European Journal of Heart Failure (2017) **19**, 1043–1052
doi:10.1002/ejhf.789

RESEARCH ARTICLE

Prognostic importance of left ventricular mechanical dyssynchrony in heart failure with preserved ejection fraction

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Received 9 August 2016; revised 11 January 2017; accepted 16 January 2017; online publish-ahead-of-print 21 March 2017

Aims Left ventricular mechanical dyssynchrony has been described in heart failure with preserved ejection fraction (HFpEF), but its prognostic significance is not known.

Methods and results Of 3445 patients with HFpEF enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, dyssynchrony analysis was performed on 424 patients (12%) by multiple speckle tracking echocardiography strain-based criteria. The primary dyssynchrony analysis was the standard deviation of the time to peak longitudinal strain (SD T2P LS). Cox proportional hazards models assessed the association of dyssynchrony with the composite outcome of cardiovascular death or heart failure hospitalization. Mean age was 70 ± 10 years, LVEF was 60 ± 8%, and QRS duration was 101 ± 27 ms. Worse dyssynchrony, reflected in SD T2P LS, was associated with wider QRS, prior myocardial infarction, larger LV volume and mass, and worse systolic (lower LVEF and global longitudinal strain) and diastolic (lower e' and higher E/e') function. During a median follow-up of 2.6 (interquartile range 1.5–3.8) years, 107 patients experienced the composite outcome. Worse dyssynchrony was associated with the composite outcome in unadjusted analysis [hazard ratio (HR) 1.04, 95% confidence interval (CI) 1.01–1.07; $P = 0.021$, per 10 ms increase], but not after adjusting for clinical characteristics, or after further adjustment for LVEF, AF, NYHA class, stroke, heart rate, creatinine, haematocrit, and QRS duration (HR 1.03, 95% CI 0.99–1.06; $P = 0.16$, per 10 ms increase).

Conclusion Worse LV mechanical dyssynchrony, assessed by speckle tracking echocardiography, is not an independent predictor of adverse outcomes in HFpEF, suggesting that mechanical dyssynchrony is unlikely to be an important mechanism underlying this syndrome. These findings warrant validation in an independent study specifically designed to assess the prognostic utility of mechanical dyssynchrony in HFpEF.
Trial registration: NCT00094302

Keywords Clinical trial • Heart failure • Heart ventricles • Preserved left ventricular function • Spironolactone • Dyssynchrony

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Introduction

Left ventricular electrical dyssynchrony is a strong prognostic marker of adverse outcomes in heart failure with reduced ejection fraction (HFrEF),[1] and resynchronization therapy targeting electrical dyssynchrony reduces heart failure (HF) morbidity and mortality.[2] Left ventricular mechanical dyssynchrony, detected by non-invasive imaging such as echocardiography, is similarly associated with worse outcomes in HFrEF—even when occurring in the absence of concomitant electrical dyssynchrony.[3] Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of HF cases in the community and causes substantial morbidity and mortality.[4,5] While LV diastolic dysfunction is accepted as the primary cardiac perturbation underlying this heterogeneous syndrome, several other cardiovascular and non-cardiovascular abnormalities also appear to contribute. As in HFrEF, LV electrical dyssynchrony—reflected in prolonged QRS duration—is an independent predictor of HF hospitalization and cardiovascular death in HFpEF.[6] Additionally, detailed echocardiographic characterization has demonstrated greater degrees of LV mechanical dyssynchrony in HFpEF compared with asymptomatic controls, even in the absence of QRS prolongation.[7,8] However, whether the presence of LV mechanical dyssynchrony is simply a marker of worse cardiac function or a central pathophysiological mechanism independently associated with worse prognosis in HFpEF is unknown.

The aim of this study was to determine the prognostic relevance of LV mechanical dyssynchrony for incident cardiovascular morbidity (HF hospitalization) and mortality in HFpEF. We studied HFpEF patients enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial who were included in the echocardiography study and had adequate images for quantitative assessment of indices of LV mechanical dyssynchrony prior to randomization.

Methods

Patient population

As previously described in detail,[9] the TOPCAT trial was a multicentre, international, randomized, double-blind, placebo-controlled trial testing the aldosterone antagonist spironolactone to reduce cardiovascular morbidity and mortality. In total, 3445 adults at least 50 years old with signs and symptoms of HF and an LVEF ≥45% per local site reading were included. Randomization was stratified by the presence of one of the following inclusion criteria: at least one hospitalization in the previous 12 months for which HF was a major component of the hospitalization or, if no qualifying hospitalization, a BNP in the previous 60 days ≥100 pg/mL or NT-proBNP ≥360 pg/mL. Detailed baseline and clinical characteristics of the trial population[10] and the primary trial results[11] have previously been published. Randomization to spironolactone did not reduce the composite endpoint of death or HF hospitalization but was associated with a lower incidence of HF hospitalization.[11]

The design and baseline findings of the TOPCAT echocardiographic substudy, including reproducibility metrics for conventional echocardiographic measures, have previously been described in detail.[12] Dyssynchrony was assessed by strain analysis, which was performed on digitally acquired images in DICOM (digital imaging and communications in medicine) format with acceptable quality. Of 935 patients in the TOPCAT echocardiography study, 663 (71%) were in DICOM format. Of those in DICOM format, 424 (64%) had adequate image quality for strain analysis in the apical four-chamber view by B-mode speckle tracking echocardiography (STE) as previously described.[13] Unacceptable image quality was defined as missing view, lack of a full cardiac cycle, >2-segment dropout, or significant foreshortening of the left ventricle. Mechanical dyssynchrony was assessed at baseline in 12% of the TOPCAT study population overall. Of the 935 patients, 305 were enrolled in the dedicated substudy, 244 of whom underwent follow-up echocardiography at 12–18 months as previously described.[12] Of patients with feasible strain-based dyssynchrony analysis at baseline, 160 had follow-up studies.[13] All patients provided written informed consent, and the study was approved by the local Institutional Review Board.

Echocardiographic methods

Quantitative measures on all study echocardiograms were performed according to the American Society of Echocardiography recommendations by dedicated analysts at the core laboratory who were blinded to clinical information and randomized treatment assignment, as previously described.[12,13] Digitally acquired echocardiography images in DICOM format with acceptable image quality were uploaded to TomTec software (Munich, Germany) for deformational analyses (2D Cardiac Performance Analysis) as previously described.[14] For deformation analysis, in the apical views and parasternal views, endocardial borders were traced at the end-diastolic and end-systolic frame, respectively, as previously described.[14] The software tracks speckles along the endocardial border throughout the cardiac cycle. Peak strain was computed automatically, generating regional data from six segments and an average value for each view. For patients in sinus rhythm, analyses were performed on a single cardiac cycle, whereas for patients in AF, strain values were calculated as the average of three selected cardiac cycles. Mechanical dyssynchrony was assessed primarily by the standard deviation of the time to peak (SD T2P) longitudinal strain (LS) in the apical four-chamber view. Additional echocardiographic measures of LV dyssynchrony assessed included: SD T2P LS of 12 segments from the apical four- and two-chamber views, SD T2P transverse strain (TS) obtained from the apical four-chamber view (six segments), and SD T2P circumferential strain (CS) and radial strain (RS) from the parasternal short-axis view at the mid-ventricular level. Peak LS was measured in the apical four-chamber and apical two-chamber views (in six segments from each view) and averaged to calculate global longitudinal strain (GLS).[13] All strain measures were performed by a single reader at the echocardiography core laboratory blinded to patient characteristics or treatment assignment. Reproducibility of SD T2P LS obtained from the four-chamber view was obtained in 20 patients with sinus rhythm and in 20 patients with AF, and expressed as the mean bias and SD using the Bland–Altmann method.[15] For intraobserver reproducibility, mean bias was 25 ± 38 ms for patients with sinus rhythm and 9 ± 70 ms for patients with AF. For interobserver reproducibility, mean bias was 23 ± 78 ms for patients with sinus rhythm and 4 ± 52 ms for patients with AF.

Outcomes

Clinical outcomes included cardiovascular death and HF hospitalization during the follow-up period. All events were reported by the primary site investigator and independently adjudicated by the Clinical Endpoints Center. Definitions of these endpoints have been previously published.[9]

Table 1 Baseline characteristics of patients enrolled in the TOPCAT trial included vs. not included in this analysis

	Non-echo ($n = 3021$)	Echo including T2P LS ($n = 424$)	*P*-value
Demographics			
Age (years)	68.3 ± 9.5	70.2 ± 9.8	<0.001
Women	1542 (51.1%)	231 (54.5%)	0.19
White	2721 (90.2%)	339 (80.0%)	<0.001
Enrolment in Russia/Georgia	1573 (52.1%)	105 (24.8%)	<0.001
Clinical data			
Enrolment strata: previous hospitalization	2192 (72.6%)	271 (63.9%)	<0.001
Myocardial infarction	782 (25.9%)	111 (26.2%)	0.89
Coronary revascularization	687 (22.8%)	126 (29.8%)	0.001
Stroke	222 (7.4%)	43 (10.2%)	0.043
Atrial fibrillation	1037 (34.4%)	176 (41.6%)	0.004
Diabetes mellitus	957 (31.7%)	161 (38.1%)	0.009
Hypertension	2756 (91.4%)	389 (92.0%)	0.69
NYHA functional class (III and IV)	974 (32.3%)	161 (38.2%)	0.017
QRS duration (ms)	99.4 ± 28.4	100.9 ± 27.1	0.32
QRS duration >120 ms	552 (18.3%)	84 (19.8%)	0.44
BMI (kg/m^2)	32.1 ± 7.3	32.5 ± 6.9	0.30
Heart rate (b.p.m.)	69.1 ± 10.3	68.7 ± 10.8	0.41
Systolic blood pressure (mmHg)	129.6 ± 13.7	126.5 ± 15.2	<0.001
Diastolic blood pressure (mmHg)	76.2 ± 10.5	72.6 ± 10.8	<0.001
Lab work			
Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3	0.002
Z score BNP	0.0 ± 1.0	−0.1 ± 1.0	0.30

BMI, body mass index; T2P LS, time to peak longitudinal strain.

Statistical analysis

Continuous variables are expressed as mean ± SD for normally distributed variables, and median and interquartile range (IQR) for non-normally distributed variables. Categorical variables are expressed as number of subjects and proportion. Clinical characteristics and conventional echocardiographic measures are presented by quartiles of SD T2P LS, with *P*-values for trend across quartiles calculated using linear regression for continuous normally distributed variables and on an extension of the Wilcoxon rank-sum test[16] for continuous non-normally distributed variables. The association between SD T2P LS and GLS, E/e', and QRS duration was assessed using cubic spline regression models.

The prognostic relevance of measures of LV mechanical dyssynchrony for the composite of HF hospitalization or cardiovascular death was assessed by time-to-event analysis using univariable and two additive multivariable Cox proportional hazards models whose derivation has been previously described in detail.[12] Model 1 was adjusted for age, sex, race, randomized treatment assignment (spironolactone vs. placebo), randomization strata (qualifying hospitalization or elevated natriuretic peptide level), and enrolment region (the Americas vs. Russia/Georgia). Model 2 additionally adjusted for history of AF, core laboratory LVEF, heart rate, NYHA class, history of stroke, creatinine, haematocrit, and QRS duration. The relationship between baseline dyssynchrony and changes in LV volumes, mass, LVEF, and left atrial (LA) size from baseline to 12 or 18 months was assessed in the 160 patients in whom follow-up echocardiograms were available using linear regression adjusting for the baseline measure and randomized treatment assignment.

As prominent differences in participant characteristics and event rates were noted between patients enrolled in the Americas compared with Russia and Georgia,[11] we also performed a sensitivity analysis restricted to patients enrolled in the Americas ($n = 319$). A two sided *P*-value <0.05 was considered significant. Statistical analysis was performed using Stata software Version 12.1 (Stata Corp LP, College Station, TX, USA).

Results

Mechanical dyssynchrony was assessed in 424 patients in TOPCAT (45% of the TOPCAT echocardiographic study; 12% of the overall study population). Strain analysis was not feasible in 55% of the TOPCAT echocardiographic studies because of non-DICOM imaging format, missing views, or poor image quality. Furthermore, due to variable missing data, a sizeable proportion of the study sample did not have deformation data from both apical four- and two-chamber view strain, or strain data from the parasternal short-axis view. *Table 1* compares baseline characteristics between patients enrolled in the overall TOPCAT trial included in this analysis (SD T2P LS measured) compared with those not included. TOPCAT participants included in this analysis tended to be older, more frequently non-white, more frequently enrolled in the Americas, had a higher prevalence of co-morbidities including CAD, previous strokes, AF, and diabetes, and had higher NYHA functional class.

The median SD T2P LS obtained from the four-chamber view was 59.0 ms (IQR 39.5–88.5 ms). Greater SD T2P LS—indicating

Table 2 Clinical parameters by quartiles of mechanical dyssynchrony

	All ($n = 424$) 59.0 (39.5–88.5) ms	Dyssynchrony as assessed by SD T2P LS in the 4CH view: T2P quartiles (ms)				
		Quartile 1 ($n = 106$) <39.5	Quartile 2 ($n = 109$) 39.5–59.0	Quartile 3 ($n = 103$) 59.1–88.5	Quartile 4 ($n = 106$) >88.5	*P* for trend
Demographics						
Age (years)	70.2 ± 9.8	69.8 ± 9.5	69.0 ± 10.4	69.7 ± 9.2	72.4 ± 9.7	0.044
Women	231 (54.5%)	55 (51.9%)	71 (65.1%)	55 (53.4%)	50 (47.2%)	0.23
White	339 (80.0%)	88 (83.0%)	87 (79.8%)	77 (74.8%)	87 (82.1%)	0.66
Enrolment in Russia/Georgia	105 (24.8%)	32 (30.2%)	29 (26.6%)	18 (17.5%)	26 (24.5%)	0.17
Clinical data						
Enrolment strata: previous hospitalization	271 (63.9%)	76 (71.7%)	69 (63.3%)	65 (63.1%)	61 (57.5%)	0.041
Myocardial infarction	111 (26.2%)	22 (21.0%)	24 (22.0%)	28 (27.2%)	37 (34.9%)	0.014
Coronary revascularization	126 (29.8%)	27 (25.7%)	35 (32.1%)	22 (21.4%)	42 (39.6%)	0.12
Stroke	43 (10.2%)	8 (7.6%)	15 (13.8%)	9 (8.7%)	11 (10.4%)	0.81
Atrial fibrillation	176 (41.6%)	46 (43.8%)	47 (43.1%)	39 (37.9%)	44 (41.5%)	0.57
Diabetes mellitus	161 (38.1%)	39 (37.1%)	41 (37.6%)	37 (35.9%)	44 (41.5%)	0.59
Hypertension	389 (92.0%)	96 (91.4%)	100 (91.7%)	94 (91.3%)	99 (93.4%)	0.65
NYHA functional class (III and IV)	161 (38.2%)	43 (41.0%)	45 (41.7%)	34 (33.0%)	39 (36.8%)	0.32
QRS duration (ms)	100.9 ± 27.1	90.8 ± 17.3	98.5 ± 22.9	102.6 ± 28.3	111.4 ± 33.2	<0.001
QRS duration >120 ms	84 (19.8%)	8 (7.5%)	18 (16.5%)	21 (20.4%)	37 (34.9%)	<0.001
BMI (kg/m^2)	32.5 ± 6.9	32.1 ± 6.3	33.6 ± 7.7	33.1 ± 6.8	31.1 ± 6.6	0.26
Heart rate (b.p.m.)	68.7 ± 10.8	68.7 ± 10.3	69.7 ± 11.6	67.3 ± 10.6	69.0 ± 10.6	0.75
Systolic blood pressure (mmHg)	126.5 ± 15.2	124.3 ± 13.3	127.1 ± 14.3	128.4 ± 17.5	126.3 ± 15.3	0.27
Diastolic blood pressure (mmHg)	72.6 ± 10.8	72.7 ± 11.2	73.5 ± 9.8	71.0 ± 11.0	73.1 ± 11.0	0.79
Lab work						
Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	0.47
Z score BNP	−0.1 ± 1.0	−0.1 ± 1.2	−0.2 ± 0.9	0.1 ± 0.9	0.2 ± 0.9	0.041

BMI, body mass index; 4CH, four chamber; SD T2P LS, standard deviation of the time to peak longitudinal strain.

greater mechanical dyssynchrony—was associated with older age, previous myocardial infarction, greater QRS duration, randomization through the prior HF hospitalization stratum, and higher natriuretic peptide levels among those with available measures (*Table 2*; *Figure 1*). Greater SD T2P LS was also associated with greater LV size, wall thickness, and mass, worse systolic function as determined by lower LVEF and GLS, and worse diastolic function reflected in lower e' and higher E/e' ratio (*Table 3*; *Figure 1*).

During a median follow-up of 2.6 (IQR 1.5–3.8) years, 107 patients (25%) experienced the composite outcome of HF hospitalization or cardiovascular death. HF hospitalization occurred in 73 (17%) patients, and cardiovascular death occurred in 51 (12%). In unadjusted analysis, greater SD T2P LS was associated with a higher risk of the composite outcome (*Figure 2*; *Table 4*). Patients in the highest quartile of SD T2P LS had approximately a twice higher risk compared with patients in the lowest quartile [fourth quartile vs. first quartile: hazard ratio (HR) 2.03, 95% confidence interval (CI) 1.17–3.50, $P = 0.011$]. After multivariable adjustment for clinical characteristics (age, sex, race, randomization strata, region of enrolment, and treatment assignment), SD T2P LS was no longer an independent predictor of the composite outcome (*Table 4*). The same result was found after further adjustment for LVEF, AF, NYHA class, stroke, heart rate, creatinine, haematocrit, and QRS duration (fourth quartile vs. first quartile: HR 1.56, 95% CI 0.85–2.86, $P = 0.15$) (*Table 4*). In addition, in models adjusting only for either GLS or E/e', SD T2P LS did not retain statistical significance (HR 1.02, 95% CI 0.98–1.06, $P = 0.21$, adjusting only for LS; HR 1.03, 95% CI 1.00–1.07, $P = 0.060$, adjusting only for E/e'). The SD T2P LS derived from the four- and two-chamber views (12 segments) demonstrated similar results to SD T2P LS from the four-chamber view (*Table 4*). Of the other strain-based measures of LV mechanical dyssynchrony assessed, none was significantly associated with the composite outcome even in unadjusted analysis (*Table 4*). Among the 160 patients with serial echocardiographic data, greater baseline dyssynchrony was not associated with changes in LV volumes, LV mass, LVEF, or LA volume at 12–18 months follow-up (*Table 5*).

Neither QRS duration (<120 ms vs. ≥120 ms; *P* for interaction = 0.79), LVEF (<60% vs. ≥60%; *P* for interaction = 0.27), nor abnormal GLS (< −15% vs. ≥ −15%; *P* for interaction = 0.27) modified the association between mechanical dyssynchrony and the composite outcome. In analyses restricted to patients enrolled in the Americas, no echocardiographic measures of dyssynchrony significantly predicted the composite outcome (Supplementary material online, *Table S1*). LV mechanical dyssynchrony, as assessed by SD T2P LS obtained from the four-chamber view, did not modify

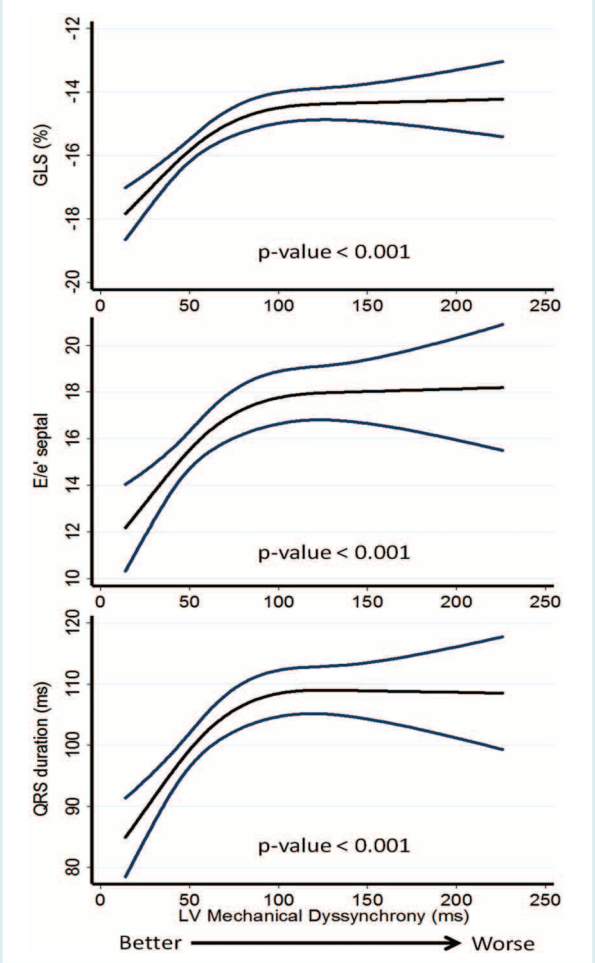

Figure 1 Association between myocardial dyssynchrony and global longitudinal strain (GLS), E/e', and QRS duration. Cubic splines regression models with 95% confidence intervals for the association between mechanical dyssynchrony as assessed by the standard deviation of the time to peak longitudinal strain and GLS (*A*), E/e' (*B*), and QRS duration (*C*), respectively.

the relationship between randomization to spironolactone and the composite outcome (*P* for interaction = 0.71). The prognostic relevance of dyssynchrony was similar among patients in sinus rhythm ($n = 247$) and those with AF ($n = 176$), and rhythm did not modify the relationship between dyssynchrony and the composite outcome (*P* for interaction = 0.94; *Table 6*).

Discussion

While LV mechanical dyssynchrony has previously been described in HFpEF, its prognostic relevance in this syndrome is unknown. We report that greater mechanical dyssynchrony as assessed by the SD T2P LS is significantly associated with the composite of HF hospitalization or cardiovascular death in unadjusted analysis, but not after adjusting for clinical characteristics. Other strain-based measures of mechanical dyssynchrony are not associated with the composite outcome even in unadjusted analyses. Together, these data suggest that the presence of mechanical dyssynchrony as assessed by STE does not provide independent prognostic information in HFpEF.

Left ventricular electrical dyssynchrony, reflected in prolonged QRS duration, is prognostic in both HFrEF[1] and HFpEF,[6] and is a validated treatment target in HFrEF.[2] Left ventricular mechanical dyssynchrony, detected by direct imaging of the LV contraction pattern, is also prognostic of adverse outcomes in HFrEF[17] even in the absence of electrical dyssynchrony.[3] Improving mechanical dyssynchrony by CRT in HFrEF patients with concomitant electrical dyssynchrony (prolonged QRS duration) has been associated with improved outcome.[17] Importantly, however, isolated mechanical dyssynchrony does not appear to be an effective treatment target, as evidenced by the neutral results of the recent Echocardiography-Guided Cardiac Resynchronization Therapy (EchoCRT) trial[3,18] which tested the efficacy of resynchronization therapy in HFrEF patients with echocardiographic evidence of mechanical dyssynchrony and a narrow QRS. Several studies have demonstrated greater mechanical dyssynchrony in HFpEF compared with asymptomatic controls,[14,19] although this has not been a universal finding.[8] The mechanisms responsible for mechanical dyssynchrony in HFpEF are unclear. Elevated LV afterload, as seen in hypertension, is associated with lower average LV LS due to lower regional strain in certain segments of the left ventricle,[20,21] with a concomitant increase in mechanical dyssynchrony.[21] Indeed, a previous study demonstrated a similar magnitude of dyssynchrony in asymptomatic persons with hypertension and HFpEF.[8]

The magnitude of mechanical dyssynchrony in this TOPCAT sample was similar to that in the Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction (PARAMOUNT) HFpEF trial,[7,22] but considerably less than in HFrEF patients with prolonged QRS enrolled in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial[23,24] and in post-myocardial infarction patients.[25] Despite a similar magnitude of mechanical dyssynchrony to other HFpEF studies, mechanical dyssynchrony did not provide independent prognostic information in HFpEF patients beyond basic clinical characteristics. The absence of independent prognostic value of mechanical dyssynchrony in HFpEF is important, as the prospect of treating HFpEF patients with mechanical dyssynchrony using CRT has been discussed.[26] The reason for the lack of independent prognostic value is unclear. Given the smaller magnitude of dyssynchrony in HFpEF compared with HFrEF, mechanical dyssynchrony in HFpEF may not be of sufficient magnitude to cause substantive LV inefficiency. Alternatively, greater mechanical dyssynchrony was significantly associated with worse systolic and diastolic function (GLS and E/e') and worse electrical dyssynchrony (QRS duration), each of which is a strong independent predictor of outcome in HFpEF.[6,12,13,27] The observed univariable association of mechanical dyssynchrony with outcomes in HFpEF may therefore simply be secondary to the association of mechanical dyssynchrony with worse systolic and diastolic function.[6,12,13] This is supported by our observation that the association of SD T2P LS with cardiovascular death or HF hospitalization was no longer significant after adjusting for GLS or for E/e'.

Table 3 Echocardiographic parameters by quartiles of mechanical dyssynchrony

		Dyssynchrony as assessed by SD T2P LS in the 4CH view: T2P quartiles (ms)				
	All (*n* = 424) 59.0 (39.5–88.5) ms	**Quartile 1 (*n* = 106) <39.5**	**Quartile 2 (*n* = 109) 39.5–59.0**	**Quartile 3 (*n* = 103) 59.1–88.5**	**Quartile 4 (*n* = 106) >88.5**	***P* for trend**
LVEDV (mL)	98.5 ± 35.1	93.0 ± 28.8	95.5 ± 35.5	101.6 ± 35.1	104.1 ± 39.5	0.009
LVEDD (cm)	4.8 ± 0.6	4.7 ± 0.6	4.7 ± 0.6	4.8 ± 0.5	4.9 ± 0.7	0.011
Mean wall thickness (cm)	1.2 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.3	<0.001
LV mass (g)	215.4 ± 68.2	194.4 ± 56.9	202.6 ± 64.0	223.5 ± 65.7	241.9 ± 75.5	<0.001
TDI E' (septal) (cm/s)	5.9 ± 2.0	6.6 ± 2.0	6.3 ± 2.1	5.6 ± 2.1	5.1 ± 1.7	<0.001
TDI E' (lateral) (cm/s)	8.1 ± 3.1	8.7 ± 2.8	8.5 ± 3.6	7.5 ± 2.8	7.6 ± 3.0	0.005
LAV (mL)	60.7 ± 27.4	58.0 ± 20.4	61.9 ± 35.2	59.9 ± 20.5	63.0 ± 29.9	0.28
E/E' (septal)	15.9 ± 6.9	13.6 ± 5.8	15.5 ± 6.3	16.8 ± 7.1	17.9 ± 7.6	<0.001
E/E' (lateral)	11.8 ± 5.9	10.1 ± 4.8	12.2 ± 6.0	12.5 ± 6.3	12.3 ± 6.4	0.023
LVEF (%)	59.9 ± 8.1	62.3 ± 5.7	60.6 ± 7.0	59.7 ± 8.0	57.0 ± 10.1	<0.001
GLS (%)	−15.6 ± 3.5	−17.1 ± 2.8	−15.5 ± 3.4	−15.6 ± 3.5	−14.1 ± 3.6	<0.001

4CH, four chamber; GLS, global longitudinal strain; LAV, left atrial volume; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; SD T2P LS, standard deviation of the time to peak longitudinal strain; TDI, tissue Doppler imaging.

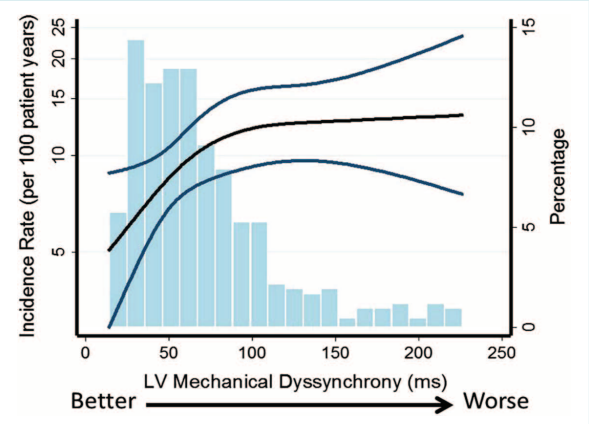

Figure 2 Association of LV mechanical dyssynchrony and incident heart failure hospitalization or cardiovascular death. Unadjusted incidence with 95% confidence intervals of the composite endpoint per 100 patient-years based on LV mechanical dyssynchrony as assessed by the standard deviation of the time to peak longitudinal strain. A Poisson model was used to estimate the incidence rate. *P* for overall relationship = 0.021; *P* for non-linearity = 0.082. Histograms shows the population distribution of LV mechanical dyssynchrony.

Dyssynchrony decreases ventricular contractile efficiency, and progressive LV remodelling—and reverse remodelling with resynchronization therapy—is one recognized mechanism mediating prognosis.[28] Previous studies in patients with a normal LVEF have suggested that electrical dyssynchrony due to chronic right ventricular pacing is associated with progressive LV enlargement, worsening LV systolic function, and LA enlargement.[29,30] The randomized controlled Pacing to Avoid Cardiac Enlargement (PACE) trial, which randomized 177 patients with bradycardia and LVEF >45% to biventricular or right ventricular pacing, demonstrated a significant increase in LV end-diastolic volume and decrease in LVEF at 12 months among patients randomized to right ventricular pacing. Biventricular pacing ameliorated these dyssynchrony-associated changes.[30] However, the association of mechanical dyssynchrony in the context of a preserved LVEF with adverse LV remodelling has not been defined. Among the 160 TOP-CAT participants with baseline dyssynchrony data and follow-up echocardiography at 12–18 months, baseline dyssynchrony was not associated with progressive worsening of LV structure or function, which is concordant with the lack of independent association of dyssynchrony with incident HF or cardiovascular death. Additionally, baseline dyssynchrony was not associated with progressive LA enlargement, an important prognostic measure in HFpEF.[31,32]

While several echocardiographic measures of LV mechanical dyssynchrony have been developed, including M-mode, Doppler, tissue Doppler imaging (TDI), and STE, we primarily evaluated STE-based measures evaluating the temporal dispersion in time to peak regional deformation. It is therefore possible that another imaging-based measure of dyssynchrony not assessed in this study would be independently predictive of adverse outcomes. However, we assessed mechanical dyssynchrony by STE using several different methods including those employed in recent CRT trials in HFrEF, MADIT-CRT[2,23] and EchoCRT.[3,18] While SD T2P LS was the metric most strongly associated with outcomes, there was uniformly no independent association of any of the dyssynchrony measures assessed with outcomes after multivariable adjustment. Metrics of the temporal dispersion in the time to peak segmental deformation assessed by TDI and STE have been the most rigorously studied measures of mechanical dyssynchrony to date.[3,18,23,33] However, both TDI and STE curves provide a substantial amount of information regarding regional patterns of deformation beyond just the

Table 4 Measures of mechanical dyssynchrony and the association with outcome

	n	Events	Hazard ratio (95% CI)	*P*-value
Obtained from the 4CH view				
SD T2P LS per 10 ms increase				
Unadjusted	424	107	1.04 (1.01–1.07)	0.021
Model 1	424	107	1.03 (1.00–1.06)	0.055
Model 2	410	105	1.03 (0.99–1.06)	0.157
SD T2P TS per 10 ms increase				
Unadjusted	424	107	1.00 (0.98–1.03)	0.785
Model 1	424	107	1.00 (0.98–1.03)	0.838
Model 2	410	105	1.00 (0.98–1.03)	0.840
Obtained from the 4CH and 2CH view				
Average of SD T2P LS per 10 ms increase				
Unadjusted	212	50	1.07 (1.00–1.15)	0.046
Model 1	212	50	1.06 (0.99–1.14)	0.083
Model 2	202	49	1.07 (0.99–1.16)	0.083
Obtained from the psax view				
SD T2P CS per 10 ms increase				
Unadjusted	243	69	1.05 (0.99–1.11)	0.094
Model 1	243	69	1.05 (0.99–1.11)	0.093
Model 2	232	68	1.05 (0.99–1.11)	0.133
SD T2P RS per 10 ms increase				
Unadjusted	243	69	0.99 (0.95–1.02)	0.467
Model 1	243	69	1.00 (0.96–1.04)	0.937
Model 2	232	68	1.00 (0.96–1.04)	0.925
T2P anteroseptal to posterior difference per 10 ms increase				
Unadjusted	243	69	0.99 (0.97–1.01)	0.495
Model 1	243	69	1.00 (0.97–1.02)	0.784
Model 2	232	68	0.99 (0.97–1.02)	0.499
T2P anteroseptal to posterior difference >130 ms				
Unadjusted	243	69	1.05 (0.56–1.95)	0.889
Model 1	243	69	1.12 (0.60–2.11)	0.719
Model 2	232	68	1.01 (0.52–1.97)	0.970

Model 1 is adjusted for age, sex, race, randomization strata (previous heart failure hospitalization or biomarker criteria), region of enrolment (Americas vs. Russia/Georgia), and randomized treatment. Model 2 includes the same variables as Model 1 + core laboratory LVEF, history of AF, heart rate, NYHA class, history of stroke, creatinine, haematocrit, and QRS duration.

2CH, two chamber; 4CH, four chamber; CI, confidence interval; CS, circumferential strain; LS, longitudinal strain; psax, parasternal short-axis; RS, radial strain; SD T2P, standard deviation of the time to peak; TS, transverse strain.

timing of peak deformation. Novel approaches have evaluated differences in the patterns of the complete velocity[34] or deformation curves,[21] based on the concept that these curves can display similar patterns of contraction despite different time to peak values, and may be superior to the time to peak methods to identify responders to CRT.[34,35]

Previous studies have described SD T2P LS as a strong predictor of ventricular arrhythmias,[36,37] although recent reports suggest limited utility of this measure to predict arrhythmic events in HFrEF.[24,38–40] No study has previously assessed whether this measure is associated with ventricular arrhythmias in HFpEF. Data regarding incident ventricular arrhythmias, short of aborted sudden death, are not available in TOPCAT. We were therefore unable to assess the relationship between SD T2P LS and ventricular arrhythmias in this analysis, and the association of this measure with ventricular arrhythmias in HFpEF remains unknown.

Strain analysis was feasible in 45% of patients in the TOPCAT echocardiography study and 12% of the overall TOPCAT study population, limiting statistical power and generalizability for these analyses. In addition, HFpEF is known to be a heterogeneous syndrome,[41] and we cannot exclude the possibility that in a subset of HFpEF patients, LV mechanical dyssynchrony is particularly relevant to disease pathophysiology and prognosis. Not all previously proposed measures of LV mechanical dyssynchrony—particularly those based on M-mode imaging or TDI—could be assessed in this study. In the TOPCAT trial, strain was not assessed in the apical long-axis view, but only in the apical four- and two-chamber views. Dyssynchrony was therefore only calculated from six segments (four-chamber view) and 12 segments (four- and two-chamber views), and was not assessed from 16 segments (four-, two-, and three-chamber views).[13] Finally, previous studies have suggested that, as opposed to greater resting dyssynchrony, HFpEF is characterized by a failure of exercise-associated decrease in LV

Table 5 Mechanical dyssynchrony at baseline and left ventricular remodelling at 12–18 months ($n = 160$)

	Dyssynchrony as assessed by SD T2P LS in the 4CH view: T2P quartiles (ms)				
	Quartile 1 ($n = 41$) <36	Quartile 2 ($n = 41$) 36–58	Quartile 3 ($n = 38$) 58–86	Quartile 4 ($n = 40$) >86	*P* for trend
LVEDV baseline (mL)	88.1 ± 24.9	99.4 ± 37.2	103.9 ± 37.7	101.7 ± 36.8	0.06
LVEDV change (mL)	2.9 ± 14.0	−1.8 ± 12.1	2.0 ± 16.4	4.9 ± 14.0	0.32*
LVESV baseline (mL)	32.7 ± 10.0	41.1 ± 23.8	45.5 ± 25.7	46.1 ± 24.3	0.004
LVESV change (mL)	1.8 ± 9.5	−0.8 ± 6.2	1.3 ± 9.9	4.0 ± 8.7	0.22*
LV mass baseline (g)	181.4 ± 50.3	197.7 ± 58.4	209.4 ± 65.4	234.4 ± 73.3	<0.001
LV mass change (g)	−1.1 ± 11.8	1.0 ± 23.9	−3.4 ± 30.1	−2.6 ± 17.8	0.84*
LAV baseline (mL)	62.8 ± 22.0	59.5 ± 21.9	60.6 ± 23.5	61.7 ± 21.8	0.91
LAV change (mL)	0.1 ± 9.4	−0.8 ± 13.1	3.3 ± 15.4	4.3 ± 17.9	0.10*
LVEF baseline (%)	62.7 ± 4.8	60.3 ± 7.5	58.2 ± 9.4	56.7 ± 10.2	<0.001
LVEF change (%)	−0.7 ± 6.1	0.6 ± 5.9	−0.7 ± 5.2	−0.4 ± 6.4	0.41*

4CH, four chamber; LAV, left atrial volume; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; SD T2P LS, standard deviation of the time to peak longitudinal strain.
*Adjusted for the baseline measure and randomized treatment assignment.

Table 6 Mechanical dyssynchrony as assessed by the standard deviation of the time to peak longitudinal strain and the association with outcome in patients with and without atrial fibrillation

	n	Events	Hazard ratio (95% CI)	*P*-value
In patients with sinus rhythm				
SD T2P LS obtained from the 4CH view per 10 ms increase				
Unadjusted	247	60	1.04 (0.99–1.08)	0.096
Model 1	247	60	1.02 (0.98–1.07)	0.273
Model 2	239	58	1.03 (0.98–1.08)	0.275
In patients with atrial fibrillation				
SD T2P LS obtained from the 4CH view per 10 ms increase				
Unadjusted	176	47	1.04 (0.99–1.08)	0.098
Model 1	176	47	1.03 (1.00–1.08)	0.129
Model 2	171	47	1.02 (0.96–1.07)	0.526
Interaction between SD T2P LS and atrial fibrillation				
Unadjusted				0.940
In fully adjusted model (Model 2)				0.154

Model 1 is adjusted for age, sex, race, randomization strata (previous heart failure hospitalization or biomarker criteria), and randomized treatment. Model 2 includes the same variables as Model 1 + core laboratory LVEF, heart rate, NYHA class, history of stroke, creatinine, haematocrit, and QRS duration.
4CH, four chamber; CI, confidence interval; SD T2P LS, standard deviation of the time to peak longitudinal strain.

dyssynchrony.[19] However, only resting state imaging was available in this study, so the prognostic relevance of exercise-induced changes in LV synchrony could not be assessed.

Conclusion

Worse LV mechanical dyssynchrony, as assessed by STE, is not an independent predictor of adverse outcomes in HFpEF. These findings suggest that mechanical dyssynchrony is a marker of worse cardiac structure and function in HFpEF, but is unlikely to be an important mechanism underlying this syndrome. These findings warrant validation in an independent study specifically designed to assess the prognostic utility of mechanical dyssynchrony in HFpEF.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Measures of mechanical dyssynchrony and the association with outcome in patients enrolled in America ($n = 319$).

Funding

This work was supported by research grants from the P. Carl Petersen foundation (to T.B.-S.), The Danish Council for Independent Research Sapere Aude research talent grant (DFF-4004-00248B; to T.B.-S.), the National Institutes of Health

(grant K08HL116792; to A.M.S.), and the American Heart Association (grant 14CRP20380422; to A.M.S.). TOPCAT was funded by National Heart, Lung, and Blood Institute, National Institutes of Health (Bethesda, MD), contract HHSN268200425207C. The content of this article does not necessarily represent the views of the sponsor or of the Department of Health and Human Services.

Conflict of interest: A.M.S. reports receiving research support from Novartis, Gilead, and Myocaria Inc. B.P. reports serving as a consultant for Bayer, AstraZeneca, Merck, Boehringer Ingelheim, KBP biosciences and Relypsa; and has a patent pending on site-specific delivery of eplerenone to the myocardium. N.S. reports consulting for Medtronic. M.A.P. reports receiving research grants from Amgen, Celladon, Novartis, and Sanofi Avantis; and serving as a consultant for Amgen, AstraZeneca, Bayer, DalCor Pharma UK, Genzyme, Lilly, The Medicines Company, MedImmune, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Salix, Sanderling, Sanofi, Takeda, Teva, Thrasos, and Vericel. The Brigham and Women's Hospital has patents for the use of inhibitors of the renin–angiotensin system in selected survivors of myocardial infarction with Novartis. M.A.P. is a co-inventor. His share of the licensing agreement is irrevocably transferred to charity. The other authors report no conflicts of interest.

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