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Left ventricular dyssynchrony in patients with heart failure and preserved ejection fraction

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Aims Mechanical dyssynchrony has been postulated to play a pathophysiologic role in heart failure with preserved ejection fraction (HFpEF).

Methods and results We quantified left ventricular (LV) systolic dyssynchrony in 130 HFpEF patients with NYHA class II-IV symptoms, ejection fraction (EF) $\geq$45%, and NT-proBNP levels $>$400 pg/mL enrolled in the PARAMOUNT trial, and compared them to 40 healthy controls of similar age and gender. Dyssynchrony was assessed by 2D speckle tracking as standard deviation (SD) of time to peak longitudinal systolic strain in 12 ventricular segments and related to measures of systolic and diastolic function. Heart failure with preserved ejection fraction patients (62% women, mean age of 71 $\pm$ 9 years, body mass index of 30.2 $\pm$ 5.9 kg/m^2, systolic blood pressure 139 $\pm$ 15 mmHg) demonstrated significantly greater dyssynchrony than controls (SD of time to peak longitudinal strain; 90.6 $\pm$ 50.9 vs. 56.4 $\pm$ 33.5 ms, $P < 0.001$), even in the subset of patients ($n = 63$) with LVEF $\geq$55% and narrow QRS ($\leq$100 ms). Among HFpEF patients, dyssynchrony was related to wider QRS interval, higher LV mass, and lower early diastolic tissue Doppler myocardial velocity (E′). Greater dyssynchrony remained significantly associated with worse diastolic function even after restricting the analysis to patients with EF$\geq$55% and adjusting for age, gender, systolic blood pressure, LV mass index, and LVEF.

Conclusion Heart failure with preserved EF is associated with greater mechanical dyssynchrony compared with healthy controls of similar age and gender. Within an HFpEF population, the severity of dyssynchrony is related to the width of QRS complex, LV hypertrophy, and diastolic dysfunction.

Keywords Heart failure with preserved ejection fraction • Dyssynchrony • Speckle tracking

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a common and increasingly prevalent health problem[1] affecting 30–55% of all patients with chronic heart failure.[2–5] The pathophysiological mechanisms underlying HFpEF are heterogeneous and complex. While abnormalities of diastolic function including abnormal active relaxation and elevated passive stiffness are most commonly implicated,[6–8] abnormalities of left ventricular (LV) systolic function have also been described.[9–11] Additionally, mechanisms also appear to contribute to HFpEF, including impaired LV systolic and diastolic functional reserve, pulmonary hypertension and abnormal pulmonary vascular resistance, impaired peripheral oxygen utilization, arterial stiffness and abnormal ventricular–vascular coupling, and chronotropic incompetence.[12]

Cardiac dyssynchrony has been associated with a higher risk of adverse outcomes in heart failure with reduced ejection fraction (HFrEF) and has also been associated with worse prognosis following myocardial infarction.[13] Furthermore, mechanical dyssynchrony and its associated inefficiencies in myocardial contraction and relaxation have also been proposed to play a role in HFpEF.[14,15] We used baseline data from the The Prospective comparison of ARNI with ARB on

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Management Of heart failUre with preserved ejectioN fraction (PARAMOUNT) Trial, a large well-phenotyped cohort of HFpEF patients, to test the hypothesis that cardiac synchrony is abnormal in HFpEF patients, and that this dyssynchrony is related to impaired diastolic as well as systolic function.

Methods

Study population

Heart failure with preserved ejection fraction patients

The PARAMOUNT trial (Clinicaltrials.gov NCT00887588) enrolled men and women older than 40 years with left ventricular ejection fraction (LVEF) $\geq$45%, documented history of heart failure with NYHA class II-IV symptoms, and NT-proBNP levels $>$400 pg/mL at the baseline visit.[16] Patients were excluded if they had a previous LVEF less than 45% at any time, isolated right heart failure due to pulmonary diseases, dyspnoea due to non-cardiac causes such as pulmonary diseases, anaemia or severe obesity, primary valvular, coronary, or cerebrovascular disease. All of the 301 patients enrolled in the PARAMOUNT trial had a baseline echocardiogram according to a study protocol. A total of 130 patients had apical two- and four-chamber image quality sufficient for speckle tracking analysis, and were appropriate for LV dyssynchrony analysis. Patients with non-DICOM images, missing view(s), poor image quality, left bundle branch block, and/or paced rhythm were excluded (*Figure 1*).

Controls

A group of 40 healthy controls was retrospectively identified from the medical records of the Brigham and Women's Hospital (BWH). The search strategy targeted patients $>$55 years who had an echocardiogram, and no ICD-9 code in their record for any of the following conditions: hypertension, ischaemic heart disease, cardiac arrhythmia, hypercholesterolaemia, chronic obstructive lung disease, diabetes mellitus, cerebrovascular disease, arterial vascular disease, and cancer .This group was further selected to have normal LVEF, no LV regional motion abnormalities, normally sized cardiac chambers, no significant valvular disease, and suitable echocardiogram image quality. Controls had a similar age and gender distribution to the HFpEF group. Our final sample was achieved from an initial searching including 2,000 participants. The study protocol was approved by the BWH Institutional Review Board.

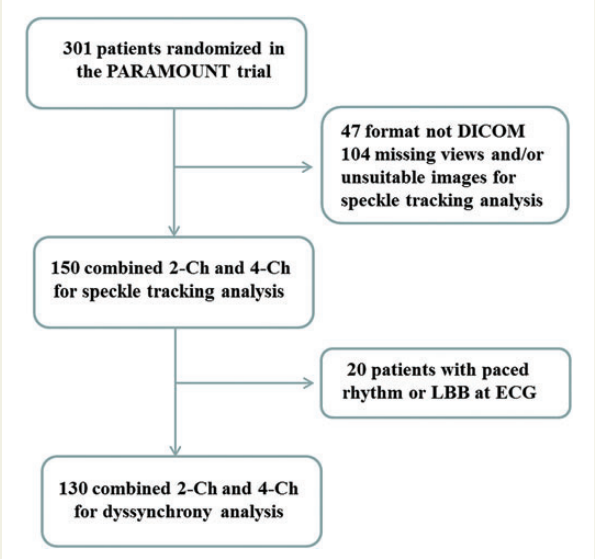

Figure 1 Feasibility of dyssynchrony evaluation by speckle tracking analysis.

Echocardiographic analyses

Standard echocardiographic and Doppler parameters were analysed using an offline analysis workstation at a core laboratory (Brigham and Women's Hospital, Boston MA, USA). All measurements were made in triplicate in accordance with the recommendations of the American Society of Echocardiography[17,18] and included LV diameter and volumes, LV wall thickness, LV mass, LVEF, left atrial (LA) volume, mitral inflow propagation, and lateral mitral annular relaxation velocities.

Dyssynchrony and contractile function indices were measured using B-mode speckle tracking software (TomTec Imaging Systems, Unterschleissheim, Germany) that circumvents angle dependency and identifies cardiac motion by tracking multiple reference points over time. The endocardial borders were traced at the end-diastolic frame of 2D images acquired from the apical two- and four-chamber views. End-diastole was defined by the QRS complex, or as the frame after mitral valve closure. Speckles were tracked frame by frame throughout the LV myocardium over the course of one cardiac cycle; basal, mid, and apical regions of interest were then created. Thereafter, each image was carefully inspected and the segments that failed to track were manually adjusted. If more than one segment could not be tracked, if there was a lack of a full cardiac cycle or significant foreshortening of the left ventricle, the measurements were considered unreliable and the patient was excluded from the analysis. Mechanical dyssynchrony of the LV was measured as the standard deviation of regional time-to-peak longitudinal strain (in milliseconds) measured during systole, across the 12 anatomic wall segments of the apical four- and two-chamber views (*Figure 2*).[14] Global longitudinal strain was calculated as the average longitudinal strain across the apical two- and four-chamber views. For patients in sinus rhythm, analyses were performed on a single cardiac cycle, while for patients in atrial fibrillation strain values were averaged over three cardiac cycles. Intra-observer variability was assessed in 30 randomly selected PARAMOUNT studies: coefficient of variation: 6.8%; intra-class correlation coefficient was 0.95 (95% CI 0.91–0.98) for global longitudinal strain.

Statistical analysis

All normally distributed data were displayed as mean and standard deviation, and non-normally distributed data were displayed as median and interquartile range. Categorical data were shown as a total number and proportion. NT-proBNP was log-transformed before analysis. Categorical variables were compared using X^2 tests and continuous variables were compared using a two-sided *t*-test with unequal variance.

We categorized the HFpEF patients in quartiles according to severity of dyssynchrony, and applied trend tests across ordered groups to illustrate the association between dyssynchrony and demographic characteristics, NT-proBNP levels, QRS interval, and echocardiographic measures of cardiac structure and function. Correlations of categorical and continuous variables were tested by Pearson's coefficient. Multivariate linear regression analysis was performed to adjust for significant clinical variables. All tests were two-sided and *P*-values of $<$ 0.05 were considered statistically significant. Stata/SE version 12.1 (StataCorp, College Station, TX, USA) was used for all analysis.

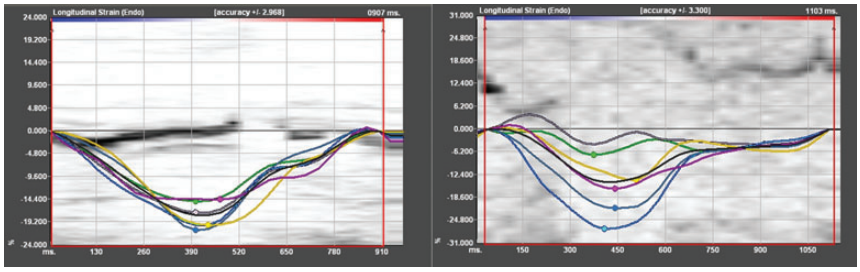

Figure 2 Two-dimensional speckle tracking imaging in the apical four-chamber view in a healthy control patient (left panel) and a patient with heart failure with preserved ejection fraction (HFpEF) (right panel). Curves represent longitudinal strain curves, which were used to measure left ventricular dyssynchrony and contractile function.

Results

Patient characteristics

Patients with HFpEF were generally elderly, obese, and mostly women (62%) (*Table 1*). Most of these patients were in NYHA functional class II (77%), and had elevated NT-proBNP levels (median 867 pg/mL, IQR 482–1459 pg/mL). Although the majority of patients were hypertensive (92%), their blood pressure was well controlled. Atrial fibrillation was present in 24 (18%) patients at the time of echocardiography. The mean QRS duration was 96.1 ± 21.6 ms and 17 (13%) patients had QRS duration greater than or equal to 120 ms. Patients included in this analysis had slightly higher LVEF (59.6 ± 7.2 vs. 56.6 ± 7.9%, $P < 0.001$), and had higher systolic blood pressure (139 ± 15 vs. 133 ± 15mmHg, $P = 0.002$) than patients not included, but were similar with respect to other baseline characteristics.

Compared with controls, patients with HFpEF had lower EF, although still within the normal range, and global longitudinal strain was lower. Heart failure with preserved ejection fraction patients had also higher LV and LA volumes, lower mitral annular relaxation velocity (E′), and higher E/E′ ratio compared with controls. The LV mass was not different between groups. The relative wall thickness was higher in controls than HFpEF patients driven by higher LV end-diastolic diameter in the HFpEF group (*Table 1*). The elevated NT-proBNP, as inclusion criteria in the PARAMOUNT trial, can favour patients with larger left ventricles. Indeed, in our study, LV end-diastolic diameter was significantly associated with NT-proBNP levels ($P = 0.03$).

Cardiac dyssynchrony

Left ventricular dyssynchrony was significantly worse in HFpEF patients compared with controls (*Figure 3*). The difference between these groups persisted even when the analysis was restricted to HFpEF patients in sinus rhythm ($n = 106$; 56.4 ± 33.5 ms in controls vs. 97.6 ± 51.8 ms in HFpEF, $P < 0.001$) or to 40 HFpEF patients (age and gender matched 1:1 with controls). Also, the differences remain in a subset of HFpEF patients with EF ≥55% and QRS ≤100 ms ($n = 63$; 56.4 ± 33.5 ms in controls vs. 88.5 ± 55.8 ms in HFpEF, $P < 0.001$), and remained significant after adjustment for age, gender, systolic blood pressure, LV mass index, and LVEF ($P = 0.013$).

Among HFpEF patients, those with more dyssynchrony had wider QRS intervals, higher LV mass indices, and progressively decreased mitral annular relaxation velocity (E′) compared with HFpEF patients in the lowest quartile of dyssynchrony (*Table 2*). Left ventricular EF, global longitudinal strain, LA volume index, E/E′, and NT-proBNP did not differ based on the degree of dyssynchrony. In a sensitivity analysis, the relationship between dyssynchrony and E′ persisted even in patients with LVEF ≥55%, and after adjustment for age, gender, systolic blood pressure, LV mass index, and LVEF (*Figure 4*).

Discussion

We observed that HFpEF patients had greater LV dyssynchrony compared with healthy controls and that dyssynchrony was present even in patients with LVEF ≥55% and narrow QRS. In HFpEF patients, worse LV dyssynchrony was associated with a wider QRS interval, lower mitral annular relaxation velocity, and higher LV mass. These findings suggest that dyssynchrony may play a pathophysiologic role in HFpEF.

In addition to the acknowledged association between HFrEF and dyssynchrony,[19–21] LV dyssynchrony has also been described in HFpEF. Studies using conventional Doppler echocardiography parameters and tissue Doppler first demonstrated that mechanical dyssynchrony is common in patients with HFpEF, regardless of QRS duration.[14,22,23] Recently, speckle tracking has emerged as a more robust technique to quantify dyssynchrony because unlike Doppler it is angle independent.[24] Phan *et al.*[14] compared 33 HFpEF patients with a narrow QRS (<120 ms) to healthy controls, and showed greater dyssynchrony in the former. More recently, speckle tracking was used to demonstrate that 85 HFpEF patients had greater dyssynchrony than patients with asymptomatic LV diastolic dysfunction.[15] Our study utilized speckle tracking; all echocardiography measurements were performed using a core laboratory[25] and included the largest sample of HFpEF patients to date. We further showed that greater dyssynchrony was present even in HFpEF patients with LVEF >55%[17] and a narrower QRS (<100 ms) than previously reported.

We found that greater LV dyssynchrony was most robustly associated with lower early diastolic relaxation assessed by E′. The association remained strong even in a subset of patients with robustly

Table 1 Baseline characteristics of the study population

	Controls (n = 40)	HFpEF (n = 130)	P-value
Age (years)	69 ± 7	71 ± 9	0.11
Women, n (%)	31 (78)	80 (62)	0.06
NYHA II, n (%)	–	100 (77)	
NYHA III, n (%)	–	29 (22)	
Previous hospitalization for HF, n (%)	0 (0%)	64 (49)	
History of atrial fibrillation, n (%)	0 (0%)	57 (44)	
History of hypertension, n (%)	0 (0%)	119 (92)	
History of diabetes, n (%)	0 (0%)	43 (33)	
History of myocardial infarction, n (%)	0 (0%)	26 (20)	
Heart rate (bpm)	69 ± 12	69 ± 14	0.96
Systolic blood pressure (mm Hg)	129 ± 15	139 ± 15	0.002
Diastolic blood pressure (mm Hg)	74 ± 10	78 ± 10	0.04
Body mass index (kg/m^2)	25.9 ± 4.0	30.2 ± 5.9	<0.001
NT-proBNP (pg/mL)	–	867 [482, 1459]	
Echocardiographic measures			
LV ejection fraction (%)	65.2 ± 4.8	59.6 ± 7.3	<0.001
Global longitudinal strain (%)	−20.0 ± 2.1	−15.1 ± 3.1	<0.001
LV end-diastolic volume (mL)	82.9 ± 18.3	111.9 ± 27.9	<0.001
LV end-systolic volume (mL)	28.8 ± 7.5	45.7 ± 16.5	<0.001
LV end-diastolic volume/BSA (mL/m^2)	47.1 ± 9.4	60.3 ± 13.4	<0.001
LV end-systolic volume/BSA (mL/m^2)	16.6 ± 4.4	24.6 ± 8.4	<0.001
Relative wall thickness (%)	0.41 ± 0.07	0.38 ± 0.08	0.008
LV mass/BSA (g/m^2)	80.3 ± 17.5	77.4 ± 21.6	0.40
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	37.2 ± 8.3	38.4 ± 11.2	0.49
E′ (cm/s)	8.8 ± 2.1	7.3 ± 2.7	<0.001
E/E′	8.3 ± 3.2	13.2 ± 6.5	<0.001
E/A	0.93 ± 0.22	1.21 ± 0.71	0.001
Left atrial volume/BSA (mL/m^2)	21.7 ± 5.6	35.5 ± 12.0	<0.001

Data are presented as n (%), mean ± SD, median [IQR].
NYHA, New York Heart Association; BSA, body surface area; E′, lateral mitral relaxation velocity; E/E′, mitral inflow to mitral relaxation velocity ratio; E/A, early to late mitral inflow velocity ratio.
P-values was calculated by t-test or X^2.

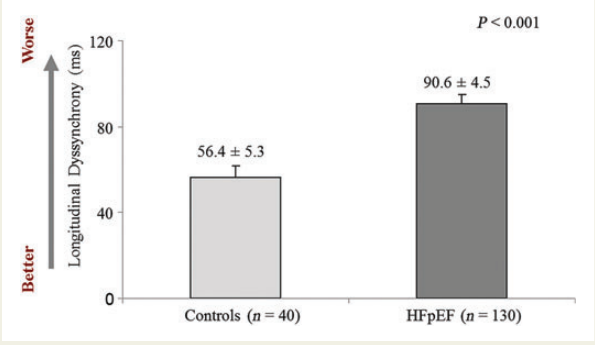

Figure 3 Left ventricular dyssynchrony in HFpEF and healthy controls. Data are presented as mean ± SE.

preserved LVEF. Temporal heterogeneity in systolic function may play an important pathophysiological role in HFpEF by interrupting the normally tightly coordinated relationship between systolic shortening and subsequent diastolic lengthening.[26] As dyssynchrony increases, it can result in decreasing of systolic shortening which has been shown to increase diastolic filling pressure.[27–29] We did not find a relationship between the degree of LV dyssynchrony and LV filling pressure (E/E′), which might result from our use of a narrower range of patients, selected for elevated NT-proBNP levels. The relationship seen between mechanical dyssynchrony and increased LV mass suggests that LV hypertrophy and/or interstitial fibrosis may be associated with dyssynchrony in HFpEF. Although there is a well-described association between LV dyssynchrony and systolic dysfunction in HFrEF,[23] we could not demonstrate one in our HFpEF cohort.

The degree of dyssynchrony observed in these HFpEF patients was considerably less than typically observed in HFrEF patients being considered for cardiac resynchronization therapy (CRT)[30,31] (126 ± 7.8 ms in HFrEF patients from MADIT-CRT[32] vs. 90.6 ± 4.5 ms in our HFpEF cohort) and less than what has been previously observed in post-MI patients.[33] To date, little evidence exists to demonstrate CRT is beneficial in patients with preserved EF, although one study showed a clinical and structural benefit from CRT in patients with

Table 2 Characteristics of heart failure with preserved ejection fraction patients by quartiles of left ventricular longitudinal dyssynchrony

	Quartiles of LV longitudinal dyssynchrony				
	Better		Worse		*P*-value for trend
	39.6 ± 7.2 ms (*n* = 33)	64.0 ± 6.3 ms (*n* = 32)	93.5 ± 9.9 ms (*n* = 33)	166.6 ± 33.6 ms (*n* = 32)	
Age (years)	71 ± 7	70 ± 9	70 ± 9	72 ± 10	0.49
Women, *n* (%)	22 (67)	21 (66)	18 (55)	19 (59)	0.39
SBP (mmHg)	136 ± 14	135 ± 17	141 ± 16	141 ± 14	0.10
NYHA III, *n* (%)	5 (15%)	8 (25%)	8 (24%)	8 (25%)	0.37
QRS (ms)	91 ± 13	97 ± 22	93 ± 16	104 ± 30	0.04
NT-proBNP (pg/mL)	911 [635, 1314]	834 [548, 1397]	863 [407, 1725]	867 [439, 1557]	0.75
LVEF (%)	59.9 ± 7.0	59.4 ± 6.1	58.8 ± 7.5	60.4 ± 8.5	0.94
GL strain (%)	−15.7 ± 3.2	−15.3 ± 3.4	−14.9 ± 2.6	−14.6 ± 3.2	0.12
LV end-diastolic volume (mL)	108.4 ± 29.7	108.6 ± 32.9	116.5 ± 24.5	114.1 ± 24.1	0.25
LV end-systolic volume (mL)	44.0 ± 18.0	44.3 ± 16.5	48.4 ± 14.6	46.1 ± 17.3	0.43
LV mass/BSA (g/m^2)	72.2 ± 25.4	75.3 ± 20.3	79.5 ± 18.4	82.6 ± 21.1	0.04
RWT	0.36 ± 0.06	0.39 ± 0.08	0.37 ± 0.07	0.40 ± 0.11	0.14
E′ (cm/s)	8.1 ± 2.8	8.0 ± 2.9	6.9 ± 2.1	6.1 ± 2.8	0.001
E/E′	12.8 ± 5.5	13.0 ± 6.1	12.5 ± 5.5	14.6 ± 8.7	0.36
LAV/BSA (mL/m^2)	40.1 ± 14.2	33.5 ± 8.4	33.8 ± 10.8	34.5 ± 13.0	0.07

Data are presented as *n* (%), mean ± SD, median [IQR].
NYHA, New York Heart Association; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; GL strain, global longitudinal strain; RWT, relative wall thickness; E′, lateral mitral relaxation velocity; E/E′, mitral inflow to mitral relaxation velocity ratio; LAV, left atrial volume.

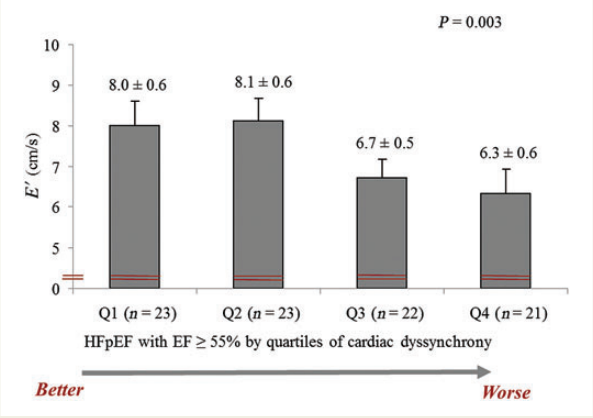

Figure 4 Diastolic function by quartiles of severity of left ventricular (LV) dyssynchrony in HFpEF (EF ≥ 55%). Data are presented as mean ± SE. *P*-value adjusted by age, gender, systolic blood pressure, LV mass, and LV ejection fraction.

mean LVEF 43 ± 7%.[34] We therefore cannot rule out the possibility that dyssynchrony plays a pathophysiologic role in HFpEF, albeit in conjunction with other abnormalities of cardiac function.

Some limitations of this analysis should be noted. Only half of the patients enrolled in the PARAMOUNT trial had echocardiograms that were eligible for dyssynchrony evaluation by combined two-chamber and four-chamber 2D speckle tracking analysis. While there were some differences between the included cohort and those who could not be included, LVEF was even higher in the patients analysed. There is no gold standard to assess cardiac dyssynchrony, but speckle tracking appears to be more accurate than Doppler-based techniques.[23] Because PARAMOUNT was a clinical trial, the generalizability of these findings to HFpEF patients in the community may be limited due to the inclusion/exclusion criteria of the PARAMOUNT trial.

In summary, we found greater LV mechanical dyssynchrony in HFpEF patients compared with healthy controls, even among those with robustly preserved LVEF and no significant electrical dyssynchrony. In HFpEF, greater mechanical dyssynchrony appears to be associated with wider QRS, greater myocardial hypertrophy, and especially impaired diastolic, but not systolic function, suggesting that mechanical dyssynchrony may play a pathophysiologic role in HFpEF. The prognostic relevance of mechanical dyssynchrony and the potential role of CRT in HFpEF remain to be determined.

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and M.L. are employees of Novartis, and A.B.S.S., E.K.K., N.B., and B.C. declare that they have no conflict of interest.

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