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ORIGINAL PAPER

Prognostic importance of mechanical dyssynchrony in predicting heart failure development after ST-segment elevation myocardial infarction

Inge Noringriis[1] · Daniel Modin[1] · Sune H. Pedersen[1] · Jan S. Jensen[1] · Tor Biering-Sørensen[1]

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Abstract

The aim of this study is to assess the prognostic value of mechanical dyssynchrony defined as the standard deviation of the time to peak longitudinal strain (SD T2P LS) in predicting the development of heart failure (HF) after an ST-segment elevation myocardial infarction (STEMI). Three hundred and seventy-three patients were admitted with STEMI and treated with primary percutaneous coronary intervention. Left ventricular (LV) mechanical dyssynchrony was examined through speckle tracking echocardiography and defined as SD T2P LS. The association with the outcome of HF hospitalization was assessed using Cox proportional hazard models. During a median follow-up of 5.12 years, 144 patients (38.6%) were admitted due to HF. Worse dyssynchrony was associated with the outcome in unadjusted and multivariable analysis (multivariable hazard ratio 1.05, 95% confidence interval 1.00–1.10, p-value 0.039, per 10 ms increase), but not after further adjustment for LV ejection fraction (LVEF), E/e′ and global longitudinal strain (GLS) (hazard ratio 1.01, 95% confidence interval 1.00–1.07, p-value 0.71, per 10 ms increase), nor in a model only adjusting for GLS (hazard ratio 1.01, 95% confidence interval 1.00–1.06, p-value 0.61, per 10 ms increase). These findings were reproduced in a competing risk analysis treating all-cause mortality as a competing risk. LV mechanical dyssynchrony, as assessed by SD T2P LS is not an independent predictor of post-STEMI HF development and mechanical dyssynchrony does not provide independent prognostic information regarding HF when GLS is known.

Keywords Dyssynchrony · Speckle tracking · ST elevation myocardial infarction · Heart failure

Introduction

Echocardiography is a routine procedure for risk stratification after an acute myocardial infarction (AMI). Ischemic injury leads to characteristic changes in regional myocardial deformation. Strain, defined as the degree of change in length, provides an objective measure of deformation [1, 2].

In the healthy myocardium, peak longitudinal strain is typically reached shortly before aortic valve closure, sometimes with a slight delay [3]. In the affected segments, acute ischemia leads to a decrease in the amplitude of systolic shortening and induces pathological changes in the timing of deformation, primarily an increase in post-systolic deformation [4, 5]. This pathological post-systolic shortening is believed to be a result of either prolonged active contraction, delayed relaxation or passive recoil of the ischemic segments [3, 4, 6]. Considerable post-systolic shortening can be observed in 78% of ischemic segments compared to only 40% of non-ischemic segments [3]. Following an AMI, this impact of acute ischemia is seen on a greater or lesser part of the myocardium which results in intersegmental variation in the timing of peak deformation. Accordingly, patients with ST-segment elevation myocardial infarction (STEMI) show significantly impaired left ventricular (LV) synchronicity shortly after revascularization when compared to control subjects [7]. Such ineffective LV contraction caused by pathophysiological dyssynchrony could possibly affect the long-term development of adverse outcomes. Therefore, the

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✉ Inge Noringriis

[1] Department of Cardiology, Herlev & Gentofte Hospital, University of Copenhagen, Niels Andersensvej 65, Post 835, 2900 Copenhagen, Denmark

potential prognostic relevance of mechanical dyssynchrony has been tested in various settings.

Previous interest in LV dyssynchrony has mainly been focused on its usefulness in predicting the response to cardiac resynchronization therapy [8]. In patients with heart failure (HF) and reduced LVEF, persisting or worsening of mechanical dyssynchrony is associated with unfavorable clinical outcomes, even in the absence of electrical dyssynchrony [9]. In contrast, such an association of mechanical dyssynchrony with adverse outcomes was not found in patients with HF and preserved LVEF [10]. In the setting of ischemic heart disease, LV dyssynchrony has been found to be independently associated with significant coronary artery disease [11] and increased risk of ventricular arrhythmias following a myocardial infarction [12, 13]. However, the prognostic relevance of dyssynchrony in predicting adverse outcomes following an AMI including HFdevelopment has been examined in several studies with conflicting results [14–17].

Speckle tracking echocardiography has proven the most robust and reproducible method for performing strain imaging [18, 19] with a lower intraobserver and interobserver variability compared to tissue Doppler imaging [19, 20]. Furthermore, assessment of apical segments can be difficult using tissue Doppler imaging, for which reason speckle tracking echocardiography provides a more comprehensive analysis of cardiac function [19]. Using speckle tracking echocardiography, curves of regional strain are generated as functions of time which makes it possible to quantify both the magnitude and timing of myocardial strain [18]. By definition, a parameter of mechanical dyssynchrony has to display the intersegmental variance in timing of contraction. In the present study, we chose to examine mechanical dyssynchrony defined as the standard deviation of the time to peak longitudinal strain (SD T2P LS) measured by speckle tracking echocardiography. We specifically chose SD T2P LS because this measure integrates strain data from all LV segments into one combined parameter of mechanical dyssynchrony.

The aim of this study was to assess the prognostic value of mechanical dyssynchrony defined as SD T2P LS within the first days after a STEMI in predicting the development of HF.

Methods

Study population

The study population has previously been described in detail [21–24]. Briefly, between September 2006 and December 2008, 391 patients were prospectively enrolled when admitted to Gentofte Hospital, University of Copenhagen. The inclusion criteria were twofold: Admission with STEMI and treatment with primary percutaneous coronary intervention. STEMI was diagnosed by following the contemporary guidelines based on the presence of chest pain, characteristic electrocardiography-patterns and the level of troponin I. After the percutaneous coronary intervention procedure, all patients underwent echocardiographic examination. Baseline data was collected upon inclusion. Hypertension was defined as using blood pressure-lowering medication, hypercholesterolemia as using cholesterol-lowering medication, and diabetes as presenting a fasting or non-fasting blood glucose concentration of $\geq$7 mmol/L or $\geq$11.1 mmol/L respectively, or as using antidiabetic medication.

The study was approved by the regional scientific ethics committee and the Danish Data Protection Agency, and in line with the second Declaration of Helsinki. Written informed consent was obtained from all study participants.

Primary percutaneous coronary intervention procedure

Reperfusion by percutaneous coronary intervention was performed according to contemporary guidelines. Treatment preceding the percutaneous coronary intervention procedure included 300 mg acetylsalicylic acid, 600 mg clopidogrel, and 10,000 international units of unfractionated heparin. Glycoprotein IIb/IIIa inhibitors were used if chosen by the operator. Location of the culprit lesion, thrombolysis in myocardial infarction flow grade and multi-vessel disease status were classified through coronary angiography. According to the contemporary guidelines, the patients started in post-myocardial infarction treatment consisting of β-blockers, antithrombotic and cholesterol-lowering medication.

Endpoint

In this study we sought to analyse the association between SD T2P LS and HF. To ensure maximum sensitivity of the outcome assessment, the end point was defined as any diagnosis of HF recorded using ICD-10 codes in the Danish National Patient Registry, thus including all HF events registered for the cohort since study inclusion. The diagnosis of HF in the National Patient Registry is highly specific [25].

Echocardiography

The echocardiographic examination was conducted at a median of 2 days after the myocardial infarction (interquartile range 1–3 days) and performed by experienced sonographers using Vivid 7 ultrasound systems (GE Healthcare, Horten Norway) and a 3.5-MHz transducer. The study participants were all examined with conventional two-dimensional echocardiography, pulsed-wave and color tissue

Doppler imaging. The collected echocardiograms were stored digitally and analysed off-line using commercially available software (EchoPac version 12, GE Healthcare, Horten Norway) by a single investigator blinded to all additional patient data. Four patients were excluded from the study population due to inadequate imaging quality and 14 due to atrial fibrillation rhythm during the examination.

LV linear dimensions (interventricular septum wall thickness, LV internal dimension, and LV posterior wall thickness) were obtained at end-diastole from the parasternal long-axis view. Measurements were carried out at an angle perpendicular to the long axis of the LV and at the level of the mitral valve leaflet tips. Using the linear method, LV mass was calculated and divided by body surface area to yield LV mass index [26]. LV end-diastolic and end-systolic volumes were estimated using the modified biplane Simpson's method. This was done by tracing the blood-tissue interface in the apical 4- or 2-chamber views at systole and diastole, respectively. These volume estimates were subsequently used to calculate LVEF [26]. Left atrial volume at LV end-systole was estimated using the area-length method. By dividing the volume with body surface area, the left atrial volume index was calculated [26]. Pulsed wave Doppler was used to assess the diastolic mitral inflow patterns. Inflow was recorded between the tips of the mitral leaflets from the apical 4-chamber view. The peak velocity of early (E) and late (A) diastolic filling were determined and used in the calculation of the mitral valve E/A ratio. Similarly, the deceleration time of the E-wave was measured [27]. Peak longitudinal early diastolic velocity (e′) was measured using pulsed-wave tissue Doppler imaging tracings with the range gate placed at the septal and lateral mitral annular segments in the 4-chamber view. A mean e′ was estimated as the average of the lateral and septal velocities. The average of mitral annular velocity was used in the calculation of the E/e′ ratio [27].

Two-dimensional strain echocardiography

Two-dimensional strain was assessed through LV speckle tracking. Longitudinal strain was analysed from the three apical windows: 4-chamber, 2-chamber and apical long-axis view, with a mean rate of 86 frames/s (standard deviation (SD) 23 frames/s). The region of interest was defined at end-diastole. Initially, the contour of the ventricular endocardium was traced by a semiautomated function and manually adjusted in case of inaccuracy. The epicardial border was outlined automatically and the width of the region of interest adjusted to include the endocardium, myocardium and epicardium. If tracking of a segment proved persistently inaccurate, the segment was excluded from analysis (the case in 14% of all segments). Segmentation was performed automatically, dividing the LV into 6 basal, 6 midventricular and 6 apical segments according to the 18-segment model. Hereby, each projection covered 6 segments [2].

The software automatically calculated an estimate of the global longitudinal strain (GLS) for each projection, and these were subsequently averaged to reach an overall GLS. The time to peak longitudinal strain was defined as the time span between end-diastole and the moment of highest strain amplitude in the cardiac cycle [1]. The time to peak strain was measured for each of the 18 segments and the standard deviation (SD T2P LS) was calculated as a measure of overall LV dyssynchrony.

Statistics

All statistical analysis was performed using STATA version 13.0. The limit for statistical significance was defined as a two-sided p-value of <0.05. The baseline clinical, angiographic, biochemical and echocardiographic variables were stratified according to outcome. Categorical variables were compared by the chi-squared test and expressed as total numbers and percentages. Continuous Gaussian distributed variables were compared using the Student's *t* test and expressed as mean ± SD, while non-Gaussian distributed variables were compared using Mann–Whitney U test and expressed as median and interquartile range. In addition, the baseline variables were stratified by tertiles of SD T2P LS. Trend across tertiles was assessed using linear regression and using an extension of the Wilcoxon rank-sum test for continuous non-Gaussian distributed variables. The association between SD T2P LS and GLS was assessed using cubic spline regression. The incidence of HF by tertiles of SD T2P LS was analysed by constructing a Kaplan–Meier failure function.

The prognostic value of SD T2P LS in predicting the development of HF was assessed through time-to-event analysis applying univariable as well as multivariable Cox proportional hazards models. Univariate Cox regressions were furthermore used to examine associations between other potential predictors and the outcome. Harrell's C statistics were calculated in order to assess the prognostic potential of the examined parameters. Two multivariable Cox regression models were carried out for assessment of adjusted associations. Model 1 was adjusted for age, sex, diabetes, mean arterial pressure, QRS duration, left anterior descending coronary artery (LAD) lesion, right coronary artery (RCA) lesion, peak troponin I, estimated glomerular filtration rate, and LV mass index. Model 2 was additionally adjusted for LVEF, E/e′ ratio and GLS. Furthermore, the prognostic relevance of SD T2P LS was assessed in a model solely adjusting for GLS.

A couple of additional analyses were performed to further examine the prognostic potential of mechanical dyssynchrony. The left ventricle was divided into three pairs of

opposing segments: posterior and anterior septal segments, anterior and inferior segments and lateral and septal segments, respectively. SD T2P LS was calculated for each pair of opposing segments. The prognostic value was assessed for each pair separately by applying the same Cox regression models as described above. A subpopulation analysis was performed, assessing the prognostic value of SD T2P LS within the subpopulation of patients presenting a LAD culprit lesion. The same Cox regression models were carried out, however not adjusting for LAD or RCA culprit lesions. Finally, a competing risk analysis treating all-cause mortality as a competing risk was performed in order to assess the potential influence of mortality on the correlation between SD T2P LS and the development of post-STEMI HF.

Results

End point and follow-up

The study population was followed for a median of 5.12 years (interquartile range 0.24–5.91 years) and follow-up was 100%. Of the 373 patients included in the study, 144 (38.6%) were hospitalized due to HF in the course of follow-up.

Baseline findings

Baseline characteristics are displayed in Tables 1 and 2, grouped by outcome and tertiles of SD T2P LS, respectively. As can be seen, development of HF and increasing values of SD T2P LS displayed a significant association with longer QRS duration, higher levels of peak troponin I and prevalence of LAD culprit lesions. Regarding echocardiographic parameters, development of HF and increasing values of SD T2P LS were significantly related to reduced systolic function as determined by lower LVEF and GLS, and reduced diastolic function demonstrated by higher E/e′ ratio. The incidence of HF stratified by tertiles of SD T2P LS is shown in Fig. 1.

Prediction of outcome

The results of the univariable and multivariable Cox regressions are displayed in Table 3. Regarding the prognostic value of SD T2P LS, the following results were found: In unadjusted analysis greater SD T2P LS was associated with a higher risk of developing HF (hazard ratio 1.08 per 10 ms increase, 95% confidence interval 1.04–1.12, p-value < 0.001) (Table 3). After multivariable adjustment for several clinical, angiographic and biochemical characteristics, including the echocardiographic variable LV mass index, SD T2P LS remained significantly associated with a higher risk of the outcome (hazard ratio 1.05 per 10 ms increase, 95% confidence interval 1.00–1.10, p-value 0.039) (Table 3, model 1). However, after further adjustment for LVEF, E/e' ratio and GLS, SD T2P LS was no longer found to be an independent predictor of HF development (hazard ratio 1.01 per 10 ms increase, 95% confidence interval 1.00–1.07, p-value 0.71) (Table 3, model 2). In this model, only peak troponin I level, LVEF and GLS were independent predictors of the outcome. The same result was found in a model including just SD T2P LS and GLS, in which only GLS was found to be a significant predictor of HF development (Table 3, two variable model).

Regarding dyssynchronous contraction of opposing segments, SD T2P LS of all three pairs were found to be significantly associated with an increased risk of HF development in unadjusted analysis. However, after multivariable adjustment, none were found to be independent predictors of the outcome (posterior and anterior septal segments, model 2: hazard ratio per 10 ms increase 1.02, 95% confidence interval 0.98–1.07, p-value 0.36) (anterior and inferior segments, model 2: hazard ratio per 10 ms increase 1.02, 95% confidence interval 0.98–1.07, p-value 0.26) (Lateral and septal segments, model 2: hazard ratio per 10 ms increase 0.99, 95% confidence interval 0.95–1.04, p-value 0.80) (Online Resource 1). Regarding the subpopulation analysis, SD T2P LS was not found to be an independent predictor of HF development in the subgroup of patients with LAD culprit lesions (model 2: hazard ratio 1.03 per 10 ms increase, 95% confidence interval 0.95–1.11, p-value 0.53) (Online Resource 2). In the competing risk analysis treating all-cause mortality as a competing risk, SD T2P LS was found to have similar hazard ratios and levels of significance in both univariable and multivariable models (Online Resource 3).

Discussion

Our results show that LV mechanical dyssynchrony is a significant predictor of HF development in unadjusted analysis. In addition, SD T2P LS remains an independent predictor after multivariable adjustment. However, SD T2P LS does not provide independent prognostic information when additionally adjusting for variables reflecting LV systolic (GLS and LVEF) and diastolic (E/e′ ratio) function.

SD T2P LS as a marker of mechanical dyssynchrony

As previously mentioned, SD T2P LS was chosen as a parameter of mechanical dyssynchrony because it integrates strain data from all LV segments. We have previously examined the prognostic power of regional longitudinal myocardial deformation in the present study sample. We found that impaired longitudinal deformation outside the culprit

Table 1 Baseline variables stratified by outcome

Variable	All patients	No HF	HF	P-value
Number	373	229	144	
Clinical				
Age (years)	62.2 (11.4)	61.1 (10.8)	64.0 (12.0)	0.015
Sex (male)	280 (75.1%)	170 (74.2%)	110 (76.4%)	0.64
BMI (kg/m^2)	26.7 (4.4)	26.7 (4.3)	26.7 (4.5)	0.91
MAP (mmHg)	99.8 (18.6)	99.1(18.3)	100.9 (19.2)	0.37
Diabetes	32 (8.6%)	14 (6.1%)	18 (12.5%)	0.032
Hypercholesterolemia	62 (16.6%)	36 (15.7%)	26 (18.1%)	0.56
Symptom to balloon time (min)	190 (126–306)	180 (120–305)	192.5 (130–311.5)	0.62
Heart rate (beats/min)	77 (24.4)	75 (21.8)	80 (27.8)	0.08
QRS duration (ms)	116.5 (21.4)	113.9 (19.6)	119.8 (23.7)	0.012
Prior MI	17 (4.6%)	8 (3.5%)	9 (6.2%)	0.21
Current smoker	193 (51.7%)	123 (53.7%)	70 (48.6%)	0.34
Angiographic				
LAD culprit lesion	169 (45.3%)	94 (41.0%)	75 (52.1%)	0.037
RCA culprit lesion	147 (39.4%)	100 (43.7%)	47 (32.6%)	0.034
Cx culprit lesion	40 (10.7%)	24 (10.5%)	16 (11.1%)	0.85
Multivessel disease	103 (27.6%)	56 (24.5%)	47 (32.6%)	0.09
TIMI 0	233 (62.1%)	138 (60.3%)	95 (66.0%)	0.27
TIMI 1	49 (13.1%)	28 (12.2%)	21 (14.6%)	0.51
TIMI 2	39 (10.4%)	25 (10.9%)	14 (9.7%)	0.71
TIMI 3	52 (13.9%)	38 (16.6%)	14 (9.7%)	0.06
Biochemical				
Peak TnI value (μg/L)	110 (28.6–232)	64.7 (22.4–198)	183.5 (60.1–316.5)	< 0.001
eGFR (mL/min/1.73 m^2)	74.2 (21.6)	75.8 (19.4)	71.5 (24.5)	0.06
Echocardiographic				
Interventricular septum wall thickness (cm)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.18
LV internal dimension (cm)	4.9 (0.7)	4.8 (0.6)	5.0 (0.7)	0.020
LV posterior wall thickness (cm)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.18
LV mass (g)	184.9 (64.4)	178.6 (59.8)	195.0 (70.2)	0.016
LVMI (g/m^2)	94.4 (29.2)	91.0 (26.6)	99.9 (32.2)	0.004
LVEF (%)	45.8 (9.0)	48.0 (8.3)	42.3 (9.1)	< 0.001
LAVI (mL/m^2)	24.6 (6.9)	24.3 (6.8)	25.2 (7.0)	0.18
E/A ratio	1.1 (0.4)	1.1 (0.3)	1.1 (0.4)	0.59
DT (ms)	198.9 (55.3)	202.6 (55.8)	193.1 (54.2)	0.11
e′ (cm/s)	7.4 (2.2)	7.9 (2.2)	6.6 (1.9)	< 0.001
E/e′ ratio	11.2 (4.2)	10.4 (3.2)	12.5 (5.1)	< 0.001
GLS (%)	− 12.4 (3.7)	− 13.5 (3.6)	− 10.6 (3.2)	< 0.001
SD T2P LS (ms)	69.3 (30.7)	64.4 (27.4)	77.1 (33.8)	< 0.001

Baseline characteristics for the entire study population and for the population stratified by outcome. Categorical variables are expressed as total numbers and percentages, continuous Gaussian distributed variables as mean and standard deviations, non-Gaussian distributed variables as median and interquartile range

A peak transmitral late diastolic inflow velocity, *BMI* body mass index, *Cx* circumflex coronary artery, *DT* E-wave deceleration time, *E* peak transmitral early diastolic inflow velocity, *e′* average peak early diastolic longitudinal mitral annular velocity determined by pulsed-wave tissue Doppler imaging, *eGFR* estimated glomerular filtration rate, *GLS* global longitudinal strain, *LAD* left anterior descending coronary artery, *LAVI* left atrial volume index, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVMI* LV mass index, *MAP* mean arterial pressure, *MI* myocardial infarction, *RCA* right coronary artery, *SD T2P LS* standard deviation of time to peak longitudinal strain, *TIMI* thrombolysis in myocardial infarction flow grade, *TnI* troponin I

Table 2 Baseline variables stratified by tertiles of SD T2P LS

Variable	Tertile 1	Tertile 2	Tertile 3	P for trend
Number	124	124	124	
SD T2P LS cut off value (ms)	< 55.6	55.6–72.8	> 72.8	
Clinical				
Age (years)	59.9 (10.8)	62.0 (11.4)	64.8 (11.5)	0.001
Sex (male)	98 (79.0%)	87 (70.2%)	95 (76.6%)	0.66
BMI (kg/m^2)	26.3 (3.8)	26.5 (4.6)	27.3 (4.7)	0.05
MAP (mmHg)	97.8 (18.8)	101.1 (18.3)	100.5 (18.8)	0.27
Diabetes	7 (5.6%)	8 (6.5%)	17 (13.7%)	0.026
Hypercholesterolemia	13 (10.5%)	25 (20.2%)	24 (19.4%)	0.06
Symptom to balloon time (min)	161.5 (117–278.5)	200 (145.5–330)	192.5 (122–301.5)	0.46
Heart rate (beats/min)	75 (21.9)	75 (13.9)	81 (33.1)	0.048
QRS duration (ms)	114.0 (21.3)	113.0 (19.7)	121.4 (22.4)	0.007
Prior MI	2 (1.6%)	7 (5.6%)	8 (6.5%)	0.08
Current smoker	75 (60.5%)	64 (51.6%)	54 (43.5%)	0.008
Angiographic				
LAD culprit lesion	42 (33.9%)	63 (50.8%)	64 (51.6%)	0.005
RCA culrit lesion	63 (50.8%)	45 (36.3%)	39 (31.5%)	0.002
Cx culprit lesion	18 (14.5%)	10 (8.1%)	11 (8.9%)	0.15
Multivessel disease	32 (25.8%)	34 (27.4%)	37 (29.8%)	0.48
TIMI 0	73 (58.9%)	83 (66.9%)	77 (62.1%)	0.60
TIMI 1	19 (15.3%)	9 (7.3%)	20 (16.1%)	0.85
TIMI 2	10 (8.1%)	17 (13.7%)	12 (9.7%)	0.68
TIMI 3	22 (17.7%)	15 (12.1%)	15 (12.1%)	0.20
Biochemical				
Peak TnI value (μg/L)	82.7 (25.8–214)	100 (27.7–246.5)	142.5 (45.7–242.5)	0.048
eGFR (mL/min/1.73 m^2)	76.5 (20.5)	76.9 (20.6)	69.2 (22.9)	0.008
Echocardiographic				
Interventricular septum wall thickness (cm)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.06
LV internal dimension (cm)	4.8 (0.6)	4.8 (0.7)	5.0 (0.7)	0.05
LV posterior wall thickness (cm)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.07
LV mass (g)	176.9 (59.1)	179.1 (63.2)	199.4 (68.6)	0.006
LVMI (g/m^2)	91.3 (27.7)	92.7 (30.4)	99.6 (28.9)	0.025
LVEF (%)	47.7 (9.0)	45.8 (9.0)	43.8 (8.7)	0.001
LAVI (mL/m^2)	24.3 (6.2)	23.9 (7.1)	25.5 (7.1)	0.18
E/A ratio	1.1 (0.4)	1.1 (0.4)	1.0 (0.4)	0.043
DT (ms)	198.9 (50.2)	202.6 (58.3)	195.8 (57.0)	0.65
e′ (cm/s)	8.4 (2.3)	7.1 (1.9)	6.8 (2.0)	< 0.001
E/e′ ratio	10.1 (3.5)	11.3 (3.7)	12.1 (5.0)	< 0.001
GLS (%)	− 14.5 (3.6)	− 12.2 (3.1)	− 10.5 (3.2)	< 0.001
SD T2P LS (ms)	44.8 (8.6)	61.9 (4.6)	101.1 (32.6)	< 0.001

Baseline characteristics for the population stratified by tertiles of SD T2P LS. Categorical variables are expressed as total numbers and percentages, continuous Gaussian distributed variables as mean and standard deviations, non-Gaussian distributed variables as median and interquartile range

A peak transmitral late diastolic inflow velocity, *BMI* body mass index, *Cx* circumflex coronary artery, *DT* E-wave deceleration time, *E* peak transmitral early diastolic inflow velocity, *e′* average peak early diastolic longitudinal mitral annular velocity determined by pulsed-wave tissue Doppler imaging, *eGFR* estimated glomerular filtration rate, *GLS* global longitudinal strain, *LAD* left anterior descending coronary artery, *LAVI* left atrial volume index, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVMI* LV mass index, *MAP* mean arterial pressure, *MI* myocardial infarction, *RCA* right coronary artery, *SD T2P LS* standard deviation of time to peak longitudinal strain, *TIMI* thrombolysis in myocardial infarction flow grade, *TnI* troponin I

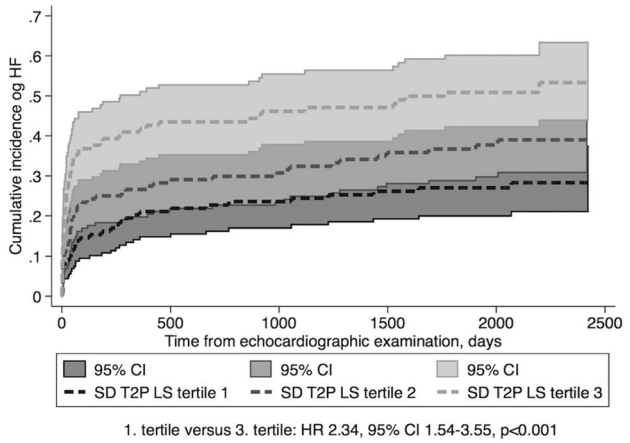

Fig. 1 Incidence of HF by tertiles of SD T2P LS. The cumulative incidence of HF with 95% confidence interval as a function of time from echocardiographic examination with the population stratified by tertiles of SD T2P LS. Tertile 1 < 55.6 ms, tertile 2 = 55.6–72.8 ms, tertile 3 > 72.8 ms. *95% CI* 95% confidence interval, *HF* heart failure, *HR* hazard ratio, *SD T2P LS* standard deviation of time to peak longitudinal strain

lesion perfusion region was a significant marker of post-STEMI adverse outcome [22]. These results indicate that all segments of the LV, not just the segments affected by ischemia, are of interest when examining ventricular function following a STEMI. Other dyssynchrony parameters focus on the variation in temporal dispersion between particular LV segments, for example the segments presenting post-systolic shortening or the segments showing minimum and maximum time to peak longitudinal strain. Compared to these parameters, SD T2P LS holds the advantage of incorporating information from all LV segments thus presenting a more comprehensive representation of LV mechanical dyssynchrony. To compare the prognostic potential of SD T2P LS of the entire LV with a regional measure of mechanical dyssynchrony, SD T2P LS limited to three pairs of opposing segments was calculated. Like SD T2P LS of the entire ventricle, dyssynchronous contraction of opposing segments was not found to be an independent predictor of HF development.

Mechanical dyssynchrony in previous studies

Using different speckle tracking echocardiography parameters, several studies have focused on the prognostic usefulness of LV dyssynchrony in predicting adverse events in patients with AMI, however with conflicting results.

In previous studies, LV dyssynchrony has been found to independently predict post-myocardial infarction adverse outcomes including the development of HF. This was the case in a publication from the VALIANT trial in which the prognosis of STEMI-patients with impaired LV systolic function was examined. Six hundred and ten patients were prospectively enrolled, yet 37% were excluded due to insufficient image quality. In this study, dyssynchrony was defined as the SD of time to peak systolic strain rate and longitudinal velocity, respectively [14]. Similar results were found in a publication from the MISSION! trial examining a population of 976 prospectively enrolled STEMI-patients treated with primary percutaneous coronary intervention. In this study, dyssynchrony was defined as the absolute difference between the shortest and longest segmental time to peak radial strain [15]. In both studies, the assessed dyssynchrony parameters remained significant predictors after multivariable adjustment. In the former, however, no echocardiographic variables but LVEF were included in the multivariable analysis [14]. In the latter, further adjustment for wall motion score index and E/e' ratio was performed [15]. None of these studies adjusted for GLS in their multivariable model.

Other studies have however presented results corresponding to ours. This was the case in a study evaluating the predictive power of mechanical dyssynchrony in a population of unselected patients with acute coronary syndrome. It was found that neither SD T2P LS nor several other examined parameters of dyssynchrony were independently associated with adverse outcomes [16]. A similar conclusion was reached by another study in which dyssynchrony was defined as the SD of time to peak systolic longitudinal strain. Here the population consisted of STEMI-patients treated with late percutaneous coronary intervention [17]. In both of these studies, and in accordance with our results, baseline LVEF remained an independent predictor of adverse outcomes after multivariable analysis [16, 17]. In the first study, GLS was not examined, but in the latter, GLS remained an independent predictor as well [17]. Likewise, a recent publication from the TOPCAT trial showed similar results in patients with HF and preserved LVEF. Several measures of mechanical dyssynchrony were examined, including SD T2P LS, and none remained independently associated with adverse outcome after multivariable adjustment including LVEF, and neither did SD T2P LS in a model adjusting only for either GLS or E/e' [10]. Thus, the studies that have examined mechanical dyssynchrony as assessed by SD T2P LS have concluded that this parameter does not seem to remain an independent predictor when adjusting.

Mechanical dyssynchrony and accordance with infarction size

These above-referenced results can cause you to question the ability of SD T2P LS to reflect the actual level of LV dyssynchrony and its ability to account for the magnitude of myocardial damage caused by an AMI. Infarction size is a powerful predictor of outcome following an AMI, and a strong graded response is present between increasing infarction size

Table 3 Cox proportional hazards models

	Hazard ratio	95% CI	C-statistic	P-value
Univariable				
Age (per year increase)	1.02	1.01–1.04	0.570	0.004
Diabetes	1.56	0.95–2.55	0.514	0.08
MAP (per mmHg increase)	1.00	1.00–1.01	0.510	0.40
QRS duration (per ms increase)	1.01	1.00–1.02	0.556	0.007
LAD culprit lesion	1.43	1.03–1.98	0.545	0.033
RCA culprit lesion	0.69	0.49–0.98	0.545	0.040
Peak TnI (per µg/L increase)	1.00	1.00–1.00	0.641	< 0.001
eGFR (per mL/min/1.73 m^2 increase)	0.99	0.98–1.00	0.554	0.033
LVMI (per g/m^2 increase)	1.01	1.00–1.01	0.576	0.001
LVEF (per % increase)	0.94	0.92–0.96	0.656	< 0.001
e′ (per cm/s increase)	0.79	0.73–0.86	0.635	< 0.001
E/e′ ratio	1.08	1.05–1.11	0.609	< 0.001
GLS (per % increase)	1.20	1.15–1.26	0.676	< 0.001
SD T2P LS (per 10 ms increase)	1.08	1.04–1.12	0.614	< 0.001
Model 1				
Age (per year increase)	1.02	1.00–1.04		0.018
Peak TnI (per µg/L increase)	1.00	1.00–1.00		< 0.001
SD T2P LS (per 10 ms increase)	1.05	1.00–1.10		0.039
Model 2				
Peak TnI (per µg/L increase)	1.00	1.00–1.00		0.008
LVEF (per % increase)	0.97	0.94–0.99		0.005
GLS (per % increase)	1.10	1.02–1.18		0.015
SD T2P LS (per 10 ms increase)	1.01	1.00–1.07		0.71
Two variable model only including GLS and SD T2P LS				
GLS (per % increase)	1.20	1.13–1.26		< 0.001
SD T2P LS (per 10 ms increase)	1.01	1.00–1.06		0.61

Model 1: adjusted for age, sex, diabetes, MAP, QRS duration, LAD lesion, RCA lesion, peak TnI, eGFR, LVMI and SD T2P LS. Model 2: adjusted for the same variables as model 1 plus LVEF, E/e′ ratio and GLS

95% CI 95% confidence interval, *E* peak transmitral early diastolic inflow velocity, *e′* average peak early diastolic longitudinal mitral annular velocity determined by pulsed-wave tissue Doppler imaging, *eGFR* estimated glomerular filtration rate, *GLS* global longitudinal strain, *LAD* left anterior descending coronary artery, *LVEF* left ventricular ejection fraction, *LVMI* LV mass index, *MAP* mean arterial pressure, *RCA* right coronary artery, *SD T2P LS* standard deviation of time to peak longitudinal strain, *TnI* troponin I

and HF development [28]. Hence, the association of SD T2P LS with long-term outcome could very likely be limited if this specific parameter does not reflect the actual extent of damaged myocardium [16]. The ischemia-induced changes in deformation pattern are mainly determined by subendocardial flow [5] meaning that the myocardial fibers most vulnerable to ischemia are the longitudinally oriented fibers of the endocardium. Consequently, measurements of longitudinal deformation appear to be the most sensitive markers of ailing myocardium in the setting of acute ischemia [22]. The slightest decrease in perfusion leads to a decrease in strain and the development of post-systolic shortening [5]. Yet, to our knowledge, it has not been investigated whether the time to peak longitudinal strain increases proportionally to increasing ischemic burden. Furthermore, SD T2P LS is a marker of the relative intersegmental difference. Following an extensive infarction, a larger number of segments might display prolonged time to peak longitudinal strain which could potentially lead to a paradoxically low intersegmental variation [16]. This means that in the setting of a large myocardial infarction, the value of SD T2P LS would not necessarily reflect the actual scale of LV impairment. Supporting this hypothesis is the fact that patients with 2-vessel coronary artery disease have been found to exhibit significantly greater SD T2P LS than patients with 3-vessel coronary artery disease [11]. In the present study, no determination of infarct size was performed besides the measurement of peak levels of troponin I. We found that peak level of troponin I was significantly associated with increasing mechanical dyssynchrony as assessed by SD T2P LS. This implies that the level of SD T2P LS does approximately reflect the size of the

infarction, but it is not possible to draw further conclusions based on the present study.

SD T2P LS and adjustment for GLS

After adjustment for the echocardiographic variables E/e′ ratio, LVEF and GLS, SD T2P LS lost its statistical significance as a predictor of HF development. E/e′ ratio is a marker of LV filling pressure and is used in the classification of LV diastolic dysfunction [27]. The variable is furthermore a powerful predictor of survival after an AMI [29]. LVEF and GLS are both indicators of LV systolic function. Traditionally, LVEF is most commonly used [30]. However, GLS is a well-known predictor of adverse outcomes following an AMI [31] and has been found to be superior to volume-based indices for early risk evaluation after STEMI [30]. Furthermore, baseline GLS is significantly associated to the extent of transmural damage following an AMI and is an independent predictor of LV remodeling [17, 32] and infarction size [33].

GLS and SD T2P LS are both derived from longitudinal strain curves but their perspective on myocardial deformation differs to some extent. The former marks the magnitude of overall LV longitudinal strain, while the latter focuses on the timing of segmental deformation and quantifies the temporal dispersion. The results of the present study show that SD T2P LS, when GLS is known, provides no independent prognostic information regarding the development of post-STEMI HF. This is demonstrated by the loss of statistical significance when carrying out a Cox regression adjusting solely for GLS. Furthermore, we found a significant and directly proportional correlation between SD T2P LS and GLS (Fig. 2). These results indicate that the observed univariable association of SD T2P LS with the development of post-STEMI HF to some degree occurs secondarily to the association of dyssynchrony with impaired GLS. A possible explanation for this connection can be found in the method through which GLS is determined. Besides the segmental strain curves, the software also drafts a GLS curve by computing the deformation of the entire myocardial line length frame by frame [1]. An estimate of GLS is then determined as the peak value of this curve. Therefore, the estimated GLS represents the global deformation at one specific point in time. In the case of synchronous LV contractions, the estimated GLS will correspond well to the average of the segmental peak strain values. However, in the case of dyssynchronous LV contractions, the temporal dispersal of segmental deformation will cause a flattening of the GLS curve and therefore a lower estimated GLS. Consequently, dyssynchrony appears to be one of several aspects integrated in the value of GLS. Perhaps the prognostic information embodied in the value of SD T2P LS, granting the variable its statistical significance in unadjusted analysis, corresponds to the information that SD T2P LS shares with GLS. This could potentially explain why SD T2P LS does not provide independent prognostic information when adjusting for GLS .

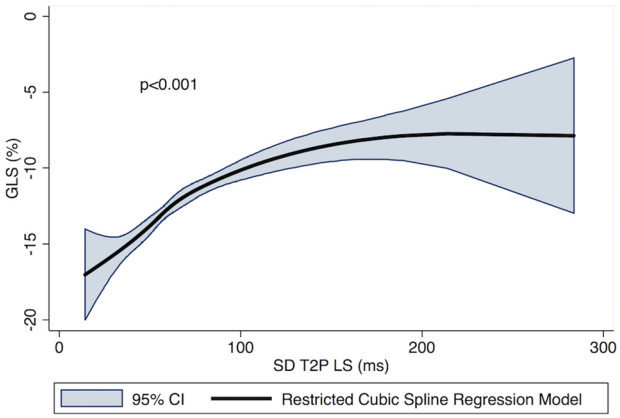

Fig. 2 Association between myocardial dyssynchrony and GLS. Cubic spline regression model with 95% confidence interval for the association between mechanical dyssynchrony as assessed by SD T2P LS and GLS. *95% CI* 95% confidence interval, *GLS* global longitudinal strain, *SD T2P LS* standard deviation of time to peak longitudinal strain

Limitations

The baseline data collected upon inclusion does not include data on the patients cardiac function prior to being admitted with STEMI. Hence, the potential presence of pre-existing cardiac dysfunction could possibly affect our findings. As described in "Methods" section, we obtained the endpoints from the Danish National Patient Registry and consequently only the recorded events of HF are included in the endpoint. Furthermore, the data obtained from the Danish National Patient Registry was not further validated. Since speckle tracking echocardiography was not performed in the parasternal short axis view we were not able to analyse transmural or radial strain. Furthermore, layer-specific analysis of myocardial deformation and three-dimensional strain analysis were not performed. We evaluated the level of dyssynchrony as measured shortly after revascularization and no follow-up echocardiography was performed. Hence, we were not able to investigate whether the level measured at a different point in time or the change in dyssynchrony over time hold prognostic power.

Conclusion

Worse mechanical dyssynchrony, as assessed by SD T2P LS, is a significant predictor of post-STEMI HF development in both univariable and multivariable analysis. However,

SD T2P LS does not provide independent prognostic information in prediction of HF development in post-STEMI patients when GLS is known.

Data availability The data used in this study is based on human patients and is therefore governed by the Danish Data Protection Agency. In order to gain access to the data, any additional researcher is required to file a formal application to the Danish Data Protection Agency. Therefore, the authors cannot grant access to the data used in this study unless anyone interested is approved by the Danish Data Protection Agency.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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