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Comparative evaluation of left atrial functions quantified by 2D echocardiography and strain imaging in patients with HFrEF and HFpEF

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Abstract

Objectives: Our study comparatively evaluates LA function quantified by 2D echo and strain imaging in heart failure patients and correlate with clinical outcome at 9 months.

Background: LA dysfunction assed by indirect parameters such as LA size and volume is an established marker of risk for adverse outcomes in heart failure. However, the independent prognostic importance of LA function assessed by LA strain is not known.

Methods and Results: The LA function measured by LA strain in103 symptomatic heart failure patients (63 had HFrEF and 40 had HFpEF) and in 100 age sex match healthy subjects. LV volumes, left atrial (LA) volumes and EF, annular mitral velocity, and LA strain during systole (LA_S), and atrial contraction (LA_A) were measured. Lower peak LA strain, indicating lower LA functions significantly reduce in patients with heart failure in comparison to healthy controls (LA_S strain - 49.8±9.3 vs 26.7±5.5 vs 18.3±6.4;P< 0.05, LA_A strain - 21.4±3.8 vs 9.2;P<0.05, Post-A-32 vs 10;P<0.05, in healthy control vs HFpEF vs HFrEF respectively). At a mean follow-up of 9 months (interquartile range, 6–13months), 21(20.3%) patients experienced the primary composite end point of cardiovascular death, recurrent HF hospitalization. Lower peak LA strain was associated with a higher risk of the recurrent HF hospitalizations (LA_S strain-14.8± 2.3 vs 21.9±4.9 p=0<05) and cardiac death (LA_S strain-11.9 vs 24.1;P=0<05) during follow up. Pearson correlation analysis showed significant negative correlation between LA dysfunction and NYHA functional class of dyspnea during follow up.

Conclusions: LA dysfunction in heart failure is associated with a higher risk of recurrent HF hospitalization, death and associated with higher functional limitation caused by dyspnea. LA strain imaging superior to volumetric method for quantifying LA functions and can serve as prognostic marker of

risk for adverse outcomes in heart failure.

Keywords: LA dysfunction, Heart failure, LV volume.

Introduction

Heart failure (HF) is a major public health problem, with a prevalence of more than 23 million worldwide[1 2]. In the American Heart Association (AHA)/American College of Cardiology guidelines, HF is defined as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood" [3].

Left atrial work with a close interdependence with left ventricular (LV) function by modulating LV filling and it is essential for maintaining an optimal LV filling in heart failure by performing as a **reservoir** for pulmonary venous return during ventricular systole governed by atrial compliance that influenced by LV end-systolic volume and descent of the LV base during systole, as a **conduit** for pulmonary venous return during early ventricular diastole, which governed by to LV compliance and LV relaxation and a **booster pump** that augments ventricular filling during late ventricular diastole but is dependent on the degree of venous return, LV end-diastolic pressures (LVEDP) [4 5].

The LA functions were conventionally assessed by indirect methods for assessing LA remodeling such as increase in LA size or volume. The prognostic implication of left atrial size was initially demonstrated in patients with LV dysfunction enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) Registry and Trials, where echocardiographic measurements increase in left atrial size (≥4.17) along with EF and LV mass were associated with significant higher mortality risk and hospitalization due to cardiovascular causes[6].

Until recently, the echocardiographic study of the left atrium was performed using two-dimensional (2D) measurements, extrapolation of phasic volumes, and Doppler flow assessment of the mitral valve and the pulmonary veins.

Speckle-tracking echocardiography (STE) is a new noninvasive imaging technique that allows a quantitative evaluation of global and regional myocardial function by measuring myocardial deformation independently from the angle of insonation and cardiac translational movements.

Although STE technique was introduced for the exclusive analysis of LV function, several studies have recently extended its applicability to other cardiac chambers, such as the LA[4 7]. The use of this novel imaging limited by lack normative and comparative data for assessing LA function in heart failure.

The aims and objective of this study to evaluation of left atrial functional quantified by 2D echocardiography and speckle tracking imaging in patients with HFpEF and HFrEF, and correlate LA strain with LVGLS and clinical outcome at 6 months.

Methods

Study population

The study included 103 symptomatic patients with NYHA class II–IV dyspnea due to HFrEF or HFpEF enrolled in heart failure group and 100 apparently healthy individuals who where refer to our institute with non-cardiac illness were also enrolled as healthy control. The institutional ethics committee approved the study protocol. The informed consent was taken from all participants at enrollment. The cardiovascular and physical examination was done at enrolment. The history for past hospitalization, medication, drug compliance and cardiovascular risk factor for were takes at enrolment. The serum Pro-BNP level (AQT 90 FLEX) was measured all patients with HFpEF at enrolment and assessment of serum Pro-BNP level in patients with HFrEF was optional. Routine

investigation and ECG done at enrolment and heart failure was defined as HFrEF and HFpEF if they fulfill current ESC criteria[8] (Table-1).

Table 1: Diagnostic criteria for heart failure

Criteria	Heart failure with reduced Ejection fraction (HFrEF)	Heart failure with preserved Ejection fraction (HFpEF)
I	Symptoms ±Signs of HF	Symptoms ±Signs of HF
II	LVEF<40%	LVEF ≥50%
III		1. Elevated levels of NPs (BNP >35pg/mL and/or NT-pro-BNP>125 pg/mL) 2. At least one additional criteria a. Relevant structural heart disease (LVH and/or LAE) b. Diastolic dysfunction

Patients with coronary artery disease, any rhythm other than sinus rhythm, candidate of CRT, patients with significant valvular lesions, congenital heart diseases, hypertrophic obstructive cardiomyopathy (HOCM), poor echocardiographic windows and those who refuse to give consent were excluded from study. CT coronary angiographies were done in all patients with heart failure to rule out underlying significant coronary artery disease.

A standard transthoracic echocardiography was performed in all patients using an iE33 Philips system and a 3.5 MHz probe during breath hold in expiration with a stable ECG recording. Echocardiographic imaging was obtained in the parasternal long, short-axis, and apical two, three and four chamber views using standard transducer positions. Measurements of left chambers' diameters were obtained by in accordance with the recommendations of the American Society of Echocardiography[9]. Ejection fraction (EF%) and LV volume were calculated by Simpson method.

Volumetric Measurements of LA

LA volumes were measured using the biplane area–length method from apical two, three and four - chamber views, according to the guidelines of the American Society of Echocardiography. Measurements are usually taken as follows:

1. At end-systole, just before the opening of the mitral valve (at the end of the T-wave on the ECG) – the LA maximum volume (LAV_{max}).
2. At end-diastole, just before mitral valve closure (at the beginning of the QRS complex on the ECG) – mini- mum LA volume (LAV_{min}).
3. At mid-diastole, just before atrial contraction (at the beginning of the P wave on the ECG) – preA volume (LAV_{preA}).

Based on the previously discussed volumetric measurements, several indices corresponding to the three basic functions (Table-2) of the LA are derived.

Table 2: Left atrium function assessment:

LA reservoir function:	LA total emptying fraction (LAEF %) = ($LAV_{max} - LAV_{min}$)/LAV- max·
LA conduit function:	LA passive emptying fraction (LApEF %)= ($LAV_{max} - LAV_{preA}$) /LAVmax
LA booster pump function:	LA active emptying fraction (LAAEF %) = ($LAV_{preA} - LAV_{min}$)/ LAV_{preA}·

Measurements of LA Deformation by STE

Apical four, two and three chamber views were obtained using conventional 2-D echocardiography. During breath hold in expiration with a stable ECG recording and 2-D sector width was adjusted to include LV and LA. Three consecutive cardiac cycles were recorded and the frame rate was keep between 60 and 80 frames per second. The endocardial surface of each LA wall; septal, lateral walls, (A4C view), anterior and inferior walls (A2C view) were manually traced by a point-and-click approach and the epicardial surface tracing was then automatically generated by the system. After manual tracing, the software (Q-LAB, CMQ-9) automatically divides each wall into 3 segments (apical, mid and basal).

Strain values corresponding to reservoir, conduit, and contractile function were recorded. The protocols for LA strain measurement have been use with the QRS complex (R-R gating) as the initiation of the strain calculation and there are two peaks with first peak that correspond to reservoir function (peak atrial longitudinal strain (LA_A strain) occur as first peak between R wave and T wave) and second peak that correspond to atrial contractile function (peak atrial contraction strain (LA_E strain) occurs just before P wave on surface ECG); the difference between reservoir strain and atrial contractile strain values reflects conduit function(Figure-1). LA contraction systolic index CSI was calculated in each LA wall by the formula CSI = (PALS/PACS)*100.[4] Peak LV Strain is the peak negative value that was obtained at or before aortic valve closure. Peak longitudinal systolic SR (SRLS), peak early diastolic SR (SRLE) and peak late diastolic SR (SRLA) were also measured (Figure-2). For LV deformation, global longitudinal strain (GLS) was also calculated as the average LV longitudinal strain across the 12 segments obtained using apical 4- and 2-chamber views.

Follow up

The patients enrolled in both the groups were treated with optimal medical therapy with maximal tolerated dose and all patients were follow up at 3 and 6 months of enrollment in OPD or telephonically interviewed and patients were evaluated for dyspnea (NYHA class) and hospitalization due to heart failure in last 6 month. Any death due to cardiac and non-cardiac cause during this period was also documented.

Study outcome

The primary outcome was to comparative evaluation of LA functions quantified by LA strain and volumetric analysis in HFrEF and HFpEF. Secondary outcome parameters were the composite of cardiovascular death, HF hospitalization, and functional class as well as alone.

Statistical analysis

All the analyses were performed using a commercially available package SPSS-21. The clinical, echocardiographic, and demographic character of patients, age- and sex- matched control subjects, and young healthy control subjects are reported. Continuous

variables are expressed as the means and standard deviations and categorical variables are expressed as proportions. Comparison of continuous variables was performed with the paired t-test between study group and age- and sex-matched control subjects and with Student's t-test between study group and young healthy control subjects. Categorical variables were compared using the $\chi 2$ test or Fisher's exact test, as appropriate. Variables are presented as mean ± SD. Two-tailed T-test for paired and unpaired data was used to assess changes between groups. Linear regression analyses and correlation assessed by Pearson method. P value considered significant as in the following: significant difference if $P < 0.05$, non-significant difference if $P > 0.05$.

Results

A total of 266 patients reffered to s.m.s.medical college and associtated hospital out of which 136 patients were exclude as, 37 patients had history of acute coronary syndrome in last 6 months, 49 patients had sever LV systolic dysfunction secondary to valvular etiology (Sever AS in 18 patients, Sever AR with AS in 15 patients, Sever MR in 16 patients), 53 patients had atrial arrhythmias, 24 patients were excluded due to poor echo window and remaining 103 patients were enrolled in study group and 100 healthy patients were also enrolled in control group.

T

able 3: Clinical Characteristics of study and control group

Variables	Control (n=100)	HFrEF (n=63)	HFpEF (40)	P value
Age (years)	47 ± 4	48 ± 5	50 ± 5	0.086
Gender n, %				0.382
Male	54(60%)	35(55%)	17(42.5%)	
Female	46(40%)	28(45%)	23(57.5%)	
DM	5 (5%)	16 (25.3%)	21(52.5%)	<0.001
HTN	6 (6%)	7 (11.1%)	32(80%)	<0.001
SMOKING	30(30%)	18(28.5%)	13(32.5%)	0.914
Obesity	3(3%)	7(11.1%)	18(45%)	<0.001
Heart Rate, min^{-1}	68±14	83±16	73±13	<0.001
SBP, mm Hg	123±12	109±16	139±17	<0.001
DBP, mm Hg	70 ±11	60±13	73±15	<0.001
NYHA CLASS- Class ≤II	-	24(38%)	23(57.5%)	0.085
Class III-IV	-	39(62%)	17(42.5%)	0.085
Recurrent Hospitalization	-	14(22.2%)	0	0.001
Pro-BNP	-	290±31	179±23	<0.001
LV mass, $gm/m^{2.}$	72± 9	118±13	133±10	<0.001

* Pro-BNP done in all patients with HFpEF and only 11 patients with HFrEF.

Out of 103 patient 63 patients were having HFrEF and 40 were having HFpEF. All the patients were enrolled in heart failure group were symptomatic and 62 % with HFrEF and 42.5% with HFpEF had NYHA class >II

dyspnea. Both group the mean age were 48 years in HFrEF, 50 years in HFpEF compare to years in 46 years in healthy controls. Smoking was the most common risk factor comparable in all three groups. The patients with HFpEF had significantly higher number of patients with diabetes (25.3% vs 52.5%, p<0.001) and HTN (11.1% vs 80%, p<0.001) compare to HFrEF but had similar functional class (p=0.085) (Table-3).

Left ventricular dimensions (LVEDD 65.3±11 mm vs 50.5±4 mm; p<0.05 and LVESD 51.1±8 mm vs 31.4±4.5; p< 0.05), volumes (EDS 198.5±58.3 vs 126.7±38.6; p<0.05 and ESV 118.8±45.3 vs 44.8±10.9 ml; p<0.05) were significantly higher in the patient with HFrEF compared to HFpEF (Table-4). Ejection fraction, mitral inflow velocities were significantly reduce (Mitral E velocity= 0.6 ± 0.2 vs 0.8 ± 0.1; P<0.05 and Mitral A velocity=0.29±0.08 vs 0.06 ± 0.1; p<0.05) in the patient with HFrEF group in comparison to the healthy controls and these patients had higher E/A ratio (2.06±0.2 vs 1.4±0.2;P<0.05) due to higher diastolic dysfunction in these patients. The patients with HFpEF had highest Mitral E velocity (0.9±0.1) with higher E/A ratio (2.0±0.3) in compare to healthy control

Table 4: Echocardiographic parameters in study and control group

Echocardiographic parameter	HFrEF	HFpEF	Control group	P value
AO mm	29±4	28±6	28±5	0.548
LA mm	43±6	39±6*	33±8*	<0.001
IVSED mm	9.0±3	11.5±2	8.3±2	0.004
IVSES mm	10.0±3	15.9±3*	11.8±2*	<0.001
LVEDD mm	65.3±11	51.2±6*	50.5±4	<0.001
LVESD mm	51.1±8	33.2±4*	31.4±4.5	<0.001
LVPWD mm	8.5±3	11.8±2	8.9±2	0.444
LVPWS mm	10.2±2	16.1±3	11.9±3	0.002
EDV ml	198.5±58.3	119.7±43.5*	126.7±38.6	<0.001
ESV ml	118.8±45.3	40.3±11.3*	44.8±10.9	<0.001
EF %	32.5±9.3	56±4.3*	64±7.3*	<0.001
SV MM	79.7±13.2	80.3±15.3	81.3±16.3	0.835
E m/s	0.6±0.2	0.9±0.1*	0.8±0.1*	<0.001
A m/s	0.29±0.08	0.43±0.1*	0.48±0.1*	<0.001
E/A RATIO	2.06±0.2	2.0±0.3	1.6±0.2*	<0.001

***** <0.05 vs HFrEF, **#** <0.05 vs HFrEF and HFpEF

The patients with HFrEF had lowest LVGLS compare to HFpEF and healthy controls (-11.8±2.3 vs-16.8±2.9 vs 20.3±3.1;P <0.001), similarly LA_ESR and LA_ASR where also lowest in patients with HFrEF group (HFrEF<HFpEF< Control) in compare to healthy control (Table-5).

Table 5: Left Atrial Volumes and Function.

	Control	HFrEF	HFpEF	P value
Maximum volume index, mL/m^2	21.5±5.6	41.6±8.1*	35.6±6.9*	<0.001
Minimum volume index, mL/m^2	9.1±3.3	22.9±9*	19.7±8*	<0.001
Pre-A volume, mL/m^2	12.3±3.9	27.3±9.8*	24.6±7.8	<0.001
LA emptying fraction, %	65±9.5	47.7±12.3*	45±10.2	<0.001
LA passive emptying fraction, %	44.3±7.3	19.1±5.6*	30.8±3.1*	<0.001
LA ejection fraction, %	38.8±8.5	15±8.9*	21.3±3.3*	<0.001
LA_S strain rate, s^{-1}	2.1±0.6	1.1±2.3*	1.6±0.3	<0.001
LA_E strain rate, s^{-1}	2.0±0.5	0.9±0.1*	1.45±0.5*	<0.001
LA_A strain rate, s^{-1}	2.3±0.4	1.1±0.2*	1.72±0.6*	<0.001
LA_S strain, %	49.8±9.3	18.3±6.4*	26.7±5.5*	<0.001
LA_A strain, %	21.4±3.8	8.5±3.3*	15.2±3.1*	<0.001
LA CSI (PACS/PALS)*100	49.9±10.2	61.2±13.5*	56.3±13.9	<0.001
LVGS%	-20.3±3.1	-11.8±2.3*	-16.8±2.9*	<0.001

***** P<0.05 vs SHF and DHF, # p<0.05 vs DHF

Patients in HF group inspite of having enlarger LA volumes and significantly lower LA reservoir, conduit and booster pump function, as measured by LAEF % (total emptying fraction), LApEF % (LA passive emptying fraction), LAAEF%(LA active emptying fraction) (P < 0.001).

Left atrial function assessed by strain (LA_S strain - 49.8±9.3 vs 26.7±5.5 vs18.3±6.4;P< 0.05, LA_A strain - 21.4±3.8 vs 9.2;P<0.05, Post-A-32 vs 10;P<0.05) were significantly lower in the patient with symptomatic HF (Healthy control > HFpEF > HFrEF respectively) compare to healthy control while LA CSI which is index of atrial boost pump function was significantly higher in HF group (49.9±10.2 vs 61.2±13.5vs 56.3±13.9;P<0.05: Healthy control vs HFrEF vs HFpEF respectively).

Table 6: Correlation between LA function and NYHA class in patients with heart failure.

	r	P value
LA emptying fraction, %	-0.31	0.038
LA ejection fraction, %	-0.33	0.076
LA_S strain, %	-0.59	0.009
LA_A strain, %	-0.53	0.010
LVGS%	-0.67	< 0.001

Incontrast to volumetric analysis where only reservoir function assessed by volumetric method correlating

with functional status measured by NYHA class (Table-6). However LA functions assessed by strain parameters (LA_S strain and LA_A strain) were significantly and inversely correlating with the NYHA class (-0.59 and -0.53,$p<0.05$ respectively).

Discussion

Our study is prospective trial from that comparatively evaluates LA functions measured by strain and volumetric method to predictive short-term clinical outcome at 6 months. In our study we also compare these patients with normative data collected from healthy control as no previous study providing normative data in healthy individual from our region.

The left atrium plays important role in patients with heart failure by improving LV filing to maintain cardiac output. The LA dysfunctions in these patients occur due to pressure and volume overload exert by failing heart [10,11] and also partially contributed by concomitant atrial muscle myopathy[12] leading to reduce LV filling and worse clinical outcome.

LA strain is a direct method for evaluating LA function by measurement of intrinsic LA myocardial deformation. LA strain is superior to volumetric method as it is has high feasibility and reproducibility[13] and it is less preload dependent than traditional volumetric parameters[14 .15]. However, its widespread use restricted due to lacks standardization and validation as no large data available in heart failure.

In a metanalysis by Pathan et al[16] to evaluate normal ranges of left atrial strain by speckle-tracking echocardiography reported methodological variation in timing of gating (P-P gating or R-R gating), inclusion of roof of the left atrium and evaluation of single apical view (apical four-chamber, two chamber or three chamber view) or combination of any of two or all three views leading to wide range of normal values of LA reservoir strain, from 27.6% to 59.8%[17 18]. In our study we use R-R gating and evaluate all three apical views by two different observers to reduce observer variation.

The LA dysfunctions were conventionally assessed by indirect methods such as increase in LA diameter and LA volume. Tsang et al[19] in a prospective study with 140 adults to evaluate correlation between LA volume and cardiovascular risk burden, demonstrated LA volume was independently associated with adverse cardiovascular outcome including congestive heart failure, vascular disease, transient ischemic attack or stroke and index LA volume independently associated with diastolic dysfunction.

D'Andrea et al[20] in a prospective study evaluate LA systolic dysfunction in idiopathic and ischemic cardiomyopathy, demonstrated inspite of similar LA volume patients with idiopathic DCM had significant lower LA function measured by peak systolic myocardial atrial strain and it is closely associated with reduced exercise capacity that further emphasis role of LA in symptomatic worsening in these group of patients.

LA Function in HFrEF

In our study patients with HFrEF had larger LA size, greater LV systolic and diastolic volume, greater LV mass index, greater diastolic dysfunction and had lower LV systolic function in compare to healthy control.

In our study, inspite of similar LA volume the LA functions were significantly depressed in patients with HFrEF in compare to HFpEF as the LA strain was significantly reduced in HFrEF as documented by significantly reduce LA strain and strain rate.

These findings are in contrast to Ahmed et al[4], and which showed to have significant decrease in reservoir function and preservation LA systolic function in

patents with systolic heart failure. The plausible cause of this contrast due to our study enrolled patients in more advance heart failure as 62% patients were having NHYA grade III-IV dyspnea and also enrolled patients with mild to moderate mitral regurgitation, producing greater volume and pressure overload on LA leading to more severe LA dysfunction in our study compare to Ahmed et al. The methodology of assessing strain was also significantly different in two studies inspite both measuring strain with R-R gating.

In our study we found the LA strain having significant and positive correlation with LV dysfunction. The LVGS were significant lower in patients with HFrEF compare to HFpEF (11.8±2.3 vs 20.3±3.1;P<0.05) and the LA strain significantly correlate with LVGLS (r=0.53, p<0.001). The LV systolic dysfunction may influence LA function due to decrease in systolic expansion of LA[21] and also by increase in afterload and wall tension[22-24].

Kurt M et al[11] a prospective study enrolled 64 patents (SHF=25, DHF=20, DD=19) undergoing right heart catheterization showed LA strain were significantly lower in HF group (*P*<0.01) and among all the 3 groups, patients with SHF had lowest atrial deformation indices (*P*<0.05). These findings were in accordance to our study findings.

LA Function in HFpEF

The patients with HFrEF in comparison HFpEF had similar LA reservoir dysfunction but significant lower LA systolic function assessed by volumetric method, However LA strain showing significant lower LA reservoir and systolic function may be due to ability of strain to identify early subclinical myocardial dysfunction. LA strain rate were also significantly less in HFpEF compare to healthy controls (LASR-healthy controls>HFpEF>HFrEF). The early negative LA strain rate shows to conduit function and late negative LA strain rate show LA systolic function in late diastole. The early positive LA strain shows LA reservoir function.

The LA dysfunctions occur in theses patient inspite of normal LV systolic function due to early pathological changes that more severely affect thin and compliant LA than ventricles.

Left Atrial Strain With Cardiovascular Outcomes

In our study LA strain showed significant negative correlation on univariate analysis between LA_S strain and morbidity caused by dyspnea (NYHA functional grade)(LAs, r=0.59, P=<0.031 and LA_A, r=0.53,p<0.021). In our study recurrent hospitalizations defined as two or more heart failure hospitalization occur in 15 patients in HFrEF during 6 month follow up, these patients were having significant less peak LA_A strain in comparison patient who were managed on outdoor basis (LA_S strain-14.8± 2.3 vs 21.9±4.9 p=0<05). Six patients were died during follow up, four patients were died due to progressive heart failure had significant lower LA strain (LA_S strain-11.9 vs 24.1;P=0<05), and one patient was died due to sepsis with heart failure, one patient had sudden cardiac death at home. Although LA strain significantly reduce who died due to progressive heart failure but our study was not powered to evaluate association with mortality and a trial with larger sample size will be required to evaluate this association.

In accordance to our study in Santos AB et al[22] enrolled 357 patients with HFpEF from TOPCAT trial and evaluate LA strain, trial shown that LA dysfunction was associated with a higher composite end point including recurrent heart failure independent of potential clinical confounders, but not reflected prognostic of outcomes (P=0.13).

Conclusion

LA plays important role of a reservoir, conduit and booster pump to improve LV filling and maintain cardiac output in patients with both HFrEF and HFpEF and these functions were progressively reduced as disease progress and contribute in higher morbidity and mortality. LA strain novel imaging superior to volumetric method for amassing LA function and can predict short term clinical outcome at 6 months.

Limitation

Our study has some limitation; first- our finding based on small sample size and not powered for evaluating its predictability of mortality. Second- we use the LV software for calculation of LA strain parameters as until now there is no specific atrial software available. Third- patients were on diuretics with different doses, which may cause change in preload that may affect our assessment of LA function by volumetric method.

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