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Research Article

Place of Global Longitudinal Strain in the Analysis of Systolic Function of Left Ventricle in Patients with Diastolic Dysfunction and Heart Failure with Preserved Ejection Fraction (HFpEF).

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Abstract

Objectives: To identify the underlying systolic dysfunction assessed by global longitudinal strain in patients presenting to Sri Jayewardenepura General Hospital with diastolic dysfunction and HFpEF.

Methods: This study analyzed 76 patients including, 26 patients with HFpEF, 27 patients with diastolic dysfunction but without heart failure, and 23 patients with hypertension but without diastolic dysfunction or heart failure who were matched for age and sex to act as controls. All of the above patients underwent detailed echocardiographic assessment including left ventricular ejection fraction measured by Simpson's method and global longitudinal strain of the left ventricle assessed by two-dimensional speckle tracking.

Results: Left ventricular ejection fraction with Simpson's method was 60.07±4.50% in diastolic dysfunction only group, 58.86±5.61% in HFpEF group and 61.30±2.19% in hypertension only group (p=0.07). Global longitudinal strain was −17.78±0.653 in diastolic dysfunction only group, −14.773±1.762 in HFpEF group and −20.9±2.27 in hypertension only group (p<0.001). And the GLS was significantly reduced in both diastolic dysfunction only group and HFpEF group despite normal ejection fraction.

Conclusion: In patients with symptoms and signs of heart failure with normal left ventricular ejection fraction, for the diagnosis of left ventricular systolic dysfunction global longitudinal strain can be considered as an important parameter.

***Keywords**: Diastolic Dysfunction, Heart failure with preserved ejection fraction, Global longitudinal strain.*

Introduction

Left ventricular (LV) diastolic dysfunction is a consequence of impaired relaxation of the LV with or without decreased restoring forces, and elevated LV chamber stiffness, which escalate cardiac filling pressures[1-4]. Diastolic function abnormalities can exist with or without heart failure which may or may not be accompanied by systolic dysfunction of left ventricle. Isolated Diastolic dysfunction (without heart failure) prevalence is unknown.

Heart failure is a clinical condition described by typical symptoms and signs of elevated tissue/organ water and reduced tissue perfusion. In their guidelines of 2016 the European Society of Cardiology suggested four criteria to establish heart failure with preserved ejection fraction (HFpEF) [5] (1) Accompanying signs and/or symptoms of heart failure ; (2) Left ventricular ejection fraction of more than 50% for 'preserved' ejection fraction and between 40–49% for Heart failure with mid-range ejection fraction(HFmEF); (3) Increased natriuretic peptides (NPs), N-terminal-proB type-natriuretic peptide (NT-proBNP) of more than 125 pg/mL and/or; B-type natriuretic peptide (BNP) of more than thirty five pg/mL and (4) Abnormal indices of left ventricular relaxation, filling, compliance or stiffness. According to previous studies almost one third of patients diagnosed with evident congestive heart failure have a normal ejection fraction and, thus, isolated diastolic heart failure.[6-8]

Since 2-dimensional (2D) echocardiographic examination is noninvasive and easy to access, it takes the major part in establishing diastolic dysfunction of left ventricle. There are several parameters of echocardiography, including tissue doppler, mitral inflow pattern doppler study, and pulmonary veins inflow doppler study, which play a crucial part in establishing diastolic dysfunction diagnosis; though, none of the above is diagnostic as a single feature. So, the diagnosis of diastolic dysfunction is strongly suggested by establishing multiple echocardiographic parameters. It is proven that tissue doppler imaging is more precise than other parameters for diagnosing diastolic dysfunction. Foremost efficient parameters are an Early diastolic flow velocity/Diastolic flow assessed with the help of tissue doppler imaging, that is the (E/e′) of ≥13 and a mean diastolic flow, which is the e′ of septal and lateral wall of less than 9 cm/s [9-12].

Myocardial deformation (strain) can be measured by global longitudinal strain with 2-dimensional echocardiography and has greater value than myocardial velocities in evaluation of left ventricular systolic dysfunction since it is not dependent of angle besides more convenient to calculate than its counterpart tissue doppler imaging. Global longitudinal strain (GLS) is derived through mean of 17 cardiac segments depicted by apical 4 chamber, 3 chamber and 2 chamber views of 2D echocardiography [13], GLS normal value range is between –18% to –21.5% [14].

Objectives

General

To identify the underlying systolic dysfunction assessed by global longitudinal strain in patients presenting to Sri Jayewardenepura General Hospital with diastolic dysfunction and HFpEF.

Specific

1.To identify systolic dysfunction established by global longitudinal strain in patients having diastolic dysfunction presenting to Sri Jayewardenepura General Hospital.

2.To identify the underlying systolic dysfunction established by global longitudinal strain in patients presenting with HFpEF to Sri Jayewardenepura General Hospital.

3.To assess the global longitudinal strain in patients who have hypertension with normal ejection fraction without diastolic dysfunction.

Literature Review

Yen-Wen Liu et al did a small group study in 2009 recruiting 49 patients including 23 with systolic dysfunction, 26 who had HFpEF and another forty patients whom he matched for age, sex, in addition to related disease and with no heart failure as controls. The mean of LV GLS (controls: -20%, HFPEF: -14%, and systolic heart failure: -8%, P <0.001) was notably reduced in HFpEF and systolic heart failure groups. They concluded that compromised left ventricular systolic function can be established by diminished global longitudinal strain in patients with HFpEF [15].

In 2012 Daniel A. Morris et al assessed overall of three hundred and twenty-two patients including those of 92 who had HFpEF and 230 who were asymptomatic but had LV diastolic dysfunction. Myocardial systolic longitudinal strain was notably diminished in HFpEF (20.13±6.02%) compared to patients who were asymptomatic but had diastolic dysfunction (25.33±6.06%, *P*<0.0001) [16].

Elisabeth Kraigher-Krainer et al evaluated both myocardial systolic and diastolic function in around 219 HFpEF patients derived through a HFpEF clinical study and compared them with 50 controls who had no cardiovascular illness and to forty-four sex & age -matched patients who had hypertension and diastolic dysfunction but without HF. When comparing with above two groups, patients who had HFpEF showed notably diminished longitudinal strain (LS) of (-20.0 +/-2.1 and -17.07+/- 2.04 vs. -14.6 +/-3.3, respectively, $p < 0.0001$). They concluded that longitudinal strain spots diminished systolic function in spite of normal LVEF in patients with HFpEF which might impart in the pathophysiology of syndrome of HFpEF[17].

In 2015 Shah et al assessed global longitudinal strain at reference point in 447 patients who had HFpEF joined in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study. Reduced longitudinal strain, demonstrated as a value of less than 15.8%, was noted in 52% of the patients[18].

In 2017 Jonathan Buggey et al evaluated left ventricular global longitudinal strain (LV GLS) and consequences in 463 patients who were admitted with acute HFpEF. In these 463 patients, the LV GLS median was 12.8% (Interquartile range, 15.8 to 10.8%) and the abnormal value was present in 352 (76%). They concluded that high frequency of diminished LV GLS is present among patients admitted with acute HFpEF which suggest obscured myocardial systolic dysfunction and reduced LV GLS is related with poor clinical outcomes at thirty days but not in one year [19].

In 2019 Hasanain Ali Hameed Bshiebish et al did a small group study recruiting 66 patients including those who had HFpEF, heart failure with reduced ejection fraction (HFrEF) and a control group. The left ventricle (LV) GLS (controls = 19.74 +/- 1.12%, HFpEF = 15.03 +/- 2.03%, HFrEF = 10.72 +/- 1.99%, $p = 0.0001$) was notably diminished in patients with HFpEF group though they had a normal LVEF. So, they concluded that there is substantial left ventricular systolic impairment spotted through GLS though they have a normal LVEF [20.]

Methodology

Study type: This study is a descriptive cross-sectional study

Study setting : Cardiac investigation unit at Sri Jayewardenepura General Hospital, Sri Lanka.

Study population : In this study we analyzed several parameters especially the global longitudinal strain of 76 patients who presented during the time period of January to December 2021 to Sri Jayewardenepura General Hospital Cardiac Investigation unit.

Inclusion criteria

1.Patients who came for 2D echocardiography and having diastolic dysfunction with normal ejection fraction on echocardiographic examination

2.Patients who had symptoms and signs of heart failure and having normal ejection fraction with diastolic dysfunction.

Heart failure status was established with New York Heart Association classification of functional status[21] and Framingham criteria for the establishment of congestive heart failure[22]

3.Control group which was matched for sex and age, those who had hypertension with normal ejection fraction and without features of heart failure or diastolic dysfunction.

Exclusion criteria

Patients who had the below mentioned criteria were not included in this study.

1.Patients who had other co-morbidities which could explain hospital admission with pulmonary oedema e.g. – Pulmonary oedema due to renal impairment

2.Patients from whom getting optimal views to do the global longitudinal strain was difficult due to chest wall abnormalities or obesity

3.Patients whose symptoms could be explained by other co-morbidities

e.g.: uncontrolled bronchial asthma or chronic obstructive pulmonary disease, anaemia, thyrotoxicosis, renal impairment, chronic liver cell disease, tight aortic stenosis, restrictive lung pathologies

Sample size

The sample size was calculated based on analysis of variance (ANOVA) for the above mentioned 3 groups using G Power software version 3.1(Buchner, Erdfelder, Faul, & Lang, 2020)[23]. At the power of 0.9, effect size (f) of 0.5 and a significance level of 0.05, the total sample size is 17.91. According to this at least 20 participants need to be analyzed separately for all three above mentioned study groups i.e., overall, of sixty patients altogether.

Sampling method and study design

Sampling method:Among the patients who presented to cardiac investigation unit at Sri Jayewardenepura General Hospital for 2D echocardiography, all the patients who fit into the inclusion criteria and give their consent to take part in our study were sampled.

Study design: From the patients who presented to the cardiac investigation unit at Sri Jayewardenepura General Hospital for 2D echocardiography in 2021 and who fit into the inclusion criteria with their informed consent were involved in the study.

Patients who are included in the study were interviewed and examined for features of heart failure including major criteria which includes paroxysmal nocturnal dyspnoea, weight loss of 4.5 Kg in 5 days due to the given treatment, elevated JVP, pulmonary oedema, S3 gallop, cardiomegaly and minor criteria which includes nocturnal cough, dyspnoea on ordinary exertion that is New York Heart Association classification of class III or IV, pleural effusion, tachycardia, hepatomegaly, ankle oedema by the echocardiographer who is always a doctor in our setup. Heart failure status was established by the New York Heart Association classification of functional status[21] which has four classes which are

Class I: No restriction of physical exertion

Class II: Minor restriction of physical exertion

Class III: Noticeable restriction of physical exertion

Class IV: Symptoms persist though the patient is at rest; difficulty with even slight physical exertion

and Framingham criteria for the diagnosis of congestive heart failure[22] with either two major or one major and two minor criteria. Accordingly, patients were classified into three groups as diastolic dysfunction without heart failure, HFpEF and controls. After this they have undergone detailed 2D echocardiographic examination.

Echocardiographic measurements

All the participants were assessed at the cardiac investigation unit at Sri Jayewardenepura General Hospital by a EPIQ 7C Philips echocardiographic machine using a X5-1(5-1 MHz) probe. Quantitative measures of left ventricular ejection fraction and left ventricular and atrial dimensions were obtained following the suggestions given by American Echocardiographic Society[24]. Echocardiographic assessment was done in left lateral decubitus position. Left ventricular ejection fraction was obtained from the method of Simpson by acquiring left ventricular systolic and diastolic volume derived from apical four-chamber and two-chamber views. Left ventricular diastolic dysfunction was established by the help of Pulse waved Doppler inflow assessment to measure the peak early flow velocity (E) & deceleration time, the sample volume was cited on the mitral valve tip perpendicularly and aligned parallel to the direction of blood flow. Mitral annulus movement was measured by pulse wave tissue doppler imaging derived from the view of apical 4-chamber with a sample volume of 2-mm kept consecutively at both the septal and lateral positions of the mitral annulus, early diastolic peak e´ was also assessed at both the septal and lateral positions of the mitral annulus. The E/e´ ratio was assessed as of the mean of the septal and lateral e´. 2-D strain images were derived from three views including apical four-chamber, apical three-chamber, and apical two-chamber long axis views with the frame rate of 40–90 frames per second.

Echocardiographic analysis

The echocardiographic evaluation was done, using Automated Cardiac Motion Quantification (aCMQ) from a EPIQ 7C Philips echocardiography machine. Algorithmically the endocardium was traced all over the cardiac cycle in a single frame. The relevant zone was adjusted by the echocardiographer manually to confirm that entire layer of myocardium is included. The left ventricular trabeculae and sub endocardium was not included. By the use of aCMQ, the longitudinal strain acquired through the

apical three, two and four chamber views were routinely assessed and mean of all the three was considered as left ventricular global longitudinal strain. In case if two of the segments are not pictured, this automated software was considered invalid.

Statistical Analysis

Statistical Analysis was completed with the use of SPSS software version 25.0. Study group comparison was done using Student t test. A p value < 0.05 was regarded as statistically significant.

Ethical considerations

Official approval was gained from Ethical review committee, Sri Jayewardenepura General Hospital. Informed consent was gained from patients following comprehensive description of the aim of the research and the kind of information needed, and participants were guaranteed of data anonymity and also the confidentiality.

Results

This study analyzed 76 patients including, 26 patients with HFpEF, 27 patients with diastolic dysfunction & without heart failure, and 23 patients with hypertension & without diastolic dysfunction or heart failure. Everyone underwent an echocardiographic evaluation but 9 of them (4 from HFpEF, 2 from hypertension only group and 3 from diastolic dysfunction only group) were excluded due to poor image quality. Demographic characteristics and echocardiographic findings are presented in Table 1.

Table 1. Demographic and echocardiographic characteristics of patients included in this study. Comparison between HFpEF group and Hypertension only group was used to obtain p value.

Variable	DD(n=24)	HFpEF (n=22)	HTN (n=21)	p
Age (y)	62± 11.59	65.55±10.098	59.38±9.724	0.048
Sex, female: male	13:11	9:13	12:9	
Body Mass Index (kg/m^2)	26.708±3.475	27.015±4.972	25.353±3.34	0.210
Diabetes Mellitus	13	10	7	
Hypertension	21	22	21	
Systolic BP (mmHg)	149.33±22.74	158.86±15.93	148.28±21.55	0.074
Diastolic BP (mmHg)	82.71±12.98	87.00±13.68	84.14±9.79	0.437
LVEF (%)	60.07±4.50	58.86±5.61	61.30±2.19	0.07
LA Volume Index (mL/m^2)	33.77±5.86	39.49±6.43	26.46±3.41	<0.001
IVRT (mS)	92.21±16.38	81.41±24.18	84.5±17.79	0.811
E/A	0.825±0.47	1.26±0.80	1.23±0.21	0.934
DT	229.33±54.48	206.23±75.27	194±9.899	0.824
E/ e´(average)	16.33±2.44	17.07±2.41	7.50±1.41	<0.001
GLS	17.78±0.653	14.773±1.762	20.9±2.27	<0.001

These data sets are presented as mean ± standard deviation or n (absolute quantity)

DD=diastolic dysfunction; HFpEF=Heart failure with preserved ejection fraction; HTN=hypertension; y=years; BP=blood pressure; LVEF=left ventricular ejection fraction; LA=left atrium; IVRT=Isovolumic relaxation time; DT=deceleration time; GLS=global longitudinal strain

When compared the echocardiographic parameters between the HFpEF group and Diastolic dysfunction only group (Table 2), it showed that GLS was significantly reduced (p<0.001) and left atrial volume index significantly increased (p=0.003) in the HFpEF group. But none of the other echocardiographic parameters showed statistically significant difference. Even though the left ventricular ejection fraction was reduced compared to diastolic dysfunction only group this was not statistically significant (p=0.425).

Table 2. Echocardiographic findings comparison between HFpEF and DD only group

Variable	**DD**	**HFpEF**	**P value**
LVEF	60.067±4.499	58.864±5.607	0.425
GLS	17.796±0.653	14.773±1.762	<0.001
IVRT	92.208±16.376	81.409±24.181	0.081
E/A	0.825±0.469	1.259±0.8	0.028
DT (mS)	229.333±54.477	206.227±75.276	0.237
E/ e´ (average)	16.333±2.347	17.086±2.409	0.549
LA volume index(mL/m^2)	33.767±5.857	39.489±6.428	0.003

These data sets are presented as mean ± standard deviation

DD=diastolic dysfunction; HFpEF=Heart failure with preserved ejection fraction; LVEF=left ventricular ejection fraction; LA=left atrium; IVRT=Isovolumic relaxation time; DT=deceleration time; GLS=global longitudinal strain

When considering the echocardiographic parameters comparison between HFpEF and Hypertension only group (Table 1), though the left ventricular ejection fraction was reduced in HFpEF group this was statistically not significant (58.86±5.61vs 61.30±2.19, p=0.07). But the left atrial volume was higher in the HFpEF group which was statistically significant (39.49±6.43 vs 26.46±3.41, p<0.001). Apart from the above, none of the echocardiographic parameters showed statistically significant difference except

the E/e´ which was higher in the HFpEF group due to diastolic dysfunction.

The GLS when compared to Hypertension only group showed statistically significant reduction in HFpEF group despite insignificant difference in the left ventricular ejection fraction (14.773±1.762 vs 20.9±2.27, p<0.001). This was also true in the comparison between diastolic dysfunction only group and HFpEF group (17.796±0.653 vs 14.773±1.762, p<0.001). The comparison between diastolic dysfunction only group and hypertension only group also revealed statistically significant reduction in GLS in diastolic dysfunction only group (p<0.001).

Discussion

From this study we can notice that, though there is no statistically significant difference in left ventricular ejection fraction in diastolic dysfunction and HFpEF patients there can be significant reduction in GLS. The noticed reduction in GLS in the above two groups most likely caused by regional reduction in longitudinal strain of the left ventricle and if this is severe give rise to symptoms as evidenced by further statistically significant reduction in GLS when compared between diastolic dysfunction only group and HFpEF group. Thus, GLS would be a promising parameter in identifying patients with HFpEF. aCMQ can be utilized for the above purpose which gives accurate measurement of GLS of the left ventricle which will be subsequently useful to identify HFpEF patients rather than any other echocardiographic parameters like LVEF or E/e´.

Though it is not statistically significant the left ventricular ejection fraction was reduced in compared to hypertension only group in HFpEF (58.86±5.61 vs 61.30±2.19) but whether this systolic function can be identified in all patients is a matter of debate. The reduction in systolic peak velocities which can be regional or global has been found in plenty of studies among patients with HFpEF [25,26]. LV systolic dysfunction was shown when measured by TDI of mitral annular peak velocity and amplitude in patients with HFpEF and left ventricular hypertrophy by Yip et al [27].

A study by Wang et al [28] showed significant reduction in both longitudinal and radial strain in patients with HFpEF compared to controls, but the controls were healthy subjects without any co-morbidities like hypertension or diabetes mellitus which can cause diastolic dysfunction and they were younger

compared to HFpEF group. But in our study, we compared our results with age and sex matched controlled group who had hypertension and diastolic dysfunction.

Hasanain Ali Hameed Bshiebish et al [20] did a study which revealed that left ventricle (LV) GLS was notably diminished in patients with HFpEF group though they had a normal LVEF. So, they concluded that there is substantial left ventricular systolic impairment spotted through GLS though they have a normal LVEF. But in this study, we also analyzed and compared the patients who had only diastolic dysfunction with HFpEF patients.

In our study the HFpEF patients had significantly reduced GLS though LVEF was not significantly reduced compared to controls which was demonstrated in above studies also. But in addition, in our study patients who had diastolic dysfunction who had no symptoms also showed significantly reduced GLS with insignificant reduction in LVEF. Interestingly when we compared HFpEF group with diastolic dysfunction only group it also showed statistically significant reduction of GLS in HFpEF group.

HFrEF and HFpEF are considered to be phenotypical differences of the same disease according to single syndrome hypothesis [29,30]. Hence HFpEF shows regional dysfunction in the form reduced longitudinal axis function and diastolic dysfunction which could reflect symptoms. But diastolic dysfunction itself may be tolerated up to some extend which varies individually before it becomes symptomatic when GLS reduces beyond certain levels [31].

Patients who develop diastolic dysfunction and subsequently HFpEF are usually old, obese and have co-morbidities like diabetes mellitus hypertension and ischaemic heart disease. These entities may cause microvascular dysfunction as well as muscle fibrosis. As the endocardium of the left ventricle is the most susceptible layer for ischemia and hypertrophy the reduction in longitudinal strain can be identified early using GLS [26,32].

HFpEF patients have reduced GLS value of left ventricle. Thus, this LV systolic dysfunction can be identified using the aCMQ in the above group of patients regardless of whether ischaemia present or not; the longitudinal fibers of the sub endocardium making them more susceptible for ventricular hypertrophy, ischaemia and subsequently abnormal relaxation and contraction [33,34]. In our study all three layers of the myocardium was analyzed using aCMQ which also reveals a

reduction, which raises the possibility of mechanisms other than subendocardial ischaemia and hypertrophy playing a role in this global reduction[31,35]. Thus, to evaluate these possibilities we need more studies.

As patients with only diastolic dysfunction also shows significant reduction in GLS it is possible that patients remain asymptomatic for a certain period before becoming overtly heart failure. This asymptomatic period varies among patients, and whether a range can be calculated for diastolic dysfunction and HFpEF using GLS needs further large group studies. And also, patients who demonstrate diastolic dysfunction and reduced GLS should be considered to be followed up to detect HFpEF earlier. Thus, further studies need to be done in these patients regarding the natural history.

In consideration of the limitation of our study, we could not perform serological markers of heart failure such as BNP or NT-proBNP for the diagnosis as this was expensive and thus not affordable so, our diagnosis of heart failure was made on clinical history, examination, electrocardiography and echocardiography.

Conclusion

In patients with symptoms and signs of heart failure with normal left ventricular ejection fraction, for the diagnosis of left ventricular systolic dysfunction global longitudinal strain can be considered as an important parameter.

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