantification: validation of the triphenyl tetrazolium chloride tissue enzyme staining technique. Am Heart J 1981;101:593-600.

12. Wagner GS, Freye CJ, Palmeri ST, Roark SF, Stack NC, Ideker RE, Harrell FE, Jr., Selvester RH. Evaluation of a QRS scoring system for estimating myocardial infarct size. I. Specificity and observer agreement. Circulation 1982;65:342-347.

13. Christian TF, Gibbons RJ, Clements IP, Berger PB, Selvester RH, Wagner GS. Estimates of myocardium at risk and collateral flow in acute myocardial infarction using electrocardiographic indexes with comparison to radionuclide and angiographic measures. J Am Coll Cardiol 1995;26:388-393.

14. Licka M, Zimmermann R, Zehelein J, Dengler TJ, Katus HA, Kubler W. Troponin T concentrations 72 hours after myocardial infarction as a serological estimate of infarct size. Heart 2002;87:520-524.

15. Remppis A, Ehlermann P, Giannitsis E, Greten T, Most P, Muller-Bardorff M, Katus HA. Cardiac troponin T levels at 96 hours reflect myocardial infarct size: a pathoanatomical study. Cardiology 2000;93:249-253.

16. Mollema SA, Nucifora G, Bax JJ. Prognostic value of echocardiography after acute myocardial infarction. Heart 2009;95:1732-1745.

17. Quinones MA, Greenberg BH, Kopelen HA, Koilpillai C, Limacher MC, Shindler DM, Shelton BJ, Weiner DH. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and trials: significance of left ventricular hypertrophy. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 2000;35:1237-1244.

18. Burns RJ, Gibbons RJ, Yi Q, Roberts RS, Miller TD, Schaer GL, Anderson JL, Yusuf S. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. J Am Coll Cardiol 2002;39:30-36.

19. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883.

20. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, . Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669-677.

21. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. Circ Cardiovasc Imaging 2009;2:356-364.

22. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, Pennell DJ. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J 2000;21:1387-1396.

23. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davidson TW, Davis JL, Douglas PS, Gillam LD. ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. Circulation 1997;95:1686-1744.

46

24.   Marwick TH. Should we be evaluating the ventricle or the myocardium? Advances in tissue characterization. J Am Soc Echocardiogr 2004;17:168-172.

25.   Carluccio E, Tommasi S, Bentivoglio M, Buccolieri M, Prosciutti L, Corea L. Usefulness of the severity and extent of wall motion abnormalities as prognostic markers of an adverse outcome after a first myocardial infarction treated with thrombolytic therapy. Am J Cardiol 2000;85:411-415.

26.   Galasko GI, Basu S, Lahiri A, Senior R. A prospective comparison of echocardiographic wall motion score index and radionuclide ejection fraction in predicting outcome following acute myocardial infarction. Heart 2001;86:271-276.

27.   Moller JE, Hillis GS, Oh JK, Reeder GS, Gersh BJ, Pellikka PA. Wall motion score index and ejection fraction for risk stratification after acute myocardial infarction. Am Heart J 2006;151:419-425.

28.   Edvardsen T, Skulstad H, Aakhus S, Urheim S, Ihlen H. Regional myocardial systolic function during acute myocardial ischemia assessed by strain Doppler echocardiography. J Am Coll Cardiol 2001;37:726-730.

29.   Lim P, Pasquet A, Gerber B, D'Hondt AM, Vancraeynest D, Gueret P, Vanoverschelde JL. Is postsystolic shortening a marker of viability in chronic left ventricular ischemic dysfunction? Comparison with late enhancement contrast magnetic resonance imaging. J Am Soc Echocardiogr 2008;21:452-457.

30.   Weidemann F, Wacker C, Rauch A, Bauer WR, Bijnens B, Sutherland GR, Ertl G, Voelker W, Fidler F, Strotmann JM. Sequential changes of myocardial function during acute myocardial infarction, in the early and chronic phase after coronary intervention described by ultrasonic strain rate imaging. J Am Soc Echocardiogr 2006;19:839-847.

31.   Langeland S, D'hooge J, Wouters PF, Leather HA, Claus P, Bijnens B, Sutherland GR. Experimental validation of a new ultrasound method for the simultaneous assessment of radial and longitudinal myocardial deformation independent of insonation angle. Circulation 2005;112:2157-162.

32.   Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation 2000;102:1158-1164.

33.   Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, Stoylen A, Ihlen H, Lima JA, Smiseth OA, Slordahl SA. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789-793.

34.   Cho GY, Chan J, Leano R, Strudwick M, Marwick TH. Comparison of two-dimensional speckle and tissue velocity based strain and validation with harmonic phase magnetic resonance imaging. Am J Cardiol 2006;97:1661-1666.

35.   Edvardsen T, Gerber BL, Garot J, Bluemke DA, Lima JA, Smiseth OA. Quantitative assessment of intrinsic regional myocardial deformation by Doppler strain rate echocardiography in humans: validation against three-dimensional tagged magnetic resonance imaging. Circulation 2002;106:50-56.

36.   Chan J, Hanekom L, Wong C, Leano R, Cho GY, Marwick TH. Differentiation of subendocardial and transmural infarction using two-dimensional strain rate imaging to assess short-axis and long-axis myocardial function. J Am Coll Cardiol 2006;48:2026-2033.

37.   Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z.
       Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of
       myocardial function. J Am Soc Echocardiogr 2004;17:1021-1029.

38.   Sachdev V, Aletras AH, Padmanabhan S, Sidenko S, Rao YN, Brenneman CL, Shizukuda Y, Lie GR,
       Vincent PS, Waclawiw MA, Arai AE. Myocardial strain decreases with increasing transmurality of
       infarction: a Doppler echocardiographic and magnetic resonance correlation study. J Am Soc Echocardiogr
       2006;19:34-39.

39.   Brown J, Jenkins C, Marwick TH. Use of myocardial strain to assess global left ventricular function: a
       comparison with cardiac magnetic resonance and 3-dimensional echocardiography. Am Heart J
       2009;157:102-105.

40.   Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA,
       Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of
       the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on
       Clinical Cardiology of the American Heart Association. Circulation 2002;105:539-542.

41.   Gjesdal O, Hopp E, Vartdal T, Lunde K, Helle-Valle T, Aakhus S, Smith HJ, Ihlen H, Edvardsen T. Global
       longitudinal strain measured by two-dimensional speckle tracking echocardiography is closely related to
       myocardial infarct size in chronic ischaemic heart disease. Clin Sci (Lond) 2007;113:287-296.

42.   Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N,
       Sahn D, Schnittger I, . Recommendations for quantitation of the left ventricle by two-dimensional
       echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on
       Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-367.

43.   Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ,
       Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for
       chamber quantification: a report from the American Society of Echocardiography's Guidelines and
       Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the
       European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc
       Echocardiogr 2005;18:1440-1463.

44.   Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves
       derived from the same cases. Radiology 1983;148:839-843.

45.   White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic
       volume as the major determinant of survival after recovery from myocardial infarction. Circulation
       1987;76:44-51.

46.   Park YH, Kang SJ, Song JK, Lee EY, Song JM, Kang DH, Kim YH, Lee CW, Hong MK, Kim JJ, Park SW,
       Park SJ. Prognostic value of longitudinal strain after primary reperfusion therapy in patients with anterior-
       wall acute myocardial infarction. J Am Soc Echocardiogr 2008;21:262-267.

47.   Barclay JL, Egred M, Kruszewski K, Nandakumar R, Norton MY, Stirrat C, Redpath TW, Walton S, Hillis
       GS. The Relationship between Transmural Extent of Infarction on Contrast Enhanced Magnetic Resonance

Imaging and Recovery of Contractile Function in Patients with First Myocardial Infarction Treated with Thrombolysis. Cardiology 2006;108:217-222.

48. Gerber BL, Garot J, Bluemke DA, Wu KC, Lima JA. Accuracy of contrast-enhanced magnetic resonance imaging in predicting improvement of regional myocardial function in patients after acute myocardial infarction. Circulation 2002;106:1083-1089.

49. Wu E, Ortiz JT, Tejedor P, Lee DC, Bucciarelli-Ducci C, Kansal P, Carr JC, Holly TA, Lloyd-Jones D, Klocke FJ, Bonow RO. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. Heart 2008;94:730-736.

50. Thiele H, Kappl MJ, Conradi S, Niebauer J, Hambrecht R, Schuler G. Reproducibility of chronic and acute infarct size measurement by delayed enhancement-magnetic resonance imaging. J Am Coll Cardiol 2006;47:1641-1645.

51. Otterstad JE, Froeland G, St John SM, Holme I. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. Eur Heart J 1997;18:507-513.

52. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343:1445-1453.

53. Brunvand H, Rynning SE, Hexeberg E, Westby J, Grong K. Non-uniform recovery of segment shortening during reperfusion following regional myocardial ischaemia despite uniform recovery of ATP. Cardiovasc Res 1995;30:138-146.

54. Skulstad H, Edvardsen T, Urheim S, Rabben SI, Stugaard M, Lyseggen E, Ihlen H, Smiseth OA. Postsystolic shortening in ischemic myocardium: active contraction or passive recoil? Circulation 2002;106:718-724.

55. Teske AJ, De Boeck BW, Melman PG, Sieswerda GT, Doevendans PA, Cramer MJ. Echocardiographic quantification of myocardial function using tissue deformation imaging, a guide to image acquisition and analysis using tissue Doppler and speckle tracking. Cardiovasc Ultrasound 2007;5:27.

56. Hanekom L, Cho GY, Leano R, Jeffriess L, Marwick TH. Comparison of two-dimensional speckle and tissue Doppler strain measurement during dobutamine stress echocardiography: an angiographic correlation. Eur Heart J 2007;28:1765-1772.

57. Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Hol PK, Smith HJ, Smiseth OA, Edvardsen T, Skulstad H. Strain echocardiography and wall motion score index predicts final infarct size in patients with non-ST-segment-elevation myocardial infarction. Circ Cardiovasc Imaging 2010;3:187-194.

58. Marwick TH. Measurement of strain and strain rate by echocardiography: ready for prime time? J Am Coll Cardiol 2006;47:1313-1327.

59. Burns AT, La GA, D'hooge J, MacIsaac AI, Prior DL. Left ventricular strain and strain rate: characterization of the effect of load in human subjects. Eur J Echocardiogr 2010;11:283-289.

60.   Smalling RW, Ekas RD, Felli PR, Binion L, Desmond J. Reciprocal functional interaction of adjacent myocardial segments during regional ischemia: an intraventricular loading phenomenon affecting apparent regional contractile function in the intact heart. J Am Coll Cardiol 1986;7:1335-1346.

61.   LeGrice IJ, Takayama Y, Covell JW. Transverse shear along myocardial cleavage planes provides a mechanism for normal systolic wall thickening. Circ Res 1995;77:182-193.

62.   Gjesdal O, Helle-Valle T, Hopp E, Lunde K, Vartdal T, Aakhus S, Smith HJ, Ihlen H, Edvardsen T. Noninvasive separation of large, medium, and small myocardial infarcts in survivors of reperfused ST-elevation myocardial infarction: a comprehensive tissue Doppler and speckle-tracking echocardiography study. Circ Cardiovasc Imaging 2008;1:189-196.

63.   Wieben O, Francois C, Reeder SB. Cardiac MRI of ischemic heart disease at 3 T: potential and challenges. Eur J Radiol 2008;65:15-28.

64.   Ripa RS, Nilsson JC, Wang Y, Sondergaard L, Jorgensen E, Kastrup J. Short- and long-term changes in myocardial function, morphology, edema, and infarct mass after ST-segment elevation myocardial infarction evaluated by serial magnetic resonance imaging. Am Heart J 2007;154:929-936.

65.   Fieno DS, Hillenbrand HB, Rehwald WG, Harris KR, Decker RS, Parker MA, Klocke FJ, Kim RJ, Judd RM. Infarct resorption, compensatory hypertrophy, and differing patterns of ventricular remodeling following myocardial infarctions of varying size. J Am Coll Cardiol 2004;43:2124-2131.

66.   Vogel-Claussen J, Rochitte CE, Wu KC, Kamel IR, Foo TK, Lima JA, Bluemke DA. Delayed enhancement MR imaging: utility in myocardial assessment. Radiographics 2006;26:795-810.

67.   Wu KC, Lima JA. Noninvasive imaging of myocardial viability: current techniques and future developments. Circ Res 2003;93:1146-1158.

68.   Cohen J, Cohen P, West SG, Aiken LS. Applied multiple regression/correlation analysis for the behavioral sciences.3rd ed. Hillsdale, NJ:Lawrence Erlbaum 2003:56.

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