University Heart Journal
Vol. 20, No. 1, January 2024

ORIGINAL ARTICLE

Evaluation of Subclinical Systolic Dysfunction in Patients with Heart Failure with Preserved Ejection Fraction, Using 2D Speckle Tracking Echocardiography

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Abstract

Background: Originally thought to be purely due to LV diastolic dysfunction, studies according to western countries have suggested that heart failure with preserved ejection fraction (HFpEF) is more complex. In patients with HFpEF, global LV systolic function is commonly considered normal as the global ejection fraction (EF) is normal. However, the EF reflects only the global cardiac contractile function and does not take the subclinical systolic function into consideration. Therefore more attention should be paid on this subset of heart failure population in which the frequency of subclinical systolic dysfunction has not been clearly identified.

Objective: The principal objective of this study was to assess the global longitudinal systolic function of the LV in Bangladeshi patients with HFpEF using from 2D speckle tracking echocardiography.

Methods: This study was conducted from May 2018 to April 2019 in department of cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. A total of 31 patients with HFpEF were enrolled in the study. Detailed history was taken including NYHA functional class, relevant physical examinations and investigations were done. 2D echocardiography, color Doppler, tissue Doppler and 2D speckle tracking echocardiography were done. GLS was obtained in a total of 31 patients with HFpEF diagnosed according to the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure.

Result: All patients with HFpEF had preserved LV ejection fraction (LVEF>50%) and evidence of diastolic dysfunction. Majority of study subjects had reduced GLS when -18% was used as the lower limit of normal as per vendor specific recommendations.

Conclusion: Subclinical systolic dysfunction was frequent in the majority of HFpEF patients. Further large scale studies are recommended to confirm the findings of this study.

Keywords: Heart failure with preserved ejection fraction, subclinical systolic dysfunction, global longitudinal strain, 2D speckle tracking echocardiography (2DSTE).

University Heart Journal 2024; 20(1): 3-9
DOI: https://doi.org/10.3329/uhj.v20i1.78462

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a growing health burden associated with increased morbidity, mortality, recurrent hospitalization and increased cost of health care.

Its prevalence is increasing over the last decade[1]. The increasing contribution of HFpEF may be related with several factors. First, there is a greater awareness that heart failure can occur in individuals with a normal ejection fraction, which may increase the frequency with which

Received: 01 November, 2023 **Accepted:** 15 December, 2023

HFpEF is diagnosed. Second, improved care for patients with acute or chronic ischemic heart disease has decreased the prevalence of reduced LVEF. Third, there is a rising burden of obesity, diabetes mellitus, and physical inactivity, compounded by the aging of the population, all risk factors for HFpEF.[2]

Currently there are no data regarding the exact incidence and prevalence of HF in Bangladesh, but cardiovascular diseases specially heart failure is expected to be one of the major causes of mortality and morbidity due to epidemiological transition from communicable to non-communicable disease.[3] Heart failure with preserved ejection fraction was previously referred to as diastolic heart failure. For nearly half a century, ejection fraction has been the mainstay of the assessment of left ventricular (LV) systolic function. Although ejection fraction has served clinicians well during the last couple of decades, it is only an indirect measure of cardiac function, derived from the change in LV volume. More recently, global longitudinal strain (GLS) derived from speckle tracking echocardiography has been developed, providing a more direct measure of systolic function. GLS is a more sensitive marker of subclinical systolic dysfunction that becomes abnormal earlier than ejection fraction. The inter-observer and intra-observer reproducibility for strain is better than for ejection fraction.[4]

Shah et al. (2014) phenotypically classified HFpEF in to following subtypes: “Garden variety” HFpEF (associated with hypertension, obesity, diabetes/metabolic syndrome, and/or chronic kidney disease), CAD-associated HFpEF, Atrial fibrillation-predominant HFpEF, Right heart failure-predominant HFpEF, Hypertrophic cardiomyopathy induced, Multi-valvular HFpEF and High output HFpEF.[5] Given the constellation of comorbidities that are almost invariably present in patients with HFpEF, the underlying pathophysiology remains subject to debate. Most widely accepted theories include, diastolic dysfunction, abnormal ventricular–arterial coupling, impaired systolic rest and/or reserve function, endothelial dysfunction and inflammation, chronotropic incompetence, altered myocardial and peripheral skeletal muscle metabolism and perfusion, pulmonary hypertension (PH), and renal impairment have been proposed. One other factor is that a preserved EF does not mean imply that systole is normal, and indeed a key set of observations using 2D speckle tracking echocardiography (2DSTE) have suggested that the longitudinal subclinical systolic function of LV is altered in HFpEF and it has favored the name change to HFpEF.

Despite the importance of HFpEF our understanding of its pathophysiology is incomplete. Complete understanding of a disease pathophysiology is vital for its management. Originally HFpEF was thought to be purely due to LV diastolic dysfunction. Moreover, in single syndrome theory, HFpEF precedes HFrEF. Therefore more attention should be paid on this subset of heart failure population in which the frequency of concomitant subclinical systolic dysfunction has not been clearly defined.

Myocardial stain is a principle for quantification of left ventricular (LV) function which is now feasible with speckle tracking echocardiography. It has recently emerged as a novel echocardiographic technique for rapid, offline, bedside analysis of regional LV strains in the longitudinal, radial and circumferential directions. The most widely used and verified strain parameter is global longitudinal strain (GLS). It is more sensitive than LVEF as a measure of systolic function and may be used to identity even subclinical systolic dysfunction of the LV.[6] This technique has been validated with measurements obtained by sonimicrometry and magnetic resonance imaging. The semi-automated nature of speckle tracking echocardiography guarantees good intra-observer and inter-observer reproducibility.[7, 8] Although assessment of GLS is now routine practice in many echocardiographic laboratories, the experience with radial and circumferential strain analyses is that they are not sufficiently reproducible for routine clinical work.[9] For the vendor GE most studies indicate -18% to be the lower limit of normal for the healthy population.[11]

This study would help us to understand more about the characteristics and presence of subclinical systolic dysfunction in patients with HFpEF and help to raise awareness regarding HFpEF and strain imaging. If the use of strain imaging can detect subclinical systolic dysfunction earlier than conventional methods using GLS, it opens up a new perspective in heart failure prevention or progression with institution of therapeutic measures before patients develop irreversible myocardial dysfunction.

Methods

This was a cross-sectional study conducted at the department of cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka from May 2018 to April 2019, after IRB approval (Protocol No. BSMMU/2018/4758). The centre is currently being ranked as one of the top hospitals in Bangladesh. A total of 31 patients with HFpEF diagnosed according to the 2016 European Society of

Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure were enrolled by consecutive sampling in the study. Patients with regional wall motion abnormality in 2D echocardiography, moderate to severe valvular heart diseases, prosthetic valves, pacemakers, congenital heart diseases, those currently having arrhythmia such as atrial fibrillation on ECG screening during enrollment, were excluded from this study.

Study Procedure

The eligible patients were explained about the study, written informed consent was taken and demographic data were recorded. Detailed history was taken. Echocardiography was performed by using Vivid E9 (GE Healthcare, Norway). ECG leads were connected before analysis. LVEF was obtained by Simpson's modified biplane method. The LV mass was estimated by using the area length method and adjusted for body surface area. Echocardiographic LV hypertrophy was defined as an LV mass index> 115 g/m^2 for men and > 95 g/m^2 for women. LV geometry was classified based on relative wall thickness (RWT), defined as (2×diastolic posterior wall thickness)/LV end-diastolic dimension and Left Ventricular Mass Index (LVMi) as recommended by the American Society of Echocardiography (ASE): normal = RWT d" 0.42 and no LVH; eccentric hypertrophy = RWT d" 0.42 and LVH; concentric remodeling = RWT > 0.42 and no LVH; concentric hypertrophy = RWT > 0.42 and LVH. Right ventricular (RV) function was assessed by tricuspid annular plane systolic excursion (TAPSE) and tricuspid lateral annular systolic velocity (S') by pulsed tissue Doppler. Peak pulmonary arterial systolic pressure (PASP) was estimated as the sum of peak RV-right atrial gradient from the tricuspid valve regurgitant jet and right atrial pressure on the basis of size and collapsibility of inferior vena cava. Presence and severity of valvular heart diseases were assessed by color Doppler imaging and image guided pulsed and continuous Doppler studies according to 2014 AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease. Patients with more than mild valvular heart diseases were excluded. Diastolic function parameters were measured as follows: peak early diastolic filling (E) and late diastolic filling (A) velocities, E/A ratio, E deceleration time, early diastolic septal and lateral mitral annular velocity (e'), average E/E', peak TR jet velocity, left atrial volume index. Left atrial volume index was calculated using biplane area–length method from apical four and two chamber views at end-systole from the frame preceding mitral valve opening and was indexed to body surface area. Diastolic dysfunction was classified into three grades according to 2016 ASE/EACVI guidelines.

LV longitudinal strains were analyzed by 2D speckle tracking echocardiography. Cardiac cycles were obtained during a breath hold in end-expiration. Special care was taken to obtain correct view and checking for foreshortening. Endocardial border was traced at end systole, with a frame rate of 50-80/second, from apical long axis, four chambers and two-chambers view. In case of poor tracking, region of interest (ROI) was readjusted. The results of all three planes were combined in a single bull's eye summary, along with a global longitudinal strain value (GLS) for the LV which was automatically calculated by automated function imaging (AFI). Two independent investigators analyzed the echocardiography recordings blinded to clinical data. The intra-observer and inter-observer variability of GLS was assessed from 10 randomly selected patients by intra-class correlation coefficient(R). The R value for intra-observer variability was 0.983 and for inter-observer variability was 0.980. This showed good reproducibility of GLS for both same and different operators.

Statistical analysis

After collection of all information, the data were checked, verified for consistency and edited. Data cleaning validation and analysis was performed using the software SPSS (Statistical Package for Social Science) version 23.0 for Windows. Descriptive statistics were used to summarize data using means and standard deviation. Categorical data were summarized by calculating percentages which were presented as frequency tables and charts. Frequency of subclinical systolic dysfunction was determined by comparing the GLS between study subjects and lower limit of normal cutoff value for vendor GE.

Results

Distribution of patients according to sex: A total of 31 patients with HFpEF were enrolled for this study. Majority of the cases were males with a male: female ratio of 1.8:1.

Age distribution of study subjects: 64.5%

Most subjects were elderly between 61-70 years (51.7%). The mean age was 61.51 ± 10.19.

Study subjects according to BMI: Most of the study subjects were overweight (48.4%). 29% patients were obese and only 22.6 patients had normal BMI.

Comorbidities of study subjects: Majority of the study subjects had multiple comorbidities and risk factors. Most common comorbidity was hypertension; present in 83.9%

of the patients. 67.7% had dyslipidemia, 54.8% had Diabetes Mellitus, 48.4% had previous history of heart failure, 38.7% patients had coronary artery disease, and 35.5% patients had chronic kidney disease. 35.5% patients were smokers and 6.5% patients had history of paroxysmal atrial fibrillation. (Table I)

Table I

Comorbidities of study subjects

Comorbidities	Frequency (n)	Percentage
Diabetes Mellitus	17	54.8
Hypertension	26	83.9
Dyslipidemia	21	67.7
CAD	12	38.7
History of heart failure admission	15	48.4
Paroxysmal AF	2	6.5
CKD	11	35.5
Smoking	11	35.5

Clinical presentation of study subjects: All cases presented with breathlessness and of those, 51.6% of patients presented in NYHA class III. Other presentations were due to fatigue (87.1%) and leg swelling (25.8%). On examination bilateral lung base crepitation was the most frequent sign, found in 93.5% cases. Anemia was found in 51.6% cases. (Table II).

Table II

Clinical presentation of study subjects

Clinical presentation	Percentage
Breathlessness	100.0
NYHA class I	12.9
NYHA class II	35.5
NYHA class III	51.6
Leg swelling	25.8
Fatigue	87.1
Anemia	51.6
Edema	29.0
Raised JVP	6.5
Audible S3	29.0
Lung base crepitation	93.5
Pulse (per min))[Mean ± SD]	96.06 ± 11.04
SBP(mmHg)[Mean ± SD]	144.52 ± 19.47
DBP(mmHg)[Mean ± SD]	90.00 ± 10.95
Mean Respiratory rate(breath/min)	22.48 ± 4.66

Frequency of subclinical systolic dysfunction in study subjects: The mean value of GLS in the study subject's cases was -14.92% ± 3.16. 80.6% of study subjects had reduced GLS when -18% was used as the cutoff value for lower limit of GLS in normal population. (Table III)

Table III

Frequency of subclinical systolic dysfunction in study subjects

GLS	Frequency (n)	Percentage
Reduced	25	80.6
Normal	6	19.4

Echocardiographic findings of study subjects: The mean LVEF was 61.71 ± 5.97. The mean of LAVI was 40.36 ± 4.77. The mean LA diameter and average E/e2 was also elevated. RV systolic function was normal as evidenced by normal TAPSE and S'. (Table IV)

Table IV

Echocardiographic findings of study subjects

Parameter	Mean ± SD
LV structure	
LV mass index (g/m^2)	91.75 ± 22.98
RWT (cm)	0.41 ± 0.12
LV systolic function	
LVEF (%)	61.71 ± 5.97
GLS (%)	-14.93 ± 3.17
LV diastolic function	
E/A ratio	1.23 ± 0.73
Average E/E'	15.95 ± 4.28
LAVi (ml/m^2)	40.36 ± 4.77
TR jet velocity	2.76 ± 0.56
Pulmonary and RV function	
PASP (mmHg)	38.75 ± 11.47
TAPSE (mm)	18.67 ± 4.03
S'(mm)	12.17 ± 2.56

LV geometry of study subjects:

Normal LV geometry was found in majority of HFpEF cases, 41.8% patients. Concentric LV hypertrophy was present in 32.3% of participants, whereas concentric remodeling was found in 19.4% of cases, & 6.5% of patients had eccentric hypertrophy. (Fig 1)

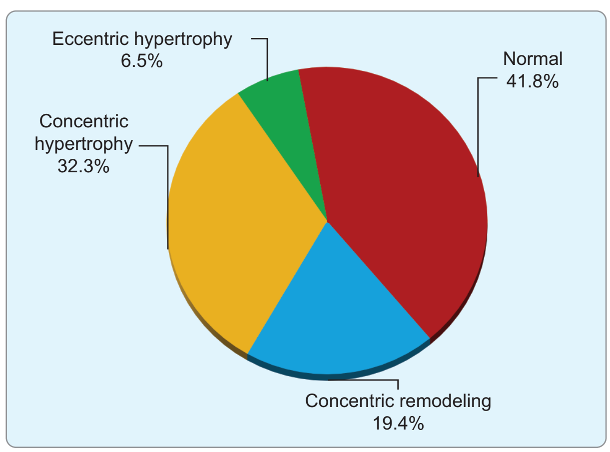

Figure 1: *LV geometry of study subjects*

Subjects according to grade of diastolic dysfunction: All HFpEF cases had some form of diastolic dysfunction. 19.4% patients had Grade I diastolic dysfunction. 61.2% patients had grade II diastolic dysfunction and 19.4% cases had grade III diastolic dysfunction. (Fig 2)

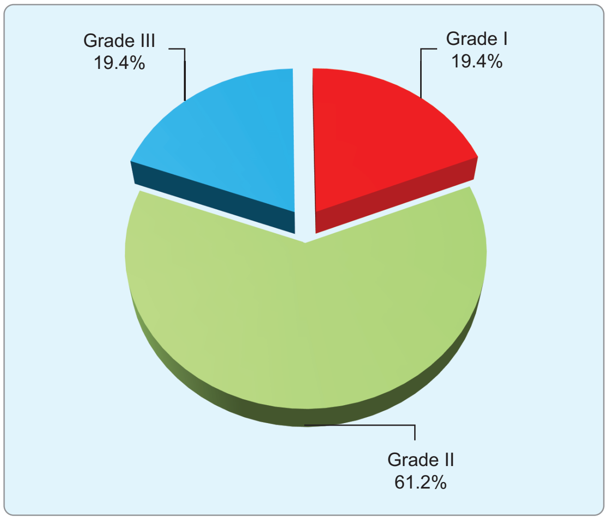

Figure 2: *Subjects according to grade of diastolic dysfunction*

Discussion

In patients with HFpEF, LV systolic function is commonly considered normal as the global EF is normal. However, the EF reflects only the global cardiac contractile function and do not take the subclinical systolic dysfunction into consideration. The principal objective of this study was to assess the subclinical systolic function of the LV of patients with HFpEF using 2D speckle tracking echocardiography.

Although the age distribution of this study is slightly lower compared with other studies, such as ADHERE database[12] and OPTIMIZE-HF registry,[13] majority of the patients with HFpEF were elderly. It shows that HFpEF occurs predominantly in elderly population. The male: female ratio of patients with HFpEF in this study was slightly different compared to other studies with slight male predominance. ADHERE[12] and OPTIMIZE-HF registry[13] both demonstrated female predominance in patients with HFpEF (62% and 68% respectively). The reason for male predominance in this study may be due to difference in population. Majority of the patients with HFpEF were either overweight or obese, and had multiple comorbidities and risk factors, the so called Garden variety phenotype.[5] Most common comorbidity was hypertension, followed by dyslipidemia. Similar trend of obesity was found in Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial[14] and also The Irbesartan in Heart failure with Preserved Ejection Fraction (I-PRESERVE) trial.[15] Internationally, heart failure registries like ADHERE,[12] OPTIMIZE HF[13] and previous studies done in different parts of the world have established that HFpEF occur in elderly, predominantly female patients, with small atrophied hearts and a majority of patients have risk factors such as hypertension, diabetes mellitus, renal disease and atrial fibrillation. Similar to our study, in the TOPCAT trial 60% of HFpEF cases were found to have dyslipidemia.[14] Elderly patients with high incidence of obesity and concomitant presence of CAD, stroke, DM, & renal impairment may explain this high prevalence of dyslipidemia.

All the patients presented with breathlessness and majority of patients presented in NYHA class III. Other presentations were due to fatigue and leg swelling. Symptoms of breathlessness, fatigue and leg swelling are common in clinical practice and may be due to a wide variety of cardiac and non-cardiac diseases in the study population. Bilateral lung base crepitation was the most frequent sign found in patients with HFpEF in this study followed by anemia. Anemia was found to be more common in HFpEF and is considered as a poor prognostic factor[16]. Higher percentage of anemia can be explained by increased number of patients with CKD in our study population. The characteristics of patients with HFpEF have varied widely between different studies due to inconsistency in the diagnostic criteria used across different trials and also due to inherent heterogeneity of the syndrome itself.

Among 31 with HFpEF, 80.6% cases had reduced GLS indicating presence of subclinical systolic dysfunction in majority of these patients. The findings of this study is similar to the study by Kraigher-Krainer et al. (2014) which showed lower LV longitudinal strain despite preserved LVEF in 66.7% patients with HFpEF.[17] The mean LVEF was 61.71 ± 5.97% and none of the patients had LVEF below 50%, which is consistent with study inclusion criteria. In the TOPCAT trial, LVEF $< 50\%$ was found in 13% cases.[14] The average E/E2 was also elevated in this study indicating high LV filling pressure in these patients. In this study, normal LV geometry was found in majority of patients with HFpEF. In the TOPCAT trial LV geometry was altered in 86% cases.[14] This difference may be explained by the slightly lower mean age, higher EF of our study population 61.51±10.19 years. vs 70 ±10 years and higher prevalence of concomitant moderate to severe valvular lesions(14.4%) in the TOPCAT trial. Although concentric hypertrophy is the expected findings of HFpEF, eccentric hypertrophy was found in 6.5% of participants which is consistent with the findings from the TOPCAT signifying the heterogeneity of the HFpEF syndrome.[14] Similar to this study, Kraigher-Krainer et al. (2014) found that majority of the HFpEF cases had normal LV geometry and did not have LV hypertrophy or concentric remodeling.[17] This finding also supports the phenotypic heterogeneity of this complex disease and supports the theory that factors other than diastolic dysfunction might be responsible for the pathophysiology of HFpEF.

2016 ASE/EACVI guideline for the evaluation of left ventricular diastolic function was used for the detection and grading of diastolic dysfunction. All of our patients with HFpEF had some form of diastolic dysfunction. Majority of the patients had grade II diastolic dysfunction. Our findings are similar to that of the PARAMOUNT trial in which the majority of patients demonstrated some echocardiographic findings of diastolic abnormalities at rest.[17]

RV systolic function was normal in this study evidenced by normal TAPSE and S'. In the TOPCAT trial RV systolic dysfunction was present in 4% cases.[14] The reason for this difference may be due to absence of RV failure predominant HFpEF patients in our study population.

The findings of this study indicate that subclinical systolic dysfunction is common among patients with HFpEF and it may be one of the contributing factors proposed for the HFpEF pathophysiology. Assessment of LV GLS using strain imaging in patients with HFpEF detected varying degrees of subclinical systolic dysfunction, despite preserved ejection fraction. Subclinical systolic dysfunction was frequent in the majority of patients with HFpEF. Further large scale studies are warranted to verify the study findings of this study. Further studies can also be carried out to find out if there is any relation with of GLS with BNP/ NT pro-BNP levels or whether GLS can be used as a cost effective prognostic marker or a predictor of clinical outcome in patients with HFpEF. 2D speckle tracking echocardiography gives unique information which may be critically important for patient management and it can be incorporated into routine echocardiographic practice to explore into its vast opportunities with its limitations kept in mind.

Limitations

This was a single center study with small sample size. Patients with current atrial fibrillation were excluded which is one of the most common associations of HFpEF.

Author Contributions : All authors participated in manuscript preparation, revising and drafting.

Conflicts of interest: The authors have none to declare.

Data & Materials: Available from the corresponding author, on reasonable request.

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