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Comparing the Performance of Tissue Doppler versus Left Atrial Strain in Predicting Left Ventricular End Diastolic Pressure in Patients with Different Left Ventricular Ejection Fractions

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Abstract

Background: Early trans-mitral inflow velocity and mitral annular tissue Doppler imaging (E/Em ratio) is widely applied to noninvasively estimate left ventricular (LV) filling pressures. However, E/Em ratio has a significant gray zone among patients with severely impaired ejection fraction. Speckle tracking echocardiography (STE) was recently proposed as an alternative surrogate to estimate LV filling pressures. This study aimed at assessing performance of tissue Doppler parameters and left atrial global longitudinal strain as non-invasive surrogates for LV filling pressures and comparing accuracy of these two parameters across different striae of LVEF.

Methods: A total of 96 patients with sinus rhythm and different ejection fraction who divided into four groups of 24 patients each according to their EF(>55%, 45–54%, 30–44%, and <30%), had an invasive measurement of the LV pressure. Both medial and lateral E/Em ratio were measured in all subjects by 2D Tissue Doppler, peak atrial longitudinal strain (PALS) and Peak atrial contraction strain (PACS) were obtained by averaging all segments measured in the 4-chamber.

Results: Significant Correlation between global PALS and invasive LVEDP in all groups (r = 0.70 P < 0.000), While Lateral E/E' shows significant correlation only in two groups; preserved and mildly impaired EF (r=0.42 P=0.023, r=0.439 p-0.032; respectively)

Conclusion: In patients with preserved or mildly reduced LV ejection fraction, global PALS and Lateral E/E' ratio presented good correlations with LVEDP. In patients with moderate or severe reduction of EF, E/E' ratio correlated poorly with invasively measured LV filling pressures. Global PALS provided an overall better estimation of LV filling pressures.

Background

Heart failure is among the most common causes for hospitalization in patients older than 65 years of age in the developed world. In Egypt alone, approximately 3 million patients are hospitalized each year with a primary or secondary diagnosis of heart failure, and AHF contributes to more than 7 million hospital days annually.[1]

Elevated left ventricular filling pressure (LVFP) is a major determinant of cardiac symptoms and prognosis in patient with chronic heart failure independent from LV ejection fraction (EF)[2]. There is conversing evidence that left atrial enlargement determined by echocardiography strongly and independently predicts many cardiovascular outcomes as it reflects chronic exposure to increase LV filling pressure.[34]

Left cardiac catheterization allows an accurate and direct evaluation of some hemodynamic variables that estimate LVFP, although it's a tool not completely free from complication.[3]

Despite its wide use, the real utility of E/e' ratio has been challenged in some studies which include patient with either very advanced heart failure or normal LV ejection fraction.[5]Recently peak atrial longitudinal strain determined by speckle tracking has demonstrated to be more accurate than E/e' ratio to estimate pulmonary capillary wedge pressure or left ventricular end diastolic pressure in patients with advanced heart failure.[6]

Methods:

Study population:

A total of 96 compensated heart failure patients indicated for left heart catheterization were enrolled. This population was selected in order to have four equal groups clustered according to LV ejection fraction (≥55% ; ≥45% to 54% ; ≥30% to 44%; and <30%). All patients were selected aged >18years, in normal sinus rhythmwho agreed to an informed written consent. All had clinical evaluation to ensure having symptoms and/or signs of heart failure. Patients were scheduled for cardiac catheterization after receiving optimal medical therapy and achieving euvolemic or near euvolemic status. All underwent a two-dimensional and Doppler echocardiographic examination within 24 hours from the catheterization. Patients with recent acute coronary syndrome <48 hours, prosthetic valves, more than grade two mitral regurgitation, any kind of implantable cardiac devices, pericardial diseases and insufficient imaging quality of the LA endocardial border were excluded.

Cardiac catheterization:

A 6F multipurpose catheter was balanced to atmospheric pressure and then inserted through a hemostasis valve into the lumen of the fluid-filled catheter to its distal end. It was advanced into the LV cavity through retrograde radial or femoral artery approach. The pressure measurements were obtained with high fidelity manometer-tipped catheter and were calibrated against the pressure measured simultaneously with the fluid filled catheter at end diastole. An elevated LVEDP was defined as >12 mmHg.[7]

Two-D Echocardiography:

All patients were studied in the left lateral decubitus position using an ultrasound system (Philips IE 33, Philips,Andover, MA) using a Philips "S5" transducer. Standard two dimensional, M-mode and Tissue Doppler echocardiograms were obtained in the apical 4 and 2 chambers and left parasternal views according to the American society of echocardiography (ASE) guidelines.Measurements of left ventricular (LV),left atrial (LA) dimensions, LV ejection fraction using biplane Simpson's method and diastolic LV filling velocities were obtained in accordance with ASE recommendations. The ratio between peak early (E) and late (A) diastolic LV filling velocities was used as standard index of LV diastolic function. LA volumes were measured using the area–length method, from the apical four- and two-chambers views, the time interval between the onset of QRS on the electrocardiogram and theaortic and mitral opening and closures were measured using pulsed wave Doppler.Early diastolic (E'), and late diastolic (A') annular velocities were obtained by averaging respective values measured at the septal and lateral sides of the mitral annulus. Mean E' and the derived E/E' ratio were used as load-independent markers of ventricular diastolic relaxation.

Speckle Tracking Echocardiography:

For Speckle tracking analysis, apical four chambers view was obtained using conventional two-dimensional gray scale echocardiography during breath hold and with a stable ECG recording and stored in cine-loop format from three consecutive beats. The frame rate for images was between 60 and 80 frames per second.[8] All analysis of recorded files was performed off-line after defining the endocardial border manually in the systolic frame and adjusting the region of interest(ROI) width. An epicardial tracing was automatically developed by the software system (Q-lab version 9.0) generating longitudinal strain curves for six atrial segments using"frame-by-frame tracking" of the natural acoustic markers throughout the cardiac cycle. Manual validation of the automatically traced endocardial borders, and modificationsif required, were performed before the software was allowed to perform data analysis.

The longitudinal peak atrial strain (PALS), measured at the end of the reservoir phase, was calculated by averaging values observed in all LA segments (global PALS). Peak atrial contraction strain (PACS) was also measured as the average of all segments (global PACS).

Statistical analysis

Statistical analysis was performed using S-Plus Statistical Software (SPSS) for Windows (version 20.0, SPSS Inc. Chicago, Illinois). All variables were tested for normality using *Kolmogrov-Smirnov test*; if the test was significant, non-normality was accepted. Otherwise double-checking using graphs, skewness and kurtosis were required to confirm normality. Continuous variables were presented as mean ± standard deviation when normality of distribution assumptions were satisfied. If not, it was presented as median and range. Categorical variables were presented as numbers and percentages.

When normality assumption was not satisfied, continuous variables were compared between two related samples using *Wilcoxon test* and two unrelated samples using *Mann Whitney U test*. When normal distribution was confirmed, data were compared using *paired and unpaired T-test*. Variables that exhibited an important association with the outcomes of interest were considered for inclusion in multiple regression modelling. Quantitative variables were compared using two-tailed unpaired student t- test, and qualitative variables were compared using Fisher's exact test. P value of < 0.05 was considered significant.

Receiver operating characteristic (ROC) curve wereplottedto test sensitivity as the y coordinate versus its 1-specificity as the x coordinate. Area under curve (AUC) wasused to as an expression forthe positive and negative prediction values.

Results

This study enrolled 96 heart failure patients, clustered into 4 equal groups according to their LVEF. Clinical, echocardiographic and catheterizationdata of the study group are summarized in (Table 1). Invasively measured LVEDPwas found to be high (≥ 12 mmHg) in 46 patients (47.9%), while normal LVEDP (< 12 mmHg)in 50 patients(52.1%).There was no statistically significant difference in clinical features between the high and normal LVEDP groups.

Analysis the tissue Doppler parameters for the whole study group showed that peak early diastolic velocity at septal and lateral mitral annuli, (septal and lateral E')showed no statistical difference across invasively measured LVEDP groups. The peak mitral inflow velocity (E) over peak annular velocity was statistically significant for both septal and lateral mitral annuli. (Table 2)

Testing the correlation between E/Lat E' ratio and LVEDP using Pearson's test, revealed an r-value of 0.369 for the septal and 0.47 for the lateral mitral annular velocity ($p < 0.001$ for both).Further analysis of this correlation after splitting the cohort into the 4 LVEF groups are shown in (Table 3). E/lat E' was showed statistically significant correlation to invasively measured LVEDP only in normal and mildly impaired LVEF, while failed to show any significant correlation in moderately or severely impaired LVEF.

On the other hand, analysis of the speckle tracking parameters showed a statistically significant difference of both PALS and PACS values between high and normal LVEDP groups (Table 1). Pearson's testingshowed significant correlation between both PALS and PACS against LVEDP (Table4).On further analysis of the correlation after dividing the patients into the 4 groups, PALS sustained a statistically significant correlation across all LVEF categories.

Receiver observational characteristic (ROC) curves were plotted for E/Sep E' (Figure 1), E/Lat E' (Figure 2), PALS % (Figure 3) and PACS % (Figure 4) to predict LVEDP. PALS showed a very good specificity (83.67%), and sensitivity (73.91%) with area under the curve of 0.857 to detect LVEDP >12 mmHg.

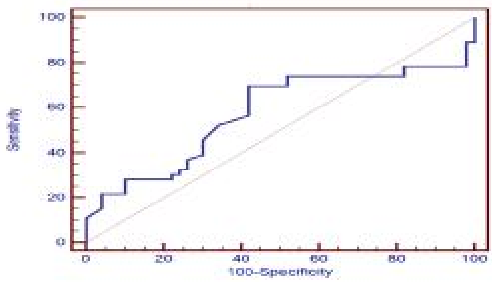

Figure 1: ROC curve for E/SepE'.cm/s

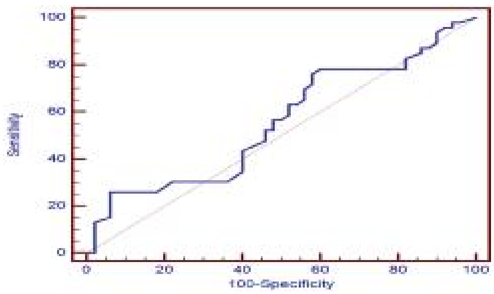

Figure 2:ROC curve for E/Lat_E'.cm/s

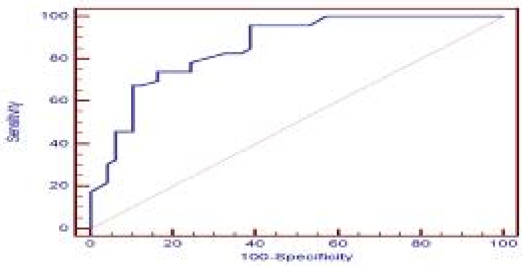

Figure 3:ROC curve for PALS %

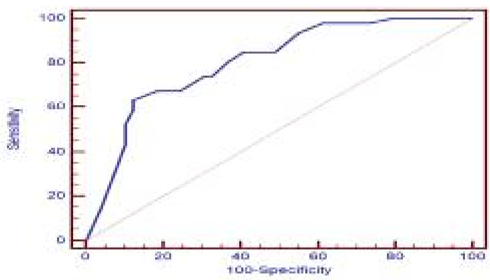

Figure 4: ROC curve for PACS %

Table1. Demographic, echocardiographic and catheterization data

Demographic features		Two-D Echo features	
Age in Years **Mean ± SD**	**50.56 ± 17.28** **(18.0 – 83.0)**	**LVEDD (cm)**	**5.29 ± 1.13 (8.5 - 3.1)**
		LVESD (cm)	**3.9 ± 1.19 (7.2 - 1.7)**
Male Gender **Count (%)**	**66 (67.7%)**	**LVEF (%)**	**49.2 ± 13.7 (75 - 15)**
DM	**27 (28.1%)**	**Tissue Doppler features**	
HTN	**29 (30.2%)**	**Peak E cm/s**	**69.9 ± 27.3 (147 - 34)**
Overweight	**26 (27.1%)**	**E/A**	**1.22 ± 0.86 (5.2 – 0.5)**
Obese	**40 (41.7%)**	**Septal E' cm/s**	**5.8 ± 2.25 (11.7 - 3)**
Pulmonary HTN	**3 (4.2%)**	**Lat E' cm/s**	**7.6 ± 2.88 (13.2 – 3.6)**
		E/Sep E' cm/s	**13.5 ± 8.11 (38.9 - 6)**
		E/Lat E' cm/s	**9.8± 5.16 (23.2 – 3.7)**
Cardiac cath. Features		**Speckle Tracking**	
Nor. Pressure	**50 (52.1%)**	**Global long strain %**	**24.4 ± 13.1 % (56.2 - 3)**
High pressure	**46 (47.9%)**	**PACS %**	**13.2 ± 8.3 % (37 - 1)**

Table 2: Comparing LVEDP against pulsed wave Doppler and tissue Doppler values

	Normal LVEDP (n=50)	High LVEDP (n=46)	p-value
Septal E' cm/s	6.23 ± 2.03	5.91 ± 2.84	0.192
Lat E' cm/s	8.01 ± 2.74	7.33 ± 2.75	0.133
E/Sep E' cm/s	11.59 ± 6.35	16.77 ± 8.13	<0.001*
E/Lat E' cm/s	8.98 ± 4.16	12.42 ± 4.37	<0.001*
Global long strain %	27.99 ± 13.14	11.89 ± 7.47	0.000*
PACS %	15.20 ± 8.56	6.28 ± 5.51	0.000*

Table 3: Correlations between Invasive LVEDP and tissue Doppler

Tissue Doppler	Invasive LVEDP	
	r-value	P-value
Septal E' cm/s	-0.093	0.366
Lat E' cm/s	-0.019	0.856
E/Sep E' cm/s	0.369	<0.001*
E/Lat E' cm/s	0.466	<0.001*
Global long strain %	-0.708	<0.001*
PACS %	-0.601	<0.001*

Table 4 : Correlations between Invasive LVEDP and tissue Doppler/Speckle tracking parameters in each group of EF

Doppler and Speckle tracking parameters	EF <30%		EF (30%-to-< 45%)		EF (45%-to-< 55%)		EF ≥ 55%	
	Invasive LVEDP		Invasive LVEDP		Invasive LVEDP		Invasive LVEDP	
	r-value	P-value	r-value	P-value	r-value	P-value	r-value	P-value
Septal E' cm/s	-0.023	0.917	-0.271	0.200	-0.310	0.141	0.142	0.509
Lat E' cm/s	0.325	0.121	0.030	0.888	-0.303	0.150	-0.507	0.011*
E/Sep E' cm/s	-0.034	0.874	0.058	0.789	0.264	0.212	-0.323	0.124
E/Lat E' cm/s	0.258	0.233	-0.245	0.248	0.439	0.032*	0.462	0.023*
Global L strain%	-0.599	0.035*	-0.548	0.042*	-0.557	0.006*	-0.512	0.011*
PACS %	0.498	0.013*	-0.177	0.409	-0.482	0.020*	-0.311	0.139

Global L strain%; Global longitudinal strain percent.

Discussion

Invasively measured left ventricular filling pressures like LVEDP or PCWP have crucial diagnostic and prognostic values in heart failure management. Being invasive, not complication free and costy; were difficult to be routinely applied in daily clinical practice, particularly in the setting of acute heart failure, when they are mostly required. Accordingly, the need for non-invasive, sensitive and specific alternatives for LV filling pressures was deemed necessary.[9 10 11]

LVEDP ≥12 mmHg was used as the cut off value defining abnormally high LV filling pressure,and was tested and validated in many previous studies.[12 13 7]TDI used to be considered as a good non-invasive tool reflecting abnormalities in invasive LV pressure for the past few decades, however, there are controversial results about TDI sensitivity and accuracy in recent published studies.

STE is a novel modality for assessment of all the 3 LA functions (Reservoir, conduit and pump), and has been validated against non-invasive[14 15] and invasive indicators of diastolic function. Reliability and accuracy of speckle tracking assessment of LA functions is supported by many studies conducted in healthy and heart failure patients.[6 16 17]Reliability and accuracy of speckle tracking assessment of LA functions is supported by many studies conducted in healthy and heart failure patients,[18 7]STE has the advantage of overcoming the angle-dependency that was considered a significant defective feature in TDI limiting the reproducibility of its results.[5 19]

In this study, E/Lat E' and global PALS (as the most closely correlated TDI parameter and STE parameter respectively) showed statistically significant difference between normal and high LVEDP, and showed significant correlation to invasively measured LVEDP values.

In the large body of evidence studying the relation between TDI derived E/e' to directly measured LV filling pressure, there was obvious variation in their degree of correlation.[20] This is possibly because TDI results are greatly angle dependent and are frequently affected by the movement of the whole heart during systole and diastole. Moreover, The reliability of TDI derived E/e' as a predictor of LV filling pressures in the special subset of severely impaired LVEF was repeatedly criticized in many studies.[5] [21]Cameli et al, had studied a group of patients with severely impaired systolic function; LVEF < 35%; and had reported a non-significant correlation between TDI-E/e' and mPCWP.[6]In a larger study on patients with LVEF ≤ 35% performed by Mullen's et al, they discovered that no correlation was found between E/e' and PCWP in those subset of patients.[5] Mullen's et al, additionally had found that E/e' lacks any sensitivity and specificity to differentiate between PCWP >18 mmHg and ≤ 18 mmHg particularly with more dilated or more impaired LV.[5]

Accordingly, in this study, correlation of E/Lat E' and PALS % to LVEDP were re-performed after splitting the study group into 4 LVEF categories. E/Lat E' was statistically correlated only in patients with normal and mild LVEF impairment, but failed to show any correlation in LVEF < 45%. On the contrary, PALS % sustained a significant correlation to LVEDP across all LVEF categories.

ROC curves had shown that E/Lat E' of ≤ 4.4 predicted LVEDP>12 mmHg withsensitivity of 26%, specificity of 94% and with a poor AUC (0.557), while PALS of ≤ 15% predicted LVEDP>12 mmHg withsensitivity of 74%, specificity of 81% and with AUC (0.857).

Similar to our results; in a recent study by Cameli et al, enrolling 4 equal groups of patients recruited according to their LV ejection fraction (normal and mild, moderate and severely impaired LVEF); E/e' showed poor correlation to invasively measured LVEDP in moderate and severely impaired LVEF, while it had reliable prediction with strong correlation in normal and mildly impaired LVEF.[7]

The lack of reliability and accuracy of E/e' in prediction of LV filling pressure and diastolic function in the subset of patients with severely impaired EF can possibly be explained by LV fibrosis and reduced cardiac output which subsequently cause restriction of mitral annular motion during systole and early diastole, so the ratio between left atrial pressure (and thus E velocity) and LV relaxation (e') become unreliable indicator of filling pressures.[5]

Limitations:

Our study had some limitations worth to be mentioned. Certain subgroups like female gender were under-represented in our study group. Tissue Doppler and speckle tracking echo are operator dependent and views dependent. Lack of dedicated software for left atrial speckle tracking is considered a current limitation where we used LV software instead. Till the time present, there are no accepted normal values for left atrial strain and strain rate. We used end hole catheters connected to digital pressure dome for invasive pressure assessment, while micromanometer tipped catheters are more accurate for direct pressure assessment, but they are expensive, unavailable and reported to be associated with higher risk of embolization.

Conclusion:

In this study, both E/Lat E' and PALS were good surrogates for LV filling pressures and were correlated to the invasively measured LVEDP during left heart catheterization. E/Lat E' showed statistical correlation (and was weak) with LVEDP only in cases with

LVEF ≥ 45%. PALS proved to be a sensitive and reliable non-invasive surrogate for LVEDP that maintains good correlation in all LVEF categories.

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