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"ROLE OF STRAIN RATE IMAGING OF LEFT VENTRICLE TO ASSESS UNDERLYING SYSTOLIC DYSFUNCTION IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF)"

Cardiology

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ABSTRACT

Introduction: HFpEFis increasing 1% per year when compared to HFrEF with an ageing population and rising risk-factors like hypertension,obesity&diabetes.Endothelial-dysfunction, proteininteractions,signaling-pathways&myocardial-bioenergetics are the suggested pathophysiological causes for HFpEF.2D-STEhas been utilised to identify HFpEF by focusing on the LV-GLS. **Aim:** To assess the predictive value of strain-rate imaging in detecting systolic-dysfunction among patients with HFpEF&Severity of diastolic-dysfunction in relation to the systolic-dysfunction by echocardiography. **Results:** Among 50 patients with HFpEF,majority of patients were in age group 56-65 years.In our observation 46% were hypertensive,32% were diabetic,2% wereobese,2% had OSA,18% had dyslipidemia,12% were hypothyroid,44% of patients were on betablocker therapy,NYHA class II,III,lV breathlessness was in 36%,42%,22% respectively at the time of presentation.We observed E/e' > 15 was noted in 22% patients and 78% had normal LV-filling pressures,40% had mitral E/A ratio 0.8-1.5,48% had mitral E/A ratio <0.8,2% had mitral E/A ratio 1.5 - 2,10% had mitral E/A ratio >2,LA-volume > 40ml in 38% patients and <40 ml in 62% patients.96% had LVEDD of 4.2-5.8 cm& 2% had LV EDD of 5.9-6.3 ,TR velocity was found to be <2.8 m/sec in 98% & 2% had >2.8 m/sec.Average LV-GLS was found to be reduced(<-16%) in 64%,borderline reduced(-16% to -18%) in 24%, >-18% in 12% patients.In HFpEF,both GLS and GCS were related to LVEF(LS,R = −0.46; p<0.0001;CS,R = −0.51;p<0.0001) but not to standard echocardiographic measures of diastolic-function(E' or E/E').Lower GLS was modestly associated with higher NT-proBNP,includingLVEF,measures of diastolic-function and LV-filling pressure. **Conclusions:** HFpEF is a major cause of morbidity and mortality,utility of GLS and GCS is cost-effective way to assess underlying systolic-dysfunction in patients with HFpEF,guides clinician for prognostication and management.

KEYWORDS

GLS(global Longitudinal Strain), HFPEF(heart Failure With Preserved Ejection Fraction)

INTRODUCTION:

In HFpEF, LV systolic-performance is abnormal, regardless of whether preload recruitable stroke-work, stress-corrected endocardial and mid-wall shortening, twisting, or circumferential and longitudinal shortening using Tissue-Doppler or Strain-Imaging are used [1-6]A causal association between metabolic, cardiac co-morbidities and lower LV longitudinal-strain has been established[7]. and HFpEF patients with microvascular-dysfunction have more aberrant systolic mechanics as measured by strain and TDI[8].Coronary microvascular-dysfunction occurs as a result of metabolic comorbidities, may contribute to subendocardial ischemia and LV longitudinal shortening deficits during stress, particularly when myocardial oxygen supply-demand imbalance exists [9]Minor abnormalities in systolic-function at rest become dramatic during exercise, resulting to decreased exercise capacity, impaired early diastolic recoil and LV suction, impaired cardiac-output, and elevated LV filling-pressures [1,3,10-12] Despite the presence of LV diastolic-dysfunction in HFpEF, the failure to increase LV end-diastolic volume, rather than the inability to lower end-systolic volume, limits stroke volume reserve during exertion[10,13,14]due in part to aberrant peripheral Vaso-relaxation, which raises LV after load [1,10,15,16]and also due to LV contractile reserve constraints[1,3,10] leading to worse LV systolic mechanics which predict a higher risk of negative outcomes[2,5] HFpEF accounts for almost half of all heart failure hospitalizations, and has a similar mean survival rate to HFrEF[17]Prevalence of HFpEF ranges from 1.1%-5.5% , with rates as high as 10% in older women[18,19] Hypertension, diabetes, CKD &obesity(Stage A)contribute to early subclinical structural disease (Stage B) which affects 1/4thof the adult population[20].However, the progression of clinical heart failure (Stages C and D) is marked by a wide range of anatomical and functional problems in the heart.

AIM:

To assess the predictive value of strain-rate imaging in detecting systolic dysfunction among patients with HFpEF and Severity of diastolic-dysfunction in relation to the systolic dysfunction by echocardiography.

Objectives:

To study normal/ abnormal GLS, GCS values in HFpEF patients.

Secondary Objectives:

1. To study the differences in demography, other base line characteristics
2. To study NTpro BNP in abnormal GLS, GCS and its significance
3. To assess the predictive value of strain-rate imaging in detecting systolic-dysfunction among patients with HFpEF.
4. Severity of diastolic-dysfunction in relation to the systolic-dysfunction
5. To identify patients already on beta-blocker therapy

MATERIALS AND METHODS:

Study site: Out-patients and in-patients in department of cardiology, Apollo Hospitals, Greams Road, Chennai.

Type of study: Observational study

Duration of study: FEB 2021- DEC 2021

Sampling: Simple random sampling

Sample size: 50 patients

Inclusion Criteria:

1. Patients with HFpEF
2. Patients with signs and symptoms of heart failure (NYHA class II - IV)
3. LVEF>50%
4. LVEDV <97 ml/m2
5. NT-proBNP level >220 pg/mL
6. Baseline ECG in sinus rhythm

Exclusion Criteria:

Patients with HFrEF, ACS, valvular heart disease and infections.

Observations And Results:

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Majority of patients were in age groups 56-60 years and 61-65 years were 16% each and percentage of HFpEF incidence is increasing with age and more in male population(70%).

Study group had variable comorbidities like Hypertension (46%), T2DM (32%), obesity (2%), history of CAD/IHD >6 months (14%), OSA(2%), dyslipidemia(18%), hypothyroidism(12%) as shown in fig 2 and 44% of patients were on beta-blocker therapy 36% had NYHA-ll, 42% had NYHA-lll, 22% had NYHA- lV breathlessness at the time of presentation to OP/IP department.

All patients were in sinus rhythm, screening NTpro-BNP was>220pg/mL &LVEF >50% at the time of presentation.Majority of patients aged more than 50 years had NTproBNP values < 900pg/mL. Males with age <50 years &NTproBNP 220-450 pg/mL are 4%, and > 450 pg/mL are 6%. Males with >50 yrs &NTproBNP <900 are 38%,and >900 pg/mL are 22%. Female with <50 yrs and NTproBNP <450 pg/mL are 2%, and > 450 pg/mL are 4%. Female with >50 yrs and NTproBNP <900 are 20%, and >900 pg/mL are 4%. LVEF was found to be between 50-54% in 32% patients, 55-59% in 28% patients, 60-65% in 16%patients and >65% in 16% patients.

Peak velocity of trans-mitral flow in early diastole by Pulse-wave Doppler was studied and 52% of patients had normal velocities (06-0.8 m/sec), 40% had > 0.8 m/sec and 8% had < 0.6 m/sec velocity. The mitral A-wave (blood flow generated by active atrial contraction) and peak A-wave velocity was increased (> 0.35 m/sec) in 98% patients. e' <0.09 are noted in 84% patients and >/= 0.09 is noted in 16% patients. 22% patients had elevated LV filling-pressures (E/e' > 15) and 78% patients have normal LV filling-pressures. Usually LVEDP is high in patients with HFpEF and systolic-dysfunction. In this study most patients having normal LV filling-pressures can be explained as most of the patients are in stable heart failure stage who attended outpatient and inpatient departments. About 40% patients had mitral E/A ratio 0.8-1.5; 48% patients had < 0.8; 2% patients had1.5 - 2; and 10% of patients had >2.

LA volume >40ml is observed in 38% patients and <40 ml is observed in 62% patients.

96% of patients had normal range LVEDD & LVESD; 98 % patients had normal range LVESV; TR-velocity was found to be <2.8 m/sec in 98% patients; TR-gradient was found to be <32 mm Hg in 98% patients.

Average LV-GLS(change in length of left-ventricle within longitudinal direction relative to its baseline length in 2-chamber ,3-chamber, 4-chamber views) was found to have abnormal strain (<-16%) in 60% patients, borderline reduced(-16%-18%) in 28% of patients, and normal (>-18%) in 12% of patients. GLS is expressed as a negative number

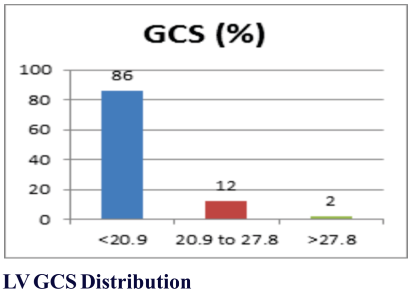

Figure – 1- LV GCS Distribution

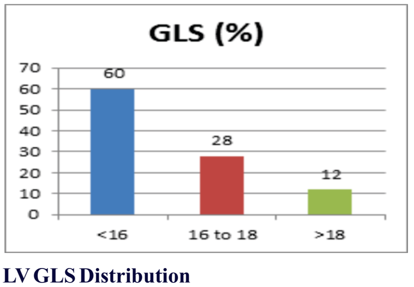

Figure – 2- LV GLS Distribution

Average LV-GCS (change in circumference of left-ventricle within circumferential direction relative to its baseline circumference in 2-chamber ,3-chamber, 4-chamber views) was found to have abnormal-strain (<-20.9%) in 86% patients, borderline-reduced (-20.9% to -27.8%) in 12% of patients, and normal (>-27.8%) in 2% of patients. GCS is expressed as a negative number.LV diastolic-function was normal in 30% patients. 54%patients had grade-l, 8% patients had grade-lland 8% patients had grade-lll diastolic-dysfunction.The systolic-function of left-ventricle is assessed by strain-rate imaging in patients with HFpEF , after comparing the different echo parameters in patients with normal LV-GCS (> -27.8%, 1 patient), borderline LV-GCS (-27.8% to -20.9%, 6 patients), and abnormal LV-GCS(<-20.9%, 43 patients), LVEF> 50% has shown p value of 0.013 .

After comparing different demographic and clinical parameters , it was observed that:

1. The average age for borderline-GLS was 55.4 +/- 12.7 years; for abnormal-GLS 63.9+/- 10.9 years; for normal-GLS 65.5 +/- 5.7 years .
2. 10 males had borderline-GLS,22 males had abnormal-GLS and 3 male patients had normal-GLS even though they were fitting into inclusion criteria.
3. 4 females had borderline-GLS,8 females had abnormal-GLS and 3 female patients had normal-LV GLS.
4. Hypertension is common in abnormal-GLS (16 patients) than borderline-GLS(6 patients)when compared to normal LV GLS(1 patient)
5. Diabetes is common in abnormal-GLS (12 patients) when compared to borderline-GLS(2patients) than in normal-GLS(2 patients)
6. Patients with H/O CAD in the past had abnormal-GLS (7 patients)
7. In hypothyroidism patients , abnormal-GLS (4 patients) is more common when compared to borderline LV GLS (1 patient) and normal LV GLS(0 patient).
8. Dyslipidemia is more common in abnormal-GLS (8 patients) when compared to borderline-GLS(1 patients) and normal-GLS(0 patients)
9. Patients presenting with NYHA class ll,lll,lV breathlessness were subjected to strain-rate imaging which revealed abnormal-GLS and borderline-GLS and normal-GLS in descending order
10. It was observed that heart rate is higher in abnormal-GLS patients (92/min), when compared to borderline LV-GLS patients(78/min) and normal-GLS patients(74/min)
11. The average systolic BP was low in abnormal-GLS patients(112.5 mmHg) when compared to normal-GLS patients(117 mmHg) and borderline-GLS patients(128 mmHg)
12. The average diastolic-BP was low in abnormal-GLS patients(69 mmHg) when compared to normal-GLS patients(74 mmHg) and borderline-GLS patients (76mmHg).
13. eventhough patients are on beta-blockers the abnormal-GLS, borderline LV GLS are more common than normal LV GLS

After comparing the different demographic and clinical parameters , it was observed that :

1. The average age for borderline-GCS was 65.5 +/- 5.7years; for abnormal-GCS it was 60.8+/-11.9years; for normal-GCS patients with average age of 77years.
2. 3,31,1 male patients had borderline, abnormal& normal LV-GCS respectively.
3. 12 females had borderline, abnormal GCS respectively.
4. Hypertension is more common in abnormal-GCS (21 patients) than borderline-GCS(1 patients) and when compared to normal-GCS(1 patient)
5. Diabetes is more common in abnormal-GCS (14 patients) when compared to borderline-GCS(2patients).
6. Obesity s is more common in abnormal-GCS (6 patients).
7. Patients with H/O CAD in the past had abnormal-GCS (6 patients).
8. In hypothyroidism patients ,abnormal-GCS (4 patients) is more common when compared to borderline-GCS(1 patient) and normal-GCS(1 patient).
9. Dyslipidemia is more common in abnormal LV GCS (9 patients).
10. Patients presenting with NYHA class ll,lll,lV breathlessness were subjected to strain rate imaging which revealed abnormal-GCS and borderline-GLS and normal-GCS in descending order
11. It was observed that heart rate is higher in normal-GCS patients (92/min) when compared to borderline-GCS patients(74/min) and abnormal-GCS patients (87/min).
12. The average systolic-BPwas low in normal-GCS patients(110

mmHg) when compared and borderline-GCS patients (117 mmHg) and abnormal-GCS patients(117.5 mmHg).

13. The average diastolic-BP was low in normal-GCS patients(70 mmHg) when compared to and borderline-GCS patients (74.7 mmHg) and abnormal-GCS patients(71.5mmHg).
14. Eventhough patients are on beta blockers abnormal-GCS is more common than borderline-GCS and normal-GCS

Left ventricular longitudinal and circumferential strain rate imaging was done andthe following observations are noted :

1. All patients had elevated screening NTpro BNP (> 220 pg/mL)
2. The average NTproBNP in normal LV GLS (>-18%) is 444.8 + 221.1 pg/mL ,in borderline LV GLS (-16% to -18%) is 673.29 + 574.8 pg/mL, in abnormal LV GCS (<-16%) is 3429.3 + 7064.6 pg/mL
3. The average NTproBNP in normal LV GCS (> - 27.8 %) is 2144 pg/mL, in borderline LV GLS (-20.9% to -27.8%) is 444.8 + 221.1 pg/mL, in abnormal LV GCS (<-20.9 %) is 2562 + 6023.7 pg/mL
4. NTproBNP values proportionally increased with abnormal GLS,GCS and p-value is 0.222 and 0.697 respectively.

In this study of 50 patients with HFpEF,

1. Diastolic-function was normal in 15 patients; Grade-l,II,III diastolic-dysfunction was noted in 27, 4,4 patients respectively.
2. In patients with normal-GLS, grade l diastolic-dysfunction was commonly observed.
3. In patients with borderline-GLS, grade l diastolic dysfunction was more common than normal diastolic-function followed by grade ll diastolic-dysfunction.
4. In patients with abnormal-GLS grade l diastolic-dysfunction was more common than normal diastolic function followed by grade ll diastolic-dysfunction and grade ll diastolic-dysfunction
5. In patients with normal-GCS , grade l diastolic-dysfunction was commonly observed
6. In patients with borderline-GCS grade l diastolic-dysfunction was more common than grade ll and grade lll diastolic-dysfunction
7. In patients with abnormal-GCS grade l diastolic-dysfunction was more common than normal diastolic function followed by grade ll diastolic-dysfunction and grade ll diastolic-dysfunction

DISCUSSION:

In this observational study of 50 patients with HFpEF, incidence is more in males, increasing with aging and majority of patients were in age group 56-65 years. In study conducted by Voigt[21], the typical values of LV GLS varied from –15.9% to –22.1% (mean 19.7%, 95% CI 20.4 % to 18.9%) in a comprehensive meta study involving over 2500 healthy volunteers(mean age 47.11 years, 51 percent male).

LVEF was found to be between 50-60% in 66% patients, 61-70% in 32% patients and >70% in 2% patients. Study conducted by Stokke concluded that "LVEF does not reflect intrinsic myocardial contractility, it can be normal in the midst of compromised LV systolic function" [22]. Furthermore, "LVEF is extremely load dependent and has significant intra and inter observer variability" [23] and was demonstrated by Barbier.

The Peak velocity of trans-mitral flow in early diastole by Pulse-wave Doppler was studied and 42% of patients have normal velocities (06-0.8 m/sec), 40% of patients have > 0.8 m/sec velocity and 18% of patients have < 0.6 m/sec velocity. The mitral A wave (blood flow generated by active atrial contraction) and peak A-wave velocity was increased > 0.35 m/sec) in 98% patients.

Several other studies also have found that patients with HFpEF have lower global or localized systolic peak-velocities[24, 25]. In patients with HFpEF and LVH, Yip et al [26] found LV systolic-dysfunction as evaluated by TDI of mitral annular peak-velocity and amplitude. In patients with HFpEF, Wang et al. discovered a reduction in LV-longitudinal and radial strain. Recent research suggests that early in the illness process, myocardial mechanics can predict the progression of heart failure phenotypes. However, the progression of clinical heart failure (Stages C and D) is marked by a wide range of anatomical and functional problems in the heart.

Elevated LV filling pressures (E/e' > 15) are noted in 22% patients and 78% patients have normal LV filling pressures. 40% patients had mitral E/A ratio 0.8-1.5; 48% patients had mitral E/A ratio < 0.8; 2% patients had mitral E/A ratio 1.5 - 2;10% of patients had mitral E/A ratio >2. LA volume >40ml is observed in 38% patients and <40 ml is observed in 62% patients. In a study conducted by Georgievska-Ismail L[27] shown that Diabetes predicts a poorer LA reservoir and contractile strain independently, implying that "glycated end products accumulate and metabolic alterations lead to considerable LA-dysfunction" [27] Study conducted by Konerman MC [28], shown that "LA myocardial mechanics may be more susceptible to coronary microvascular disease than LV myocardial-mechanics" [28] We observed that 96% of patients had LVEDD of 4.2-5.8cm & 2% had LVEDD of 5.9-6.3 TR-velocity was found to be <2.8 m/sec in 98% patients & 2% patients had >2.8 m/sec.

TR-gradient was found to be <32 mmHg in 98% patients & 2% patients had >32 mmHg.

Average LV-GLS was found to be reduced (<-16%) in 64% patients, borderline reduced (-16% to -18%) in 24% patients, and normal (>-18%) in 12% patients. The aged, as well as male patients appear to have more diminished LV-GLS [29] in a meta-analysis conducted by Ying et al.

Study conducted by Yu CM, the GLS differs significantly among patients with HFpEF and is linked to age, comorbidities (IHD, T2DM, hypertension, obesity), and all of which can lower the GLS value [24] LV diastolic-function was assessed and found to be normal in 30% patients. 54%, 8%and 8% of patients had grade l, II, III diastolic dysfunction respectively. Studies conducted by Savji N[30]von Bibra[31] Kitzman[32] shown that "although diastolic-dysfunction is important in HFpEF, it is also vital to recognize that LV relaxation and compliance deteriorate with age,cardiometabolic comorbidities[30-32].

Studies conducted by Nayor M[33],Shah[34] demonstrated that "Not all diastolic-dysfunction patients have or will develop clinical HFpEF"Study conducted by kraigher[35],the HFpEF patients had evidence of diastolic dysfunction. Compared to both normal controls and hypertensive heart disease patients,HFpEF patients demonstrated significantly lower GLS(−20.0± 2.1 and −17.07 ± 2.04 vs. −14.6 ± 3.3, respectively, p < 0.0001 for both) and GCS (−27.1 ± 3.1 and −30.1 ± 3.5 vs. −22.9 ± 5.9, respectively; p < 0.0001 for both).

In HFpEF, both LS and CS were related to LVEF(LS, R = −0.46; p< 0.0001; CS, R = −0.51; p< 0.0001) but not to standard echocardiographic measures of diastolic-function (E' or E/E'). Lower LS was modestly associated with higher NT-proBNP, even after adjustment for 10 baseline covariates including LVEF,measures of diastolic function, and LV filling pressure (multivariable adjusted p = 0.001).

According to Donal[36,37] the incidence of hospitalizations for HF and deaths was high and E/e′ predicted adverse clinical outcomes. These observations should help in the risk stratification and therapy of HFpEF.

In patients suffering from HFpEF, the combination of enlarged LA and elevated estimated pulmonary pressure has a strong prognostic impact that defines a specific high-risk phenotype of HFpEF.

In studies conducted by Stamphel [38] &Pellicori [39] 76% and 37% of patients were women with mean age of 60+/- 1 year and 78+/-10 years respectively.

In some studies the abnormal-GLS cut off was considered as -16. [25],[40],[41],[36],[42] Biering-Sorensen[43] conducted a study and Higher CS/LS ratio was predictive of elevation in PCWP with exercise patients during exercise

CONCLUSION:

HFpEF is a major cause of morbidity and mortality, utility of GLS and GCS is cost effective way to assess underlying systolic dysfunction in patients with preserved ejection fraction, guides clinician for prognostication and management.

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