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Effect of Early Metoprolol during ST-Segment Elevation Myocardial Infarction on Left Ventricular Strain: Feature Tracking Cardiovascular Magnetic Resonance Substudy from the METOCARD-CNIC trial

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ABSTRACT

Objectives: To evaluate the effect of early intravenous metoprolol on left ventricular (LV) strain assessed with feature tracking cardiovascular magnetic resonance (CMR).

Background: Early intravenous metoprolol before primary percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) portends better outcomes in the METOCARD-CNIC trial.

Methods: A total of 197 patients with acute anterior STEMI who were enrolled in the METOCARD-CNIC trial (100 allocated to intravenous metoprolol before primary PCI and 97 controls) were evaluated. LV global circumferential strain (GCS) and global longitudinal strain (GLS) were measured with feature tracking CMR at 1 week and 6 months after STEMI and compared between randomization groups.

Results: Patients who received early intravenous metoprolol had significantly more preserved LV strain compared to the controls at 1 week after STEMI (GCS: -13.9±3.8% versus -12.6±3.9%, respectively; *P*=0.013; GLS: -11.9±2.8% versus -10.9±3.2%, respectively; *P*=0.032). In both groups, LV strain significantly improved during follow-up (mean difference between 6-month and 1-week strain for the metoprolol group: GCS: -2.9%, 95% CI: -3.5% to -2.4; GLS: -2.9%, 95% CI: -3.4 to -2.4; both *P*<0.001; the control group: GCS: -3.4%, 95% CI: -3.9% to -2.8%; GLS: -3.4%, 95% CI: -3.9% to -3.0%; both *P*<0.001). When dividing the overall cohort of patients in quartiles of GCS and GLS, there were significantly less patients in the first quartile (i.e. the worst LV systolic function) who received early intravenous metoprolol compared to controls at 1 week and 6 months (*P*<0.05 for GCS and GLS at both time points).

Conclusions: In patients with anterior STEMI, early administration of intravenous metoprolol before primary PCI was associated with significantly less patients with severely depressed LV GCS and GLS, both at 1 week and 6 months. Feature tracking CMR represents a complementary tool to evaluate the benefits of cardioprotective therapies.

Keywords: feature tracking, cardiovascular magnetic resonance, global circumferential strain, global longitudinal strain, intravenous metoprolol, ST-segment elevation myocardial infarction.

CONDENSED ABSTRACT

Feature tracking CMR allows myocardial strain assessment from standard CMR cine images. In 197 patients with acute anterior STEMI (100 randomized to intravenous metoprolol before primary PCI and 97 controls) GCS and GLS were evaluated with feature tracking CMR at 1 week and 6 months after STEMI. Overall, GCS and GLS improved from 1 week to 6 months after STEMI. Early intravenous metoprolol before primary PCI was associated with significantly less patients with severely depressed LV GCS and GLS at both time points, supporting its use in clinically stable STEMI population. Feature tracking CMR represents a complementary tool to evaluate the benefits of cardioprotective therapies.

ABBREVIATIONS LIST

CI – confidence interval

CMR – cardiovascular magnetic resonance

GCS – global circumferential strain

GLS – global longitudinal strain

LGE – late gadolinium enhancement

LV – left ventricle/left ventricular

LVEF – left ventricular ejection fraction

PCI – percutaneous coronary intervention

STEMI – ST-segment elevation myocardial infarction

INTRODUCTION

The long-term treatment with beta-blockers after ST-segment elevation myocardial infarction (STEMI) is well established and the benefit appears to be greatest for patients with myocardial infarction complicated by heart failure, left ventricular (LV) systolic dysfunction, or ventricular arrhythmias (1,2). Current European and American guidelines recommend initiating oral beta-blockers in the first 24 hours after STEMI (1,2). The role of routine early, intravenous beta-blockers administration prior to primary percutaneous coronary intervention (PCI) is less firmly established. In the context of reduced oxygen supply during myocardial infarction, beta-blockers have the potential to reduce ischemic injury when administered prior to PCI, through their effect on slowing of heart rate, decreasing myocardial contractility, and lowering systemic blood pressure. In addition, some beta-blockers have shown to be able to reduce reperfusion-injury by inhibiting neutrophils function (3). The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial showed that early administration of intravenous metoprolol before primary PCI significantly reduced infarct size 1 week post-STEMI as evaluated by cardiovascular magnetic resonance (CMR) imaging (4). In addition, early metoprolol administration was associated with improved long-term LV ejection fraction (LVEF), fewer indications for cardioverter-defibrillator implantation, and fewer heart failure readmissions (5). Accordingly, current European guidelines indicate that intravenous beta-blockers should be considered at the time of presentation in STEMI patients undergoing primary PCI provided that there are no contraindications, no signs of acute heart failure, and the systolic blood pressure is >120 mmHg (1).

The impact of early intravenous metoprolol on LV myocardial strain has not yet been evaluated. In contrast to LVEF, LV strain does not rely on geometrical assumptions, shows superior intra- and inter-observer reproducibility and can detect subtle systolic dysfunction in patients with preserved LVEF (6,7). Recent development of feature tracking CMR allows multidirectional myocardial strain assessment from standard cine images without the need for specialized pulse sequences or additional scanning time (8). In the METOCARD-CNIC

trial population, we evaluated LV global circumferential (GCS) and longitudinal (GLS) strain measured with feature tracking CMR both at 1 week and 6 months after primary PCI.

METHODS

Patient population

The present study included patients who were enrolled in the METOCARD-CNIC trial and completed 1-week and 6-month CMR study. Briefly, the multicenter randomized METOCARD-CNIC clinical trial recruited patients with first anterior STEMI undergoing primary PCI (9). A total of 270 patients were randomized to receive up to 15 mg intravenous metoprolol before reperfusion versus conventional therapy. All patients received oral metoprolol, first dose 12-24 hours after STEMI. Exclusion criteria were Killip class III to IV acute heart failure, systolic blood pressure persistently <120 mmHg, PR interval >240 milliseconds (or type II–III atrioventricular block), heart rate persistently <60 beats/min, or active treatment with any beta-blocker agent. Of the initial population, 202 patients underwent 2 CMR studies, at 1 week (5 to 7 days) and 6 months after STEMI. Conventional CMR parameters of LV dimensions, function and myocardial scar and LV GCS and GLS measured with feature tracking analysis were evaluated at both time points for the overall population as a single group, and for each randomization treatment arm individually.

The study was approved by the ethical committees and institutional review boards at each participating center. All eligible patients gave written informed consent.

Cardiovascular magnetic resonance

The CMR protocol has been described in detail elsewhere (9). Data acquisition was performed with 1.5 and 3.0 T CMR scanners. LV 2-, 3- and 4-chamber views and a stack of contiguous short-axis slices covering the whole LV were acquired with steady-state free precession functional cine imaging. Typical acquisition parameters were: voxel size 1.6×2 mm, slice thickness 8 mm, gap 0 mm, cardiac phases 25-30, TR 3.5, TE 1.7, flip angle 40, SENSE 1.5, averages 1, FOV 360 × 360 mm. Subsequently, segmented inversion recovery

gradient echo sequence acquired 10-15 minutes after a cumulative dose of 0.2 mmol/kg intravenous gadolinium contrast agent (Magnevist, Schering AG, Berlin, Germany) was employed for myocardial necrosis/fibrosis imaging. LV volumes, LV mass, LVEF and late gadolinium enhancement (LGE) data were analyzed with dedicated software (QMass MR 7.5; Medis, Leiden, the Netherlands) as described before (9).

Feature tracking CMR analysis

Feature tracking CMR analysis was performed on steady-state free precession cine images with dedicated software (CVI[42] v5.3, Circle Cardiovascular Imaging, Calgary, Canada) (Figure 1, Videos 1 and 2 in supplementary material). First, the LV endo- and epicardium were delineated at end-diastole in the LV 2-, 3- and 4-chamber views and contiguous short-axis slices and the LV reference points were defined: the mitral annulus and the LV apex in long-axis views and the anterior right ventricular insertion point in the short-axis slices. The most basal short-axis slices, in which the image plane showed LV myocardium only at end-diastole but not at end-systole were excluded. The outlined myocardium borders were automatically tracked throughout the cardiac cycle with fully automated feature tracking analysis. The quality of the myocardium tracking was visually evaluated. Global time-strain curves were obtained and peak LV GCS and GLS values were recorded.

A single observer (TP) performed feature tracking analysis of CMR data. The same observer repeated the analysis of 20 randomly selected CMR scans after 4 weeks to assess the intra-observer variability. A second observer (JMMC), blinded to the results of the first observer, re-measured a different subset of 20 randomly selected CMR scans for the assessment of inter-observer variability.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies (percentages). Patients were divided into 2 groups according to the treatment received. Comparisons between the early metoprolol group and the control group were

performed using independent samples t-test for continuous variables and Pearson's Chi square test or Fischer's exact test for categorical variables. Fischer's exact test was used when the expected value of a categorical variable was <5. Comparisons between 1-week and 6-month CMR data were performed using paired samples t-test. In addition, the study population was divided in quartiles of LV GCS and GLS. The number of patients within the first quartile of LV GCS and GLS (worst LV systolic function) at each randomization treatment arm (early intravenous metoprolol vs controls) was compared with Pearson's Chi square test at 1 week and 6 months of follow-up. In addition, logistic regression analysis was performed to assess the value of LV GCS and GLS 1 week after STEMI to predict LVEF normalization (≥50%) at 6 months. Odds ratios and 95% confidence intervals (CI) were calculated and adjusted for infarct size (LGE extent) at 1-week CMR, demographic and clinical variables (age, sex, body mass index, presence of hypertension, diabetes, dyslipidemia, smoking status) and treatment randomization arm (early intravenous metoprolol vs. controls).

The intra- and inter-observer agreement for GCS and GLS measurements were assessed with intraclass correlation coefficients. A two-sided *P*-value of <0.05 was statistically significant and excellent agreement was defined as an intraclass correlation coefficient >0.9. All statistical analyses were performed using IBM SPSS Statistics 23 (IBM, Armonk, New York).

RESULTS

Of the initial 202 patients who underwent 2 CMR studies, feature tracking CMR analysis was feasible in 197 patients (early metoprolol group: N=100; control group: N=97) and they formed the population of the present analysis. LV GLS analysis at 6 months was feasible in 195 patients (early metoprolol group: N=99; control group: N=96).

Patients demographics, cardiovascular risk factors, clinical characteristics at recruitment and procedural characteristics of the overall population (mean age 58.1 years, 88% male) and the patients divided according to received randomization treatment

(metoprolol vs control) are presented in Table 1. There were no statistically significant differences between both groups. Conventional and feature tracking CMR parameters of LV structure and function, evaluated at 1 week and 6 months after STEMI for the overall population and for each randomization treatment arm individually, are presented in Table 2.

LV conventional and feature tracking CMR parameters 1 week after STEMI

One week after intervention (metoprolol or control), patients who received early intravenous metoprolol showed significantly smaller LV end-systolic volumes, higher LVEF and smaller infarct sizes assessed by LGE (Table 2, Figure 2). In addition, patients who received early intravenous metoprolol had more preserved LV GCS and GLS than patients in the control group (GCS: -13.9±3.8% versus -12.6±3.9%, respectively; *P*=0.013; GLS: -11.9±2.8% versus -10.9±3.2%, respectively; *P*=0.032).

Changes in LV conventional and feature tracking CMR parameters between 1-week and 6-month follow-up after STEMI

There were significant changes in conventional CMR parameters and LV strain between 1-week and 6-month follow-up in the overall population and in both study treatment arms (Table 3, Figure 2 and 3). LV end-diastolic and end-systolic volumes significantly increased over time. However, LV dilation was more pronounced for LV end-diastolic volumes than for LV end-systolic volumes, partly explaining the significant improvement of LVEF over time. The percentage of LV myocardium with LGE significantly decreased over the 6 months of follow-up. In addition, LV GCS and GLS significantly improved over the 6-month follow-up (mean difference between 6-month and 1-week strain for the metoprolol group: GCS: -2.9%, 95% CI: -3.5% to -2.4; GLS: -2.9%, 95% CI: -3.4 to -2.4; both *P*<0.001; the control group: GCS: -3.4%, 95% CI: -3.9% to -2.8%; GLS: -3.4%, 95% CI: -3.9% to -3.0%; both *P*<0.001).

LV GCS and GLS at 1 week after STEMI were significant predictors of LVEF normalization (LVEF ≥50%) at 6-month follow-up (Supplementary Table 1). Each 1 percent increase in LV GCS was associated with 40.8% higher likelihood of LVEF normalization

(*P*<0.001) and each 1% of increase in LV GLS was associated with 40.9% higher likelihood of LVEF normalization at 6 months after STEMI (*P*<0.001). Both, LV GCS and GLS, remained significant predictors of LVEF normalization after adjusting for the extent of LGE on 1-week CMR, demographic and clinical variables and treatment randomization arm (*P*<0.001 for both).

LV conventional and feature tracking CMR parameters 6 months after STEMI

The improvements in LV conventional and feature tracking CMR parameters resulted in non-significant differences in LV end-diastolic volumes, LV mass and LGE between both treatment arms at 6 months (Table 2, Figure 2). However, patients who received early intravenous metoprolol still had significantly smaller LV end-systolic volumes and higher LVEF. In addition, patients who received early intravenous metoprolol showed a non-significant trend for more preserved LV strain compared to patients in the control group (GCS: -16.9±4.0% versus -15.9±4.4%, respectively; *P*=0.122; GLS: -14.8±2.9% versus -14.4±3.0%, respectively; *P*=0.379).

The effect of early metoprolol on severe LV systolic dysfunction

When dividing the overall cohort of patients in quartiles of GCS and GLS, there were significantly less number of patients receiving early intravenous metoprolol in the first GCS and GLS quartile (i.e. the worst LV systolic function), both at 1 week and at 6 months (Table 4, Figure 4). At 1 week after STEMI, there were 18 patients who received early intravenous metoprolol versus 31 patients with the conventional treatment in the first GCS quartile group (≥-10.0%) (*P*=0.023) and 13 patients who received early metoprolol versus 36 controls in the first GLS quartile group (≥-9.3%) (*P*<0.001). At 6 months after STEMI, there were 17 patients who received early intravenous metoprolol versus 32 patients with the conventional treatment in the first GCS quartile group (≥-13.1%) (*P*=0.009) and 18 patients who received early metoprolol versus 31 controls in the first GLS quartile group (≥-12.8%) (*P*=0.023).

Reproducibility of global left ventricular strain measurements

Excellent intra- and inter-observer variabilities for the feature tracking CMR analysis of GCS and GLS were obtained. The intra-observer intraclass correlation coefficients (95% CI) for the measurement of LV GCS and GLS were 0.990 (0.975-0.996) and 0.982 (0.955-0.993), respectively. Furthermore, the inter-observer intraclass correlation coefficients (95% CI) for the measurement of LV GCS and GLS were 0.995 (0.987-0.998) and 0.990 (0.976-0.996), respectively.

DISCUSSION

The present study demonstrates that in patients with anterior STEMI treated with primary PCI, early administration of intravenous metoprolol was associated with more preserved LV GCS and GLS at 1 week after myocardial infarction as compared to controls. In addition, early administration of intravenous metoprolol before primary PCI was associated with significantly less patients with severely depressed GCS and GLS both at 1 week and 6 months. Altogether, these data indicate that early intravenous metoprolol before reperfusion improves short and long-term LV systolic dysfunction as evaluated with feature tracking CMR.

LV conventional and feature tracking CMR parameters 1 week after STEMI

Acute myocardial infarction results in myocardial cell necrosis and changes in extracellular collagen matrix that portend adverse consequences on LV structure and function (10). While early intravenous beta-blocker administration offers physiological rationale for lowering the myocardial infarction burden, their routine use has been disputed over the last decades due to the conflicting data on patients outcome (11) The METOCARD-CNIC trial was the first randomized control trial in the modern era of primary PCI in STEMI patients, showing that early administration of intravenous metoprolol resulted in significant reduction of LV end-systolic volumes, increase in LVEF and smaller LGE-assessed infarct size 1 week after anterior STEMI, as evaluated by CMR imaging (4). The present study provides additional

information on the effect of early intravenous metoprolol on LV systolic function by means of circumferential and longitudinal shortening, assessed with novel feature tracking CMR algorithm. This is important since LV strain with speckle tracking echocardiography has been shown to be a more sensitive marker of LV dysfunction (7) and to provide incremental prognostic information over LVEF in the STEMI population (12). Recently, clinical implications of feature tracking CMR in STEMI have been demonstrated (13,14). Our results show that GCS and GLS were more preserved in patients who received early intravenous metoprolol, supporting the rationale to use beta-blocker intravenously in clinically stable STEMI patients before primary PCI (1).

Time course of LV structural and functional changes after STEMI

In the healing process of acute myocardial infarction important structural and functional changes take place in both the infarct area and the remote zone (10). Several studies have focused on LV remodeling after acute myocardial infarction (15-17). In a large prospective STEMI registry including 507 patients treated with primary PCI and imaged with CMR at 1 week and 6 months, LV end-diastolic volume increased (from 79±21 mL/m^2 to 81±23 mL/m^2; *P*=0.06) and LV end-systolic volume decreased (from 41±19 mL/m^2 to 39±21 mL/m^2; *P*=0.02) over time (16). This resulted in a significant increase in LVEF (from 50±12% to 54±13%, respectively; *P*<0.001). In the present study including a homogenous population with anterior STEMI patients treated with primary PCI, LV end-diastolic and LV end-systolic volumes both increased significantly over time in patients receiving early intravenous metoprolol as well as in controls (Table 3, Figure 2 and 3). However, the increase was proportionally larger for LV end-diastolic volume than for LV end-systolic volume, resulting in an increase in LVEF. Furthermore, several authors have reported a reduction in infarct size, assessed with LGE CMR in STEMI patients treated with primary PCI (16,18). Engblom et al. (18) showed a progressive decrease of LGE, expressed as the percentage of total LV mass, from days 1, 7, 42 to 182; however, there was no significant additional reduction of hyperenhanced myocardium at 1 year. The LGE reduction occurred predominantly during

the first week after infarction (63% of the total 1-year reduction). In addition, Bodi et al. (16) reported significant reduction of LGE from 1 week to 6 months after STEMI (21±14% and 17±12%, respectively; *P*<0.001). This is in line with the results of the present study, which also demonstrated a decrease in LV hyperenhancement from 1 week to 6 months post-infarction.

In addition, the present study evaluated LV strain with feature tracking CMR. LV strain has been extensively studied with speckle tracking echocardiography after acute myocardial infarction (19). On the other hand, global LV strain with CMR after myocardial infarction has been less extensively evaluated, but a few studies investigated the time changes of regional LV strain, using different myocardial tagging techniques (20,21). Kidambi et al. (20) showed an improvement of infarct zone peak systolic circumferential strain from day 2 to day 90 in 39 patients after STEMI treated with primary PCI, using complementary spatial modulation of magnetization myocardial tagging technique. Neizel et al. (21) demonstrated an improvement in peak systolic circumferential strain in the myocardial segments with >50% transmural LGE (*P*<0.05) with strain-encoded imaging. The present study is, however, the first to assess the time course of GCS and GLS in a large anterior STEMI population with feature tracking CMR. We demonstrated an overall improvement of 3.2% of GCS and GLS between 1-week and 6-month follow-up (*P*<0.001 for both).

The effect of metoprolol on long-term results

The results of the METOCARD-CNIC trial have shown long-term benefit of early intravenous metoprolol after acute anterior STEMI (5). Patients who received early intravenous metoprolol had smaller LV end-systolic volumes and more preserved LVEF at 6 months after STEMI, however there were no statistically significant differences in LGE-assessed infarct size between both treatment arms. In the present analysis, GCS and GLS showed a tendency towards more preserved values in the metoprolol group, but the differences did not reach the level of statistical significance. These results suggest that GCS and GLS are more

closely related to myocardial infarct size, assessed with LGE CMR, than to changes in LV volumes, described by LVEF. This is in line with the literature, showing that GLS with echocardiography is a better predictor of LGE-assessed infarct size compared to LVEF, whether measured in the acute phase after revascularization or at follow-up (22,23).

The different effects of metoprolol on GCS and GLS between 1-week and 6-month follow-up might be explained by the kinetics of the healing process of myocardial infarction. Edema is a very dynamic process during the first week after myocardial infarction (24), and strain closely associates with its intensity and volume (20). Moreover, cardioprotective therapies may affect the extent and intensity of post-myocardial infarction edema (25). We may reasonably assume that the differences in LV GCS and GLS between both treatment arms were more pronounced in the acute phase because of a blunted edematous reaction in metoprolol treated patients as compared to controls and have diluted at 6-month follow-up due an overall large resorption of edema and necrotic tissue (26,27).

Importantly however, when dividing the overall cohort of patients in quartiles of GCS and GLS, there were significantly less number of patients receiving early intravenous metoprolol in the first GCS and GLS quartile (i.e. the worst LV systolic function), both at 1 week and at 6 months after STEMI (Figure 4). This shows that early metoprolol administration has a long-term beneficial effect on the healing process of STEMI and prevents severe LV systolic dysfunction. Our results support the use of early intravenous metoprolol in STEMI patients without contraindications to beta-blockers undergoing primary PCI.

Study limitations

Feature tracking is a novel technique to assess LV strain with CMR. Recommendations on how to perform feature tracking analysis are lacking, there are no accepted standard reference values for LV strain and the agreement between different vendors of feature tracking software is largely unknown (28). However, LV strain with feature tracking CMR has shown to closely correlate with myocardial tagging and speckle tracking echocardiography

and demonstrated superior intra- and inter-observer variability compared to both methods (29,30). Furthermore, evaluation of LV strain was not a predefined study endpoint of the METOCARD-CNIC trial. Of the initial 202 patients who underwent 2 CMR studies in the METOCARD-CNIC trial, 5 patients were excluded from the LV strain analysis (7 patients from the analysis of GLS at 6 months) due to poor CMR cine image quality, which may have influenced our results. However, 98% (97%) feasibility of strain assessment with feature tracking CMR is similar to what has been described before (29,30).

CONCLUSION

Early intravenous metoprolol is associated with improved LV strain at 1 week after the acute anterior STEMI. Furthermore, early intravenous metoprolol is associated with less patients having worst LV systolic function at 1-week and at 6-month follow-up, compared to controls. In conclusion, early metoprolol administration before primary PCI reduces the incidence of severe LV systolic dysfunction, both at short- and long-term follow-up as evaluated by feature tracking CMR.

PERSPECTIVES

Competency in medical knowledge

Recent development of feature tracking CMR allows multidirectional myocardial strain assessment from standard CMR cine images without the need for specialized pulse sequences or additional scanning time. Early intravenous metoprolol in acute anterior STEMI before primary PCI was associated with significantly less patients with severely depressed LV strain at follow-up. Feature tracking CMR provides a powerful complementary tool to evaluate the benefits of cardioprotective therapies.

Translational outlook

Further studies are required to elucidate whether LV strain assessment with feature tracking CMR provides incremental prognostic information on LV remodeling and patients outcome after STEMI.

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Figure 1: Feature tracking cardiovascular magnetic resonance. A: Left ventricular (LV) mid-cavity short-axis and 4-chamber long-axis end-diastolic steady-state free precession images. LV endo- and epicardium (red and green lines) were delineated and LV reference points were defined: the anterior right ventricular insertion point in the short-axis view and the mitral annulus and LV apex in the 4-chamber view. The same method was repeated in the remaining long- and short-axis slices. **B** and **C**: Visual evaluation of myocardium tracking (Video 1 and 2 in supplementary material). The interventricular septum and LV anterior wall in the short-axis view and the mid-to-apical septum and apex in 4-chamber view (infarcted area) show impaired deformation compared to the other myocardial segments (**B** = end-diastole, **C** = end-systole). **D**: Global time-strain curves were obtained and peak global circumferential strain (-11.9%, top image) and peak global longitudinal strain (-10.2%, bottom image) values were recorded.

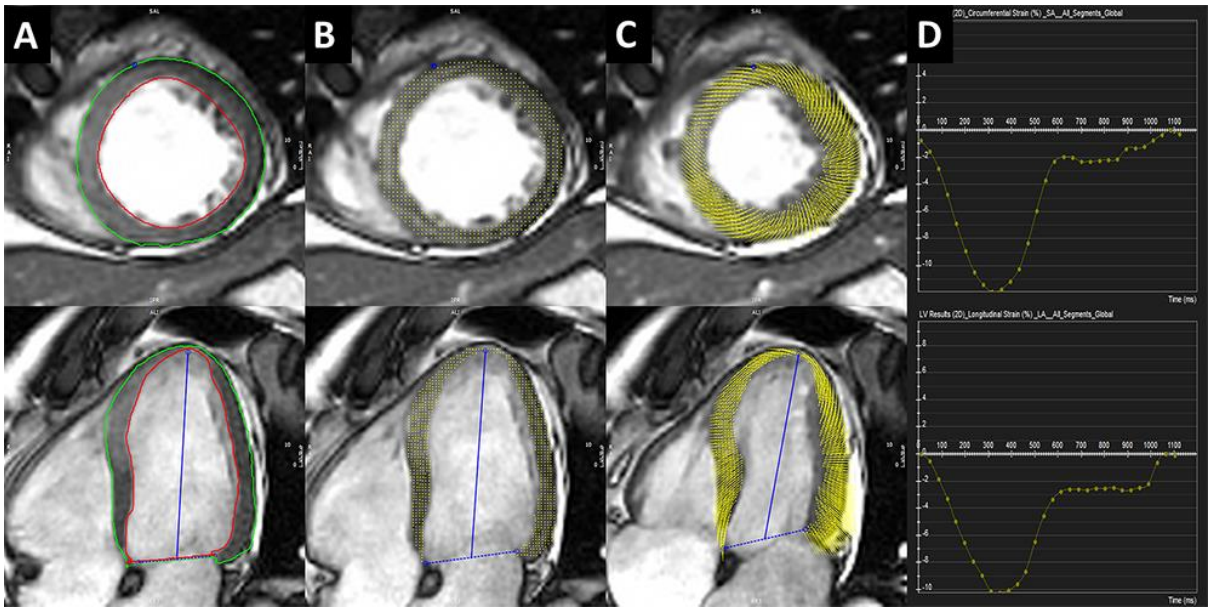

Figure 2: Time course and effect of treatment randomization on conventional and feature tracking cardiovascular magnetic resonance parameters after ST-segment elevation myocardial infarction. Left ventricular end-diastolic volume (LVEDV) (**A**), left ventricular end-systolic volume (LVESV) (**B**), left ventricular ejection fraction (LVEF) (**C**), late gadolinium enhancement (LGE) (**D**), peak global circumferential strain (GCS) (**E**) and peak global longitudinal strain (GLS) (**F**) in the early intravenous metoprolol and the control group, at 1 week and at 6 months after the acute event. The asterisks represent the mean values and the error bars represent the standard errors of the mean. *P*-values describe the statistical significance between both treatment arms at each time point.

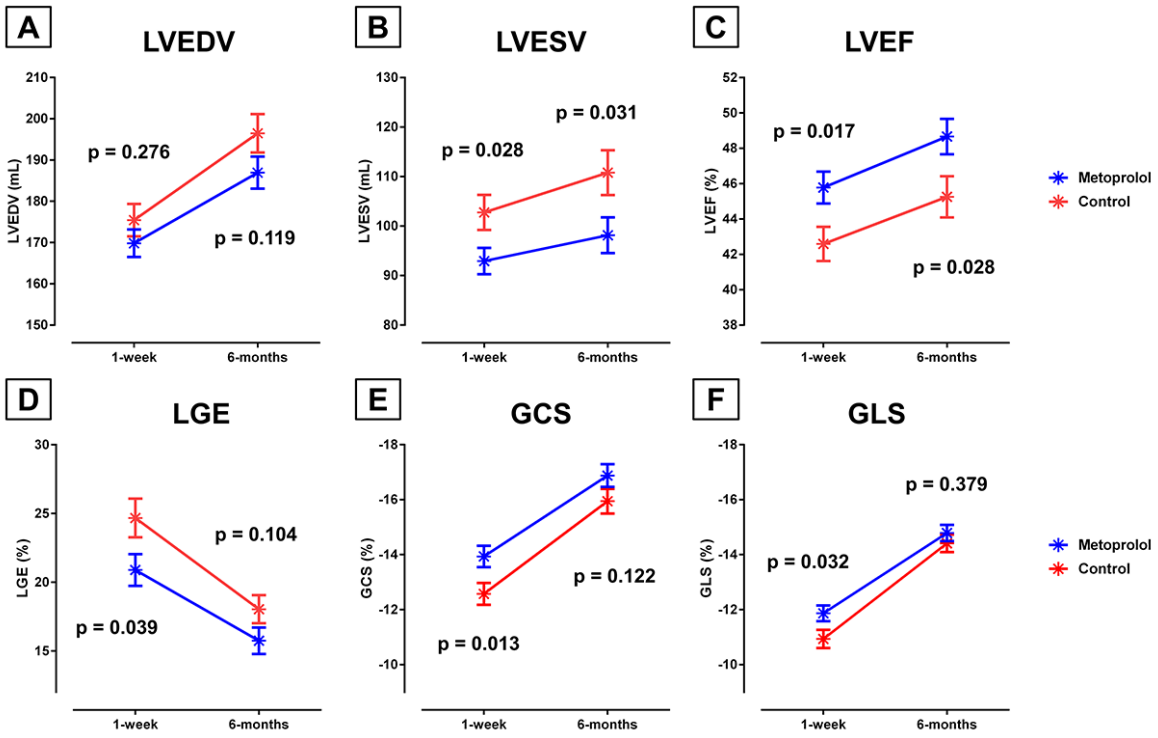

Figure 3: Time course of conventional and feature tracking cardiovascular magnetic resonance parameters after ST-segment elevation myocardial infarction in the overall population. Left ventricular end-diastolic volume (LVEDV) (**A**), left ventricular end-systolic volume (LVESV) (**B**), left ventricular ejection fraction (LVEF) (**C**), late gadolinium enhancement (LGE) (**D**), peak global circumferential strain (GCS) (**E**) and peak global longitudinal strain (GLS) (**F**) in the overall population at 1 week and at 6 months after the acute event. Dots are individual patient data. Blue lines represent the mean ± standard error of the mean. *P*-values describe the statistical significance between the two time points.

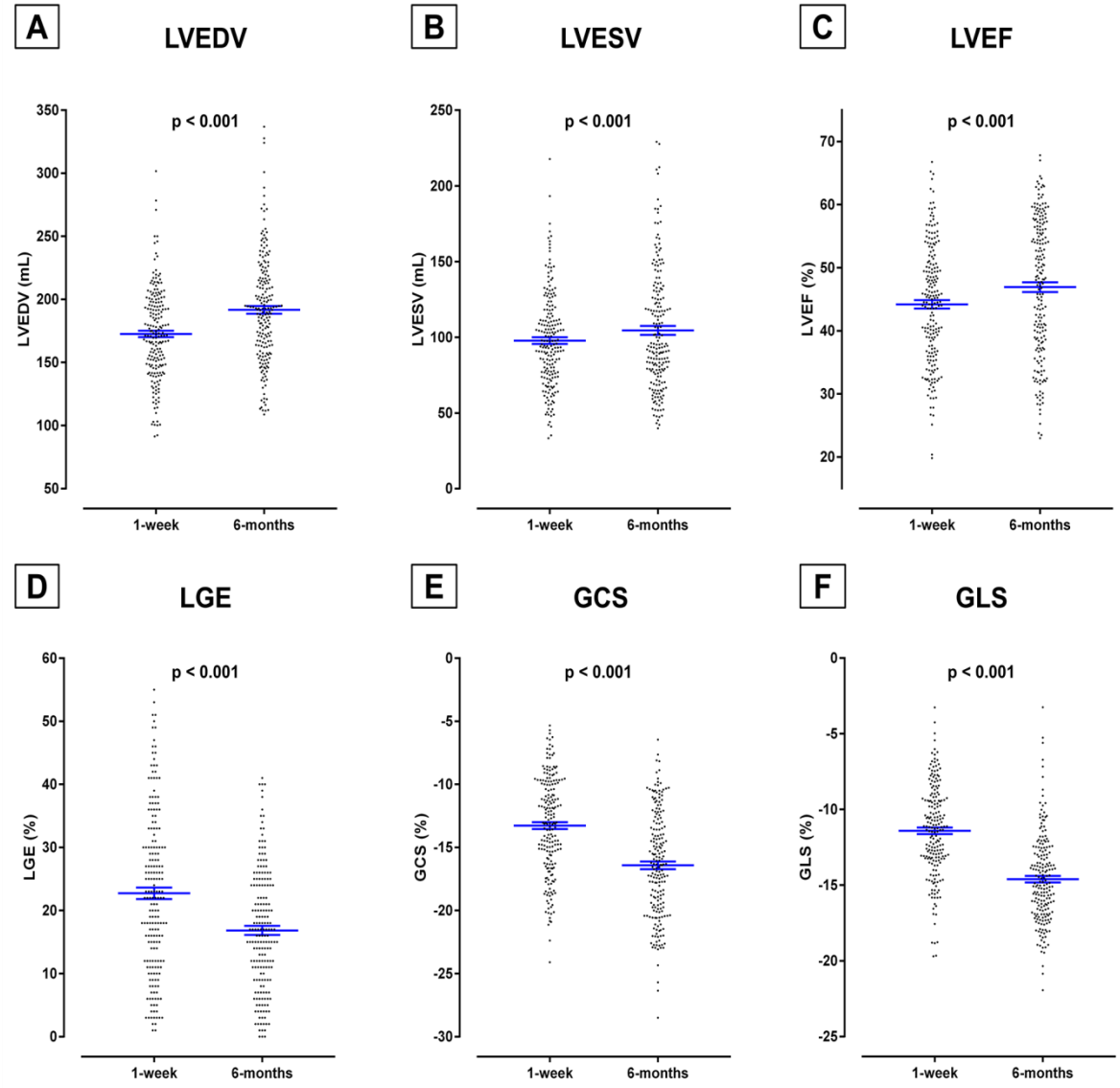

Figure 4: Number of patients within the first quartile of LV GCS and GLS (worst LV systolic function) in the early metoprolol group versus controls at 1-week and 6-month follow-up. Patients in the first global circumferential strain (GCS) and global longitudinal strain (GLS) quartile (worst LV systolic function) were compared according to the treatment received (early intravenous metoprolol vs conventional therapy) at 1 week and at 6 months after acute ST-segment elevation myocardial infarction.

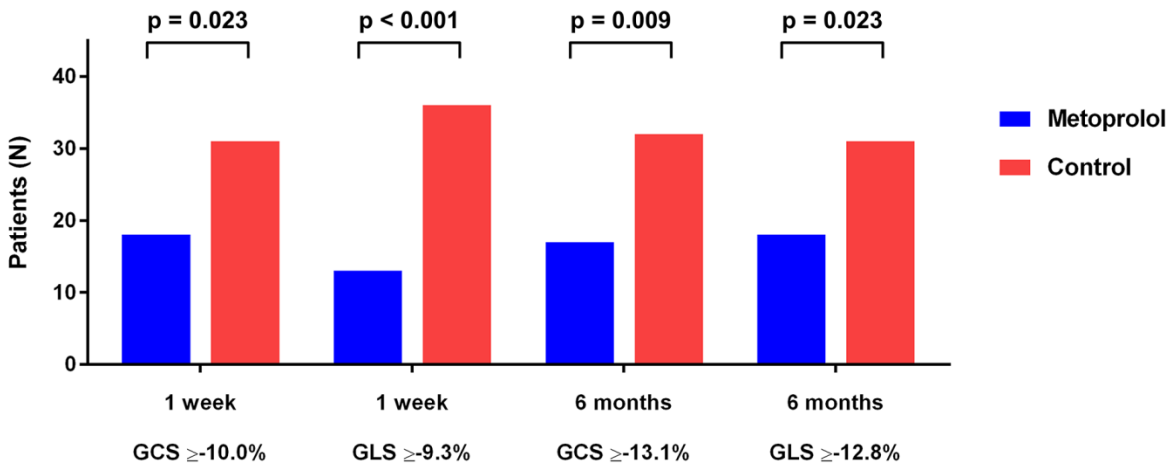

Table 1: Patients demographics, cardiovascular risk factors, procedural characteristics and discharge medication

	Total (N=197)	Metoprolol (N=100)	Control (N=97)	p-value
Demographics				
Age (years)	58.1±11.3	57.8±12.3	58.4±10.1	0.698
Sex (male)	173 (88)	87 (87)	86 (89)	0.865
BMI (kg/m^2)	27.6±3.5	27.6±3.5	27.6±3.5	0.900
Cardiovascular risk factors				
Hypertension	74 (38)	37 (37)	37 (38)	0.955
Diabetes mellitus	39 (20)	21 (21)	18 (19)	0.616
Dyslipidemia	85 (43)	43 (43)	42 (43)	0.935
Smoking*	126 (64)	64 (64)	62 (64)	0.839
Clinical status at recruitment				
Killip class II†	19 (10)	8 (8)	11 (11)	0.441
Systolic BP (mmHg)	142±19	142±18	142±19	0.949
Diastolic BP (mmHg)	88±16	89±16	87±15	0.266
Heart rate (bpm)	82±13	82±14	81±13	0.539
Procedural characteristics				
Ischemia duration (min)	194±65	197±62	191±68	0.488
TIMI grade 0-1 flow before primary PCI	163 (83)	80 (80)	83 (86)	0.373
Successful PCI (TIMI grade 2-3 flow)	194 (99)	100 (100)	94 (97)	0.117

BMI = body mass index; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.

*smoking was defined as current or quitted <10 years ago

†all other patients were Killip class I (Killip class III to IV were study's exclusion criteria)

Table 2: Effect of treatment randomization on conventional and feature tracking CMR parameters

	1 week					6 months				
	Overall (N=197)	**Metoprolol (N=100)**	**Control (N=97)**	**Mean difference [95% CI]**	**p-value**	**Overall (N=197)**	**Metoprolol (N=100)**	**Control (N=97)**	**Mean difference [95% CI]**	**p-value**
LVEDV (mL)	172.6±36.2	169.8±33.4	175.5±38.8	-5.6 [-15.8 to 4.5]	0.276	191.6±42.6	187.0±38.8	196.5±45.9	-9.5 [-21.5 to 2.5]	0.119
LVESV (mL)	97.8±31.3	92.9±26.6	102.8±34.9	-9.8 [-18.6 to -1.1]	0.028	104.4±40.8	98.2±36.1	110.8±44.5	-12.6 [-24.1 to -1.2]	0.031
LVEF (%)	44.2±9.4	45.8±9.1	42.6±9.6	3.2 [0.6 to 5.8]	0.017	47.0±10.8	48.7±10.0	45.3±11.4	3.4 [0.4 to 6.4]	0.028
LV mass (g)	111.5±25.4	109.1±25.2	113.9±25.5	-4.7 [-11.9 to 2.4]	0.192	85.7±17.6	84.6±17.4	86.8±17.7	-2.3 [-7.2 to 2.7]	0.371
LGE (%)	22.7±12.8	20.9±11.6	24.7±13.8	-3.8 [-7.4 to -0.2]	0.039	16.9±9.7	15.7±9.5	18.0±9.7	-2.3 [-5.1 to 0.5]	0.104
LV GCS (%)	-13.3±3.9	-13.9±3.8	-12.6±3.9	-1.4 [-2.4 to -0.3]	0.013	-16.4±4.2	-16.9±4.0	-15.9±4.4	-0.9 [-2.1 to 0.3]	0.122
LV GLS (%)	-11.4±3.0	-11.9±2.8	-10.9±3.2	-0.9 [-1.8 to -0.1]	0.032	-14.6±3.0	-14.8±2.9	-14.4±3.0	-0.4 [-1.2 to 0.5]	0.379

CI = confidence interval; CMR = cardiovascular magnetic resonance; GCS = global circumferential strain; GLS = global longitudinal strain; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

Table 3: Time course of LV conventional and feature tracking CMR parameters after STEMI

	Overall (N=197)			Metoprolol (N=100)			Control (N=97)		
	Mean difference	**95% CI**	**p-value**	**Mean difference**	**95% CI**	**p-value**	**Mean difference**	**95% CI**	**p-value**
LVEDV (mL)	18.9	15.3 to 22.5	<0.001	16.4	11.6 to 21.2	<0.001	21.5	16.2 to 26.8	<0.001
LVESV (mL)	6.7	3.4 to 9.9	<0.001	4.9	0.4 to 9.3	0.032	8.5	3.6 to 13.4	0.001
LVEF (%)	2.7	1.8 to 3.6	<0.001	2.9	1.5 to 4.2	<0.001	2.6	1.3 to 3.9	<0.001
LV mass (g)	-25.8	-28.5 to -23.2	<0.001	-24.6	-28.3 to -20.9	<0.001	-27.0	-30.9 to -23.1	<0.001
LGE (%)	-5.8	-6.7 to -4.8	<0.001	-5.1	-6.5 to -3.8	<0.001	-6.5	-7.8 to -5.1	<0.001
LV GCS (%)	-3.2	-3.5 to -2.8	<0.001	-2.9	-3.5 to -2.4	<0.001	-3.4	-3.9 to -2.8	<0.001
LV GLS (%)	-3.2	-3.5 to -2.8	<0.001	-2.9	-3.4 to -2.4	<0.001	-3.4	-3.9 to -3.0	<0.001

CI = confidence interval; CMR = cardiovascular magnetic resonance; GCS = global circumferential strain; GLS = global longitudinal strain; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; STEMI = ST-segment elevation myocardial infarction.

Table 4: Number of patients in GCS and GLS quartiles at 1 week and 6 months after STEMI

	LV GCS 1 week			
	1st quartile (≥-10.0%)	2nd quartile (-10.0% to -13.1%)	3rd quartile (-13.1% to -16.3%)	4th quartile (<-16.3%)
Metoprolol	18	22	34	26
Control	31	28	15	23
	LV GLS 1 week			
	1st quartile (≥-9.3%)	2nd quartile (-9.3% to -11.3%	3rd quartile (-11.3% to -13.2%)	4th quartile (<-13.2%)
Metoprolol	13	34	25	28
Control	36	16	25	20
	LV GCS 6 months			
	1st quartile (≥-13.1%)	2nd quartile (-13.1% to -16.4%)	3rd quartile (-16.4% to -19.8%)	4th quartile (<-19.8%)
Metoprolol	17	30	27	26
Control	32	20	22	23
	LV GLS 6 months			
	1st quartile (≥-12.8%)	2nd quartile (-12.8% to -15.0%)	3rd quartile (-15.0% to -16.8%)	4th quartile (<-16.8%)
Metoprolol	18	26	29	26
Control	31	23	20	22

GCS = global circumferential strain; GLS = global longitudinal strain; STEMI = ST-segment elevation myocardial infarction.

SUPPLEMENTARY MATERIAL

Table 1: Left ventricular ejection fraction (LVEF), left ventricular global circumferential (GCS) and longitudinal (GLS) strain at 1 week after myocardial infarction as predictors of LVEF normalization (LVEF ≥50%) at 6 months after the acute event

	Univariate analysis			**Multivariate analysis 1***			**Multivariate analysis 2****		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
LVEF (%)	1.289	1.203-1.382	<0.001	1.190	1.100-1.286	<0.001	1.231	1.129-1.342	<0.001
GCS (%)	0.592	0.513-0.682	<0.001	0.723	0.619-0.843	<0.001	0.715	0.610-0.839	<0.001
GLS (%)	0.591	0.505-0.692	<0.001	0.718	0.600-0.860	<0.001	0.666	0.542-0.819	<0.001

CI = confidence interval.

*adjusted for the extent of late gadolinium enhancement (LGE) on 1-week cardiovascular magnetic resonance (CMR)

** adjusted for the extent of LGE on 1-week CMR, age, sex, body mass index, presence of hypertension, diabetes, dyslipidemia, smoking status and treatment randomization arm (early intravenous metoprolol vs control)

Video 1: Visual evaluation of feature tracking in left ventricular short-axis slices

Video 2: Visual evaluation of feature tracking in left ventricular long-axis slices