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Evaluation of left atrial dysfunction by speckle tracking echocardiography in systolic and diastolic heart failure

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Abstract

The study aimed to assess the accuracy of two-dimensional speckle tracking echocardiography (2DSTE) to evaluate the left atrial (LA) function in patients with heart failure. Additionally, if 2DSTE can differentiate accurately between heart failure preserved ejection fraction (HFpEF, HF with mid-range ejection fraction (HFmrEF=EF 41-49%) and heart failure with reduced ejection fraction (HFrEF= EF≤40%). The study included 186 patients of heart failure who were classified into 74 patients with HFpEF (LVEF≥50%), 56 patients with HFmrEF (LVEF 41-49%), 56 patients with HFrEF (LVEF<40%), and 50 normal matched subjects. B-type natriuretic peptide (BNP) was more than 35 pg/mL for all patients. The conventional echocardiography evaluated left ventricle systolic and diastolic functions. The 2DSTE evaluated the LV global strain (LVGS), and strain and strain rate (SR) in each phase of LA function. LVGS was -19.3±2.3%, -18.0±1.7%, -16.1±2.0%, and -14.3±2.2 in controls, HFpEF, and HFmrEF, and HFrEF, respectively (p<0.0001); GPALS was 34.1±6.7%, 27.5±4.7%, 21.7±4.8% and 16.9±4.9% in controls, HFpEF, HFmrEF, HFrEF, respectively (p<0.0001); the GPACS was 14.8±4.3%, 12.3±2.2%, 9.7±2.3%, and 7.5±2.6% in controls, HFpEF, HFmrEF, and HFrEF, respectively (p<0.0001); the PALS-PACS was 19.4±3%, 15.1±4.4%, 12.0±3.4%, and 9.3±3.3% in controls, HFpEF, HFmrEF, and HFrEF (p<0.0001). Therefore, early LA dysfunction in heart failure can be detected accurately and easily by speckle tracking technique that could be a promising independent tool to better understand of heart failure and its classification.

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Introduction

The left atrium plays an integral role in cardiac performance by modulating left ventricle (LV) filling [1]. Left atrial (LA) analysis by strain and strain rate imaging is based on both longitudinal and radial strain. However, current techniques do not have a sufficient resolution to measure the radial strain of the thin-walled LA; therefore, LA deformation assessment is only based on longitudinal strain, using the apical 4, 3 and 2 chamber-views [2]. The longitudinal strain curves for each segment of LA are generated automatically by software. These curves reflect the pathophysiology of atrial function [3]. Several studies have documented the prognostic role of peak-atrial longitudinal strain (PALS) in different clinical settings, including general population [4], myocardial infarction [5], aortic stenosis [6], and HFpEF [7]. Assessment of LA phasic function using 2D-speckle-tracking echocardiography (2D-STE) has gained considerable attention due to its high feasibility and reproducibility [8] and has led to the early detection of LA impairment in a number of conditions including HF [9]. Left ventricular ejection fraction (LVEF) is typically used to classify heart failure (HF) patients into HF with preserved LVEF ≥50% (HFpEF), HF with reduced LVEF <40% (HFrEF) and HF with mid-range LVEF 40-49% (HFmrEF) according to European Society of Cardiology guidelines [10].

HFpEF patients constitute approximately more than half of the HF population [11]. Patients with HFmrEF account for approximately 10-20% of the HF population [12]. In patients with HFrEF, LA reservoir strain is strongly associated with estimated elevated filling pressure, impaired LV and right ventricle (RV) systolic function. Furthermore, it provides incremental prognostic information over LA volume, LV filling pressures, and GLS, so it allows powerful prognostication, independently of LA volume and left ventricular longitudinal contraction [13]. The aim of the study was to assess the accuracy of 2DSTE to evaluate the LA function in patients with heart failure. And can it differentiate accurately between HFpEF, HFmrEF and HFrEF?

Materials and Methods

Study population

Consecutive 186 patients from cardiology clinics in Fayoum University, Egypt, fulfilling HF recommendations of ESC at 2016 were prospectively enrolled in the study from February 2018 to January 2020. All patients were in optimal medical treatment and were hemodynamically stable. Inclusion criteria were patients in sinus rhythm, BNP more than 35 pg/mL, and echocardiographic criteria of HFpEF (n=74), HFmrEF (n=56), and HFrEF (n=56) [10,14]. Exclusive criteria were any rhythm other than normal sinus rhythm, valvular heart diseases, congenital heart diseases, pacemaker insertion, pericardial diseases, patients with poor echocardiographic window and patients with renal or liver cell failure.

Fifty matched normal subjects with no history of medical diseases and normal echocardiography were selected from cardiology clinics in Fayoum University, Egypt to be included in the study. The study protocol was approved by the local Research Ethics Committee.

Conventional echocardiography

The standard echocardiographic Study was performed by one experienced sonographer, using a high-quality echocardiograph machine (Philips iE33). All subjects were in left-lateral decubitus position. The 2D, M-mode and Doppler techniques including tissue Doppler were performed to evaluate the left ventricular systolic and diastolic function [10]. LV volumes and LVEF were calculated using the modified biplane Simpson's method [14,15]. The trans-mitral E wave velocity in early diastole and the peak left ventricle filling velocity in late diastole (A wave) were estimated therefore E/A ratio was calculated automatically. An E/e´ ratio was calculated as the ratio between E wave velocity and mean lateral and medial e´ wave velocities (16). The LA volume at end systole would be maximum LAV (Max AV) therefore the Left atrium volume index (LAVI) was calculated by Max AV/BSA. (17). An LAVI cut off >34 ml/m^2 and E/e´ ratio cut off ≥14 were used as markers of LV diastolic dysfunction. The patients were classified accordingly [10].

Speckle tracking echocardiography

Acquisition of image for longitudinal strain and strain rate

Using conventional 2-D gray scale echocardiography and during breath hold with a stable ECG recording, the apical four, two and three-chamber views were obtained. The 2-D sector width was adjusted and care was taken to optimize visualization of the LV and LA cavity and to maximize LA area in apical views, avoiding foreshortening of the left atrium [18]. The frame rate was set between 60 and 80 frames per second and three consecutive cardiac cycles will be recorded and averaged.

Left ventricular global strain

Three points were anchored in the LV, apex and annular hinge points in apical 4, 3, 2 chamber views. The system will be allowed to process the data. After finishing tracing and auto processing the three views, the LV global strain will be obtained. Strain is the peak negative value that obtained at or before aortic valve closure [19].

Left atrium strain and strain rate

The machine software allowed off-line semiautomated analysis of speckle-based strain and strain rate. LA endocardial surface of each LA wall (septal, lateral, anterior and inferior walls) was manually traced in both 4 and 2 chamber views by a point and-click approach. An epicardial surface tracing was then automatically generated by the system, thus creating a region of interest (ROI) [20]. Automatically, the QRS onset is taken as a reference point, therefore enabling the measurement of PALS, corresponding to atrial reservoir. The P wave will be taken as the second reference point, therefore enabling the measurement of a first negative PALS corresponding to atrial systole, a second positive peak atrial strain, corresponding to LA conduit function, and their sum [21]. Lastly the software generated strain, strain rate curves to reflect the pathophysiology of LA phasic function [22]. The atrial function has three phases: The first is LA reservoir phase which is represented by GPALS and peak of left atrium strain rate at systole (LASRs), The second is LA pump function which is represented by GPACS and peak of left atrium strain rate at late diastole (LASRa), and the third is LA conduit phase which is represented by GPALS-PACS and peak of left atrium strain rate at early diastole (LASRe) [23].

Statistical analysis

The data were collected, organized, tabulated and statistically analyzed using SPSS software statistical computer package v. 18 (SPSS Inc, USA). The mean and standard deviation (SD) were calculated to qualitative the data. One-way ANOVA test was used as a test of significant. For qualitative data were presented as number and percentages, chi square (χ^2) was used to test significance of data. Pearson correlation was run to identify relation between different study parameters. Principle component analysis (PCA) was performed including all parameters of conventional and speckle tracking echocardiography. Varimax with Kaiser Normalization was chosen as a method for rotation. Coefficients <0.4 were excluded from analysis. Kaiser-Meyer-Olkin measure of sampling adequacy equals 0.838 while Bartlett's test of septicity was a statistically significant, p<0.0001. Six components with eigenvalue more than one were extracted. After that, multivariate logistic regression analysis was conducted to determine the significant components as predictors for different types of HF. Components 6 was excluded from regression analysis because it contains 2 variables only. The receive operating characteristic (ROC) curve was used to determine the discrimination value of the different parameters for prediction of different conditions and to define the optimal cut-points for sensitivity and specificity. Significance of results was adopted at p<0.05.

Results

Demographic, clinical and laboratory data

Baseline characteristics of the study population were matched regarding age, gender, height, weight and body surface area (BSA). Also, no significant differences were found regarding smoking, HTN, DM, CAD, and hypercholesterolemia. The NYHA class ranged from I to IV was high significant in between the groups ($p<0.0001$). The BNP was 82±52.5 in HFpEF, 202±154.4 in HFmrEF, and 321±227 in HFrEF with high significant ($p<0.0001$) (Table 1).

Conventional echocardiography assessment

LV dimensions (LVEDD and LVESD), LV volumes (LVEDS and LVESV), E/E´ ratio and LAVI were significantly higher in HFrEF than these of HFmrEF which were significantly higher than these of HFpEF (Table 1).

Speckle tracking echocardiography assessment

LVGS, GPALS, LASRs, GPALS-PACS, LASRe, GPACS, and LASRa were significantly lower in HFrEF when compared to the corresponding values in HFmrEF which were significantly lower than the corresponding values in HFpEF which were significantly lower than the corresponding values in normal subjects (Table 1).

Principle component analysis

All parameters of conventional and speckle tracking echocardiography in HFpEF, HFmrEF, and HFrEF were extracted into six components. LVEF%, LVGS and all 2DSTE parameters for left atrial phasic function were collected in the same component. The diastolic dysfunction parameters by conventional echocardiography were collected in three different components. (Table 2).

Multivariate logistic regression analysis

Component of LVEF%, LVGS and all STE parameters for LA dysfunction was significantly predictor for all different types of HF. Whereas the component of diastolic dysfunction parameters obtained by conventional echocardiography including E/E ratio, LA diameter, LA area, MAX LAV and LAVI" was significantly predictive of HFpEF and HFmrEF (Table 3).

Receiver operating characteristic (ROC) curves and cutoff point for LV systolic function and left atrial function

The high sensitivity and specificity of LVGS and all STE parameters for LA dysfunction including GPALS, LASRs, GPALS-PACS, LASRe, GPACS and LASRa make them a novel predictor parameters to discriminate and early diagnose of HFpEF, HFmrEF and HFrEF (Table 4, Figure 1).

Discussion

Brain natriuretic peptide (BNP) is a cardiac hormone produced in the heart and an established biochemical marker for heart failure [24]. Stretching of ventricular cardiomyocytes is the most important stimulus of BNP regulation [25], but LV diastolic wall stress also reflects an increased BNP Therefore, BNP can be used in the diagnosis of HFpEF [26]. In our study the BNP level was significantly higher in HFrEF than HFmrEF which was higher than HFpEF and these results was concordant to the study of Iwanaga *et al.* [25] and Modin *et al*. [27]. In our study, LVEDS and LVESV were significantly higher in HFrEF (LVEF<40%) than these of HFmrEF (LVEF 41-49%) which were significantly higher than these of HFpEF (LVEF>50%). As known, chronically stressed LV leads to increase the tension of left ventricular wall causing remodeling and hypertrophy of the LV which lastly dilates [28]. When LV dysfunction occurs, both LVEDV and LVESV increase which in turn increase LV end-diastolic pressure [29] and this was concordant in our study. Several mechanisms that could be related to the development of HFpEF have been proposed. Previous studies [30] reported LV diastolic dysfunction and LV systolic longitudinal dysfunction, as shown by reduced longitudinal myocardial velocities and deformation, suggesting that DHF could be an HF stage preceding SHF [31,32]. In our study, the most patients of HFpEF had history of HTN (68.9%), Zakeri *et al*. explained that in early stage hypertensive HFpEF, LA cardiomyocyte hypertrophy, titin hyperphosphorylation, and microvascular dysfunction occur in association with increased systolic and diastolic LA chamber stiffness, impaired atrioventricular coupling and decreased LV stroke volume [33]. In SHF, the left atrium is exposed to high LV filling pressures, thus the LA pressure rise to maintain adequate LV filling, and the rise in wall tension contributes to its enlargement. However, gradual increase in LA dimension disturb frank -starling relationship, decrease in atrial compliance and increase LA stiffness with decrease in LA reservoir function [34]. Our results demonstrated if LVEF % was 29.1±6.9 %, the LAVI, LVGS, and GPALS would be 38.4±5.3 ml/m2, -14.3, and 16.9 respectively (Table 1). Study on systolic HF by Carluccio *et al*. (n= 454 including 136 patients with LVEF 33%) demonstrated if the LVEF was 33%, the LAVI, LVGS, and GPALS would be 42.9±13.6 ml/m^2, -10.4, and 20.5%, respectively [13]. The differences between the two studies could be explained by worse LVEF%, lower number of patients, and exclusion of valvular heart diseases in our study compared to Carluccio *et al*.'s study. It was observed that LVGS, GPALS, LASRs, GPALS-PACS, LASRe, GPACS, and LASRa had high sensitivity, specificity and AUC to predict and early diagnose HFpEF, HFmrEF and HFrEF (Table 4, Figure 1). Furthermore, the component which include these parameters of 2DSTE was significantly predictor for all different types of HF (Tables 2 and 3). It is likely that intrinsic disorders with LA myocardial contractility as LA ischemia or fibrosis may play a role and mediated by increased work load imposed on the LA myocardium due to increased LV diastolic stress which overtime, will lead to intrinsic left atrial dysfunction and gradual decrease in LA contribution in LV filling [35]. These can be explained by the fact of heart failures were associated with the progressive conversion of the LA function from a storage and contractile chamber to a more passive-conduit chamber. Intrinsic alterations of LA myocardial contractility may play an important role. However, it is not clear that these myopathic changes happen firstly or occur lately as a consequence of LA enlargement and myofibrils stretching [36]. Many studies suggest that LV diastolic dysfunction and elevated filling pressure cannot completely account for LA dysfunction and that LA fibrosis may play an important role [37,38]. Atrial strain has been used also in transplanted patients to assess LV filling pressure [39]. Morris *et al*. suggested that LA dysfunction in HFpEF is likely to be related to the same fibrotic process, which influences the LV subendocardial layer secondary to several comorbidities such as diabetes mellitus, hypertension, and coronary artery disease [37]. The study by Al Saikhan *et al*. [29] compared the patients with HFpEF (n=110) and HFmrEF (n=61).

Table 1. Characteristics of the study population including demographic, clinical, laboratory, conventional echocardiography, and speckle tracking echocardiography data.

		Control (n=50)	HFpEF (n=74)	HFmrEF (n=56)	HFrEF (n=56)	Overall p-value
Age (years)		58.0±6.2	57.7±9.4	57.8±9.8	57.4±8.8	0.999
Gender	Female Male	21 (42) 29 (58)	34 (45.9) 40 (54.1)	25 (44.6) 31 (55.4)	27 (48.2) 29 (51.8)	0.933
Height (cm)		170.3±9.1	171.8±7.3	173.1±7.7	169.5±7.7	0.074
Weight (kg)		78.1±8	78.3±6.9	78.0±7.8	78±8.8	0.977
BSA (m^2)		1.9±0.1	1.9±0.1	2±0.1	1.9±0.1	0.737
Smoking n, %	No Yes	30 (60) 20 (40.0)	37 (50) 37 (50.0)	24 (42.9) 32 (57.1)	31 (55.4) 25 (44.6)	0.318
Hypercholesterolemia n, %	No Yes	50 (100) 0 (0.0)	35 (47.3) 39 (52.7)	26 (46.4) 30 (53.6)	27 (48.2) 29 (51.8)	0.982
Diabetes mellitus n, %	No Yes	50 (100) 0 (0.0)	29 (39.2) 45 (60.8)	23 (41.1) 33 (58.9)	22 (39.3) 34 (60.7)	0.973
CAD n, %	No Yes	50 (100) 0 (0.0)	29 (39.2) 45 (60.8)	18 (32.1) 38 (67.9)	13(23.2) 43 (76.8)	0.155
Arterial hypertension n, %	No Yes	50 (100) 0 (0.0)	23 (31.1) 51 (68.9)	12 (21.4) 44 (78.6)	10 (17.9) 46 (82.1)	0.185
NYHA	I II III IV	0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)	53 (71.6) 19 (25.7) 2 (2.7) 0 (0.0)	14 (25.0) 34 (60.7) 8 (14.3) 0 (0.0)	2 (3.6) 12 (21.4) 17 (30.4 25 (44.6)	<0.0001
BNP (ng/L)		18.4±5.7	82±52.5	202.2±154.4	321.7±227	<0.0001
IVSD, cm		0.8±0.2	0.9±0.3	1.1±0.3	1.2±0.2	<0.0001
LVPWD, cm		0.9±0.2	0.9±0.2	0.9±0.2	1.1±0.2	<0.0001
IVSS, cm		1.2±0.3	1.2±0.3	1.3±0.2	1.3±0.2	0.002
LVPWS cm		1.3±0.5	1.3±0.3	1.1±0.3	1.3±0.2	0.006
LVEDD, cm		4.6±0.8	4.7±0.8	5±0.7	6.6±0.7	<0.0001
LVEDS, cm		2.8±0.4	3.2±0.6	4±0.6	5.4±0.7	<0.0001
FS, %		39.6±5.2	31.7±7	20.6±2.7	18.1±3,9	<0.0001
LVEDV, ml[b]		107.1±27.4	108±27.3	113.8±19.5	156.3±20.6	<0.0001
LVESV, ml[b]		39.6±13.3	45.5±12.6	62.8±11.7	111.1±18.8	<0.0001
LVEF%[b]		63±6.4	57.7±4.8	45±2.8	29.1±6.9	<0.0001
E wave, cm/s		90.6±16.2	100.1±18.5	109.4±22.1	122.2±25.1	<0.0001
A (cm/s)		66.2±15.2	79.9±21.9	73.9±22	76.4±25.1	<0.0001
E/A ratio		1.4±0.3	1.3±0.3	1.5±0.3	1.7±0.5	<0.0001
Medial e'		9.9±2.1	6.6±1.7	6.8±1.6	6.7±2.3	<0.0001
Lateral e'		12.6±2.9	8.1±2.3	8.1±2	8.3±2.3	<0.0001
E/e' ratio		8.5±2.1	14.6±3.6	15.3±3.5	17.6±4.8	<0.0001
LA diameter cm[a]		3.3±0.6	3.8±0.8	3.8±0.7	3.7±0.7	<0.0001
LA area mm^2		18.7±3.5	21.1±3	23.6±2.5	23.7±4	<0.0001
MAX LAV ml		52.8±13.8	69.1±9.2	74.2±7.6	73.8±10.7	<0.0001
LAVi mL/m^2		24.6±4.6	36.0±4.6	37.4±4.4	38.4±5.3	<0.0001
Diastolic dysfunction grading	I II III	0 0 0	35 (47.3) 33 (44.6) 6 (8.1)	24 (42.9) 25 (44.6) 7 (12.5)	19 (33.9) 23 (41.1) 14 (25.0)	0.092
LVGS, %		-19.3±2.3	-18.0±1.7	-16.1±2.0	-14.3±2.2	<0.0001
GPALS, %		34.1±6.7	27.5±4.7	21.7±4.8	16.9±4.9	<0.0001
LASRs		1.2±0.2	1.1±0.2	0.9±0.2	0.7±0.1	<0.0001
GPALS – PACS, %		19.4±3.0	15.1±4.4	12.0±3.4	9.3±3.3	<0.0001
LASRe		1.1±0.2	0.9±0.2	0.9±0.2	0.8±0.2	<0.0001
GPACS,%		14.8±4.3	12.3±2.2	9.7±2.3	7.5±2.6	<0.0001
LASRa		1.6±0.3	1.1±0.3	0.8±0.3	0.7±0.3	<0.0001

[a]by M mode; [b]by biplane Simpson method; A, atrial trans-mitral flow velocity; BNP, brain natriuretic peptide; BSA, body surface area; CAD, coronary artery diseases; E, early trans-mitral flow velocity; EDV, end diastolic volume; ESV, end systolic volume; FS, fraction shortening; GPACS, global peak atrial contraction strain; GPALS, global peak atrial longitudinal strain; GPALS-PACS, refers to LA longitudinal strain at end of atrial contraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IVSD, interventricular septum at diastole; IVSS, inter-ventricular septum at systole; LA, left atrium; LASRs, left atrial strain rate at systole; LASRe, peak of left atrial strain rate at early diastole; LASRa, peak of left atrial strain rate at late diastole; LAVi, LA volume indexed; LVEDD, left ventricular end diastolic diameter; LVEDS, left ventricular end systolic diameter; LVEF %, Left ventricular ejection fraction; LVPWD, left ventricular posterior wall diameter diastole; LVPWS, left ventricular posterior wall diameter systole; Max AV, maximum atrial volume; just before the opening of mitral valve; NYHA, New York Heart Association.

Table 2. Principle component analysis (PCA) for conventional and 2DSTE parameters in all types of heart failure.

Extracted components upon PCA	Coefficient parameters	
Component of LV systolic function, and LA phasic function by speckle tracking echocardiography.	FS, % LVEF, % LVGS, % GPALS, % LASRs GPALS-PACS, % LASRe GPACS, % LASRa	0.696 0.779 0.7278 0.885 0.633 0.811 0.653 0.774 0.644
Component of systolic and diastolic LV walls.	IVSD, cm LVPWD, cm IVSS, cm LVPWS, cm	0.780 0.842 0.835 0.788
Component of systolic and diastolic LV dimensions and volumes.	LVEDD, cm LVEDS, cm LVEDV, ml LVESV, ml	0.906 0.797 0.897 0.780
Diastolic dysfunction component including parameters of LA enlargement and E/E ratio.	E/E ratio LA diameter, cm LA area, mm^2 Max LAV, ml LAVI, mL/m^2	0.646 0.802 0.799 0.775 0.723
Diastolic dysfunction component including early diastolic filling velocities.	E wave, cm/s Medial E Lateral E	0.576 0.801 0.804
Diastolic dysfunction component including late diastolic filling velocity and its ratio to early diastolic filling velocity.	A wave, cm E/A ratio	0.939 -0.823

A, atrial trans-mitral flow velocity; E, early trans-mitral flow velocity; EDV, end diastolic volume; ESV, end systolic volume; FS, fraction shortening; GPACS, Global peak atrial contraction strain; GPALS, Global peak atrial longitudinal strain; GPALS-PACS, refers to LA longitudinal strain at end of atrial contraction; IVSD, interventricular septum at diastole; IVSS, inter-ventricular septum at systole; LA, left atrium; LASRs, left atrial strain rate at systole; LASRe, peak of left atrial strain rate at early diastole; LASRa, peak of left atrial strain rate at late diastole; LAVI, LA volume indexed; LVEDD, left ventricular end diastolic diameter; LVEDS, left ventricular end systolic diameter; LVEF %, left ventricular ejection fraction; LVGS, LV global strain; LVPWD, left ventricular posterior wall diameter diastole; LVPWS, left ventricular posterior wall diameter systole; Max AV, maximum atrial volume; just before the opening of mitral valve.

Table 3. Multivariate logistic regression showing the significant components* for prediction of different types of heart failure.

Extracted components	p-value	Odds ratio	95% CI for OR	
			Lower	Upper
HFpEF				
1. Component of LV systolic function, and LA phasic function by speckle tracking echocardiography.	<0.001	2.525	1.639	3.891
2. Component of systolic and diastolic LV dimensions and volumes.	0.046	0.708	0.505	0.993
3. Component of systolic and diastolic LV walls.	<0.001	0.240	0.144	0.401
4. Diastolic function component including parameters of LA enlargement and E/E ratio.	0.003	1.797	1.227	2.631
5. Diastolic function component including early diastolic filling velocities.	<0.001	0.352	0.234	0.530
Constant	<0.001	0.245		
HFmrEF				
1. Component of LV systolic function, and LA phasic function by speckle tracking echocardiography.	<0.001	0.353	0.222	0.562
2. Component of systolic and diastolic LV dimensions and volumes.	0.250	0.826	0.596	1.144
3. Component of systolic and diastolic LV walls.	<0.001	0.563	1.398	0.797
4. Diastolic function component for LA enlargement and E/E ratio.	<0.001	1.014	1.382	2.937
5. Diastolic function component for early diastolic filling velocities.	0.708	0.935	1.660	1.326
Constant	<0.001	0.207		
HFrEF				
1. Component of LV systolic function, and LA phasic function by speckle tracking echocardiography	<0.001	0.009	0.001	0.078
2. Component of systolic and diastolic LV dimensions and volumes.	0.013	5.291	1.426	19.627
3. Component of systolic and diastolic LV walls.	<0.001	293.614	23.912	3605.294
4. Diastolic function component for LA enlargement and E/E ratio.	0.060	3.414	0.979	12.52
5. Diastolic function component for early diastolic filling velocities.	0.725	0.839	0.316	2.227
Constant	<0.001	0.004		

*Component number 6 in PCA was excluded from Multivariate regression analysis because it contains 2 variables only.

The mean average of GPALS (26.2 in HFpEF and 20.6 in HFmrEF), GPACS (13.1 in HFpEF and 9.8 in HFmrEF), and GPALS-PACS (13.0 in HFpEF and 10.7 in HFmrEF) were similar to our results; GPALS (27.5 in HFpEF and 21.7% in HFmrEF), GPACS (12.3 in HFpEF and 9.7 in HFmrEF), and GPALS-PACS (15.1 in HFpEF and 12.0 in HFmrEF) And similar to our study, the worst of LVEF was associated with worse LA functions. These slightly differences can be explained firstly by higher patient's numbers of HFpEF and HFmrEF of that study than our study, secondly higher mean of LVEF which was 64.9% *versus* 57.7% in HFpEF and 44.9% *versus* 45 % in HFmrEF in our study [29]. In our study, it was observed that the component of LVEF, LVGS and LA dysfunction which obtained by 2DSTE had high significance prediction for all type of HF. on the other hand the component of LA dysfunction which obtained by conventional echocardiography had significance prediction in HFpEF and HFmrEF only, and this could be explained by LV fibrosis and restricted mitral annular motion in HFrEF make E/e' unreliable for quantifying LV diastolic pressure [40].

Table 4. Receiver operating characteristic (ROC) curves and cutoff point for LV systolic function and left atrial function in HFpEF, HFmrEF, HFrEF, and controls.

STE parameters	LVGS %	LA reservoir phase		LA conduit phase		LA pump function	
		GPALS	LASRs	GPALS - PACS	LASRe	GPACS	LASRa
HFpEF *versus* control groups							
AUC	0.663	0.792	0.673	0.769	0.775	0.662	0.883
p-value	0.002	<0.0001	0.001	<0.0001	<0.0001	0.002	<0.0001
Cut-off point	-20.5	34.5	1.3	15.5	1.2	15.5	1.2
Sensitivity	89.2	95.9	94.6	60.8	91.9	93.3	63.5
Specificity	40.0	56.0	48.0	84.0	54.0	44.0	98.0
HFpEF *versus* HFmrEF							
AUC	0.768	0.792	0.738	0.712	0.487	0.798	0.686
p-value	<0.0001	<0.0001	<0.0001	<0.0001	0.800	<0.0001	<0.0001
Cut-off point	-15.5	19.5	1.1	9.5	1.1	10.5	0.6
Sensitivity	44.6	55.4	85.7	33.9	83.9	69.7	35.7
Specificity	100.0	100.0	59.5	98.6	29.7	79.7	94.6
HFpEF *versus* HFrEF							
AUC	0.899	0.907	0.929	0.842	0.654	0.928	0.777
P-value	<0.0001	<0.0001	<0.0001	<0.0001	0.003	<0.0001	<0.0001
Cut-off point	-15.5	19.5	1.0	9.5	0.8	9.5	0.6
Sensitivity	62.5	71.4	100.0	60.7	57.1	82.1	48.2
Specificity	100.0	100.0	75.7	98.6	68.9	91.9	100.0
HFmrEF *versus* control							
AUC	0.847	0.917	0.818	0.933	0.785	0.847	0.959
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Cut-off point	-17.5	30.0	1.1	16.5	1.1	12.5	1.2
Sensitivity	78.6	100.0	89.3	87.5	83.9	85.7	82.1
Specificity	72.0	66.0	66.0	80.0	68.0	66.0	98.0
HFmrEF *versus* HFrEF							
AUC	0.702	0.774	0.793	0.732	0.682	0.737	0.640
p-value	<0.0001	<0.0001	<0.0001	<0.0001	0.001	<0.0001	0.011
Cut-off point	-13.5	16.5	1.0	7.5	0.7	6.5	0.4
Sensitivity	41.1	60.7	96.4	41.1	37.5	39.3	33.9
Specificity	96.4	89.3	53.6	100.0	100.0	100.0	94.6
HFrEF *versus* controls							
AUC	0.940	0.974	0.949	0.984	0.871	0.931	0.972
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Cut-off point	-16.5	26.5	1.0	14.5	0.9	10.5	1.2
Sensitivity	80.4	100.0	96.4	91.1	82.1	91.1	85.7
Specificity	90.0	84.0	86.0	92.0	80.0	78.0	98.0

AUC, area under curve; GPALS, global peak atrial longitudinal strain; GPALS-PACS, refers to LA longitudinal strain at end of atrial contraction; GPACS, global peak atrial contraction strain; LA, left atrium; LASRa, peak of left atrial strain rate at late diastole; LASRe, peak of left atrial strain rate at early diastole; LASRs, left atrial strain rate at systole.

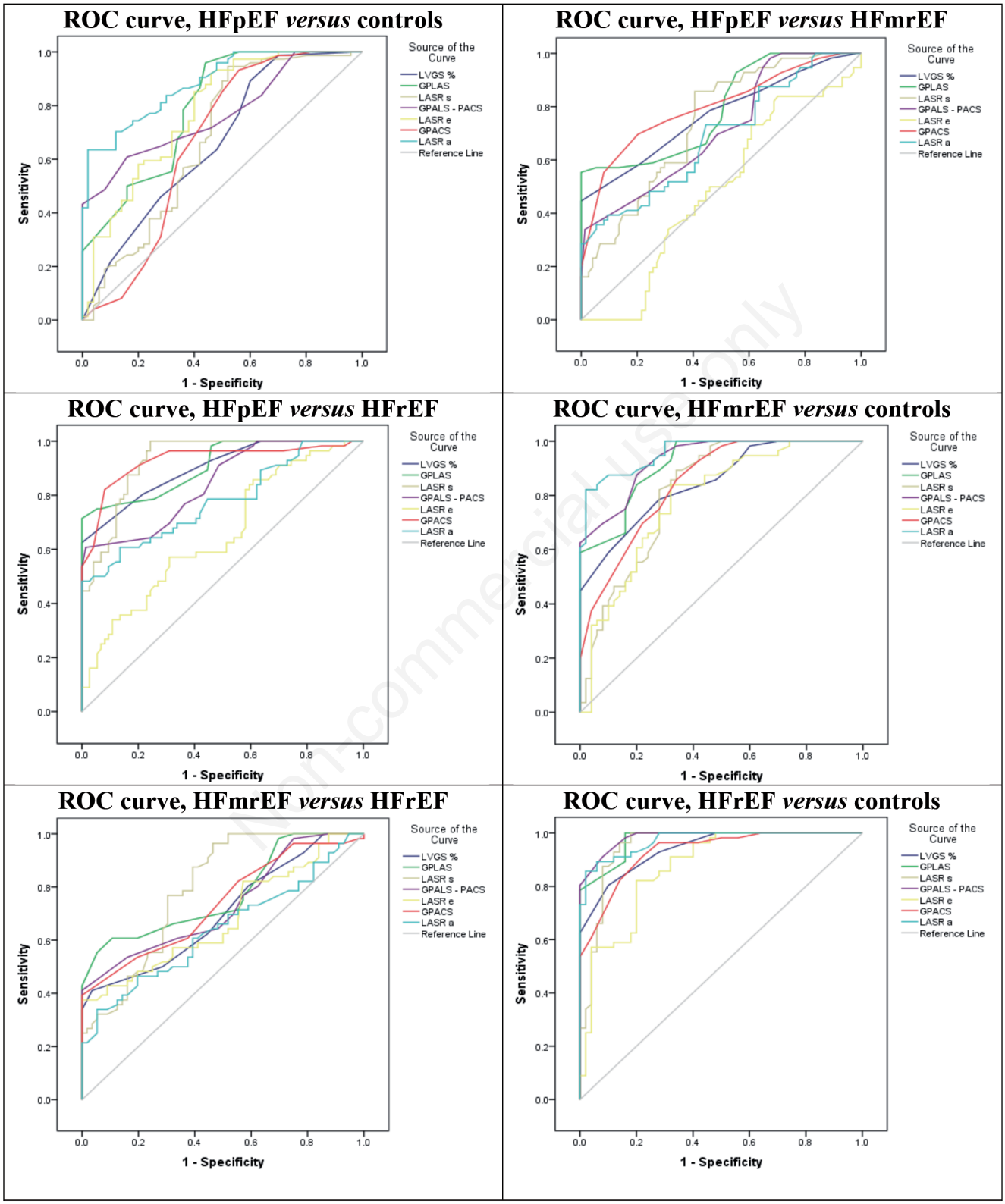

Figure 1. Receiver operating characteristic (ROC) curves for STE parameters of left atrial function in HFpEF, HFmrEF, HFrEF and controls.

The strain imaging has enabled a deeper understanding of atrial function. Some authors have proposed GPALS as a better predictor of cardiovascular events than LAEF and LA function index [41]. The LA strain as a functional adaptive marker may provide valuable information on left atrium stiffness and indirectly estimate the LV end-diastolic pressure. It may identify atrial impairment at an early stage before dilatation occurs [42]. Kurt and colleagues [43] found significantly lower LA systolic strain levels in patients with HFpEF than in patients with LV diastolic dysfunction without HF. The reservoir strain is reduced in patients with SHF or DHF, furthermore SHF patients showed a more significant reduction in left atrium strain proportional to LVGS [44].

Conclusions

Early LA dysfunction in heart failure can be detected accurately and easily by speckle tracking technique that could be a promising independent tool to better understand of heart failure and its classification. The LVGS, GPALS, GPACS and GPALS-PACS are a novel independent parameter in early LA dysfunction to distinguish and predict HFpEF, HFmrEF and HFrEF.

Study limitations

Relatively small number of the study population. Time factor, there was no specific time interval between occurrences of HF and beginning of the study, non accurate selection of the patient group according to the cause of heart failure. The measurements of LA strain require good delineation of LA endocardial borders. This resulted in the exclusion of many patients from the analysis.

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