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Original Research Article

A study of right ventricular structure and function in patients with heart failure with preserved ejection fraction

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ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is now considered as distinct syndrome. Epidemiological studies have observed its prevalence to be about 50% among the heart failure patients. Heart failure with reduced ejection fraction (HFrEF) there is an eccentric ventricular remodeling whereas, in HFpEF there is concentric remodeling. The steeper end-systolic pressure– volume relationship is steeper leading to a marked sensitivity to volume changes. There is also a substantial drop in blood pressure with vasodilator therapy. Right ventricular (RV) structure and function show chronic changes. The present study was carried out to find out the changes in RV structure and function over time in patients with HFpEF using established echocardiographic parameters.

Materials and Methods: The longitudinal study was carried out on a convenience sample of 100 patients with heart failure and having preserved ejection fraction. Patients were managed as per the standard guidelines of ESC heart failure management. The outcome variables like systolic blood pressure, diastolic blood pressure, heart rate, NYHA functional capacity class, number of re-hospitalizations for heart failure during the study period and cardio-vascular mortality were measured at baseline and at 12 months. Apart from routine investigations, transthoracic echocardiography was performed. Descriptive statistics was used to present the data. Data analyis was done using GraphPad Prism 7.0 (trial version).

Results: Majority of patients of HFpEF were between 71-80 years of age. Systemic hypertension was the commonest co-morbidity. 58% patients were in NYHA functional class I and 28% patients had NYHA class IV. 23% patients had RV dysfunction at baseline based on the fractional area change criteria with FAC < 35%. The incidence of RV dysfunction for follow up period of one year was 7.8. RV dysfunction defined as FAC<35% was present in 23 patients at baseline and increased to 29 patients at the end of follow up. Also, there was an increase incidence of atrial fibrillation (from 32 to 43%).

Conclusion: Right ventricular dysfunction marked by a significant structural and functional deterioration is an important pathophysiological aspect in patients with HFpEF.

1. Introduction

Heart failure (HF) is a complex clinical syndrome and is a consequence of structural and functional impairment of ventricular filling or ejection of blood. It remains an important health burden in both developed as well as developing nations. Recent data indicates that estimated worldwide prevalence of HF is around 37.7 million and it is projected by the end of the next decade, the number of HF patients would increase by another 25%.[1] In India,

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accurate epidemiological data regarding heart failure is lacking, however, there are multiple smaller registries which have focused on HF epidemiology in various regions in India. Huffman and Prabhakar in their study have estimated that the prevalence of heart failure in India due to coronary heart disease, hypertension, obesity, diabetes and rheumatic heart disease is in the range from 1.3 to 4.6 million, with an annual incidence of 0.4–1.8 million.[2] In the Indian contex, the incidence of HF varies from 1.3 to 23 million. Heart failure with preserved ejection fraction (HFpEF) which was initially known as diastolic heart failure is now considered as distinct syndrome but it has the signs and symptoms of HF. Though diastolic dysfunction is prevalent in most patients of HFpEF, there is definite transition between mere diastolic dysfunction and HFpEF. It comprises almost half the HF population making it a distinct entity.[3] The end-systolic pressure–volume relationship in HFpEF is steep and more so there is a marked sensitivity to volume changes. The blood pressure drops substantially with vasodilator therapy.[4] LV diastolic dysfunction has a basic role in the pathophysiology of HFpEF. Elevated filling pressures lead to dyspnea, impair exercise capacity, increase risk for HF hospitalization, and decrease survival in HFpEF.[5–7] The diagnostic evaluation is much more challenging, given that the ejection fraction is normal and therefore similar to that of patients with non-cardiac dyspnea. The diagnosis fundamentally depends on the demonstration of evidence of congestion or high filling pressures.

The Trivandrum Heart Failure Registry (THFR) has reported that HFpEF accounted for about 25% of the total HF burden. Thus, in Indian clinical practice, it is a fairly common type of heart failure.[8] Globally, about one-half of patients with heart failure have a preserved ejection fraction (HFpEF) and proportion of cases with HFpEF are ever increasing.[9] Compared to heart failure with reduced ejection fraction, outcomes are poorer in HFpEF. Traditionally thare has been a focus on the pathological changes affecting the left ventricle in HFpEF. Some recent studies have shown that, a significant number of patients also display right ventricular dysfunction (RVD).[10] Robust data regarding natural history, predictors and prognostic impact of RVD in HFpEF is lacking and current evidence is based exclusively on cross sectional studies.[6–9] Characterization of the natural history of right ventricular (RV) structure and function in HFpEF using appropriate and easily accessible investigations, finding the underlying mechanisms and risk factors causing right ventricular disease is necessary to supplement the pathophysiological understanding. This will lead to formulate the strategies for its treatment and prevention. With this background the present study was carried out to find out the changes in RV structure and function over time in patients with HFpEF using established echocardiographic parameters to characterize the incidence of RVD.

2. Materials and Methods

The longitudinal study was carried out on a convenience sample of 100 patients with heart failure with preserved ejection fraction in the Department of cardiology, MKCG Medical College, Berhampur from March 2019 to February 2020. The baseline study parameters and the parameters at 12 month were recorded. Systolic blood pressure, diastolic blood pressure, heart rate, NYHA functional capacity, number of re-hospitalizations for heart failure were the outcome variables. The associated cardio-vascular mortality were also observed. Patients of either gender and age with diagnosed heart failure and preserved ejection fraction as per the ESC Guidelines (2016)[11] and willing to participate were included in the study. Patients co-existing with valvular heart disease, congenital heart disease or patients who are planned for or require surgical intervention for management of heart failure, with pulmonary disorders such as chronic obstructive airway disease, bronchial asthma, pericardial effusion, constrictive pericarditis, high output heart failure, with acute coronary syndrome were excluded. For the present study, a diagnosis of HFpEF was made using ESC criteria (2016). Patients with symptoms and/or signs of HF and normal LVEF (>50%) and elevated levels of natriuretic peptide (BNP ≥ 35 pg/mL and/or NT-proBNP ≥ 125 pg/mL) plus an objective evidence of other cardiac functional and structural alterations underlying HF such as demonstration of left ventricular hypertrophy or left atrial enlargement and/or presence of diastolic dysfunction were diagnosed as HFpEF. Patients were managed as per the standard guidelines of ESC heart failure management. Systolic blood pressure, diastolic blood pressure, heart rate, NYHA functional capacity class, number of re-hospitalizations for heart failure during the study period and cardio-vascular mortality were the outcome variables measured at baseline and at 12 months. Apart from routine investigations, transthoracic echocardiography was performed according to the American Society of Echocardiography guidelines using Philips HD7 XE machine with a 3.5 MHz transducer including second harmonic and tissue Doppler imaging technology. Conventional M-mode and two-dimensional echocardiography from a left parasternal, apical and RV focused windows were done. Descriptive statistics was used to present the data. Data analyis was done using GraphPad Prism 7.0 (trial version). The study was approved by the Institutional Ethics Committee of MKCG Medical College, Berhampur (Approval No. 666). Informed consent was obtained from the study participants before including them in the study.

3. Results

The study included patients diagnosed with HFpEF and on medications for heart failure. Out of 100 patients 53

patients were females and 47 were male. 72 patients were from age group 71-80 years. 32% of the study participants had BMI in range 26-30 kg/m^2. Systemic hypertension was the commonest co-morbidity observed in 88% of cases. On NYHA scale 58% patients were in functional class I and 28% patients had NYHA class IV. RV dysfunction was defined using fractional area change criteria (FAC) and patients with FAC < 35% were considered to have RV dysfunction. Using this definition 23% patients had RV dysfunction at baseline. [Table 1] Dyspnea was the most common symptom (78%) followed by orthopnea (54%), palpitations (32%) and chest pain (26%). Raised jugular venous pressure was observed in 32% cases followed by presence of rales on chest auscultation in 29%. [Table 2] Evidence of left ventricular hypertrophy by ECG was found in 40% patients where as atrial fibrillation was observed in 32% patients. Commonly used medications were beta blockers, being used by 76% patients followed by renin angiotensin aldosterone blockers in 63% patients and diuretics in 40%. 58% patients had normal chest x-ray. Though cardiomegaly is not a feature of HFpEF, 8% of patients had mild cardiomegaly determined by cardio-thoracic ratio. 9% patients had severe mitral regurgitation and 3% patients had severe tricuspid regurgitation at baseline.

After follow up period of 1 year, total 6 patients were found to have developed RV dysfunction. There was no improvement in patients who had RV dysfunction at baseline. So, in this study incidence of RV dysfunction for follow up period of one year was 7.8. [Table 3] At the end of one year follow up, there was an increase in the number of patients with atrial fibrillation (from 32 to 43%), left ventricular ejection fraction reduced and at the end 9 patients had LVEF <50% which was below the diagnostic criteria for HFpEF. Patients with NYHA class IV symptoms reduced from 28 to 21. Patients with severe mitral regurgitation increased from baseline 9 to 12 at the end of follow up. There was an increase in number of patients with severe tricuspid regurgitation which increased from 3 at baseline to 16 at the end of follow up. Mean pulmonary artery pressure (calculated indirectly from RV peak systolic pressure) had modest increment, with mean PAP > 40 mmHg in 16 patients at baseline to 19 patients at follow up. Finally, RV dysfunction defined as FAC<35% was present in 23 patients at baseline and increased to 29 patients at the end of follow up. [Table 4]

4. Discussion

The present study was carried out on patients diagnosed with heart failure with preserved ejection fraction. Traditionally, studies have focused on left ventricular function only. There are very few studies which have

Table 1: Clinico-demographic profile of study participants

Parameter	**N=100**
Gender	
Male	47
Female	53
Age (in years)	
Less than 20	0
21-40	0
41-60	26
61-80	72
81-100	2
BMI (kg/m2)	
Less than 20	4
21-25	10
26-30	32
31-35	30
36-40	20
41-45	3
46-50	1
Co-morbidities	
Diabetes mellitus	31
Hypertension	88
CKD	16
CAD	30
NYHA class at baseline	
I	58
II	8
III	6
IV	28
Right ventricle functional area change	
FAC < 35	23
FAC > 35	77

Table 2: Frequency of presenting symptoms and signs in patients with HFpEF

Symptom	**Frequency (N=100)**
Dyspnoea	78
Orthopnoea	54
Palpitation	32
Chest Pain	26
Raised JVP	32
Pedal Oedema	21
LVS3	8
Rales	29
Hepatomegaly	6

Table 3: Incident Right ventricular dysfunction (RVD) at follow up

Category	**Frequency (N=100)**
No RVD at baseline	77
RVD at baseline	23
Incident RVD	6
Total patients with RVD	9

Table 4: Parameters at baseline and at 1 year of follow up

Parameter	Baseline (N = 100)	1year followup (N = 100)
Atrial fibrillation	32	43
LVEF < 50%	0	9
NYHA IV	28	21
Severe MR	9	12
Severe TR	3	16
Mean PAP > 40 mmHg	16	19
RV dysfunction	23	29

*LVEF = Left ventricular ejection fraction, MR = Mitral Regurgitation, TR = Tricuspid regurgitation, PAP = Pulmonary arterial pressure.

been done to find out right ventricular structure and function changes in HFpEF patients. Patients with HFpEF display significant decline in RV systolic function that is driven by adverse right ventricular remodelling and dilatation evident from echocardiographic parameters. The longitudinal changes in right heart structure and function greatly exceed corresponding changes in the left ventricle. At baseline 23 patients had right ventricular disease (RVD) and out of total 77 patients who did not have right ventricular (RV) dysfunction at baseline, 6 patients developed the same at the end of 1 year indicating the incidence of RV dysfunction 7.8% per year and total prevalence of RVD in this study as 29 %. These results are consistent with study done by Melenovsky et al[12] in which they found prevalence of RVD as high as 32%. In this study as well, the patients developed persistent arterial fibrillation during the follow-up period, this was also associated with incident RVD. This was possibly attributed in part to a greater biatrial dilation and worsening of tricuspid insufficiency. Other parameters like pulmonary artery systolic pressure, RV basal dimension, RV length, RV fractional area change (FAC), LVEDD and LVEF also were associated with RVD. Similar to our study, in this study transmitral early diastolic flow velocity "E" was not significantly associated with RVD. In another study by Mohammed et al[13] it was observed that age, atrial fibrillation, heart rate, LAVI, systolic blood pressure and presence of moderate to severe TR were significantly associated with presence and severity of RVD. In a metanalysis of 38 studies which had evaluated RV dysfunction in HFpEF by Gorter et al[5] the overall prevalence of RV dysfunction was 28% which is almost similar to prevalence of RVD in our study which is 29%. In this metanalysis regarding the strong predictors for the development of RV dysfunction found that male sex, atrial fibrillation, coronary artery disease and obesity were led to the development of RV dysfunction. Thus, atrial fibrillation, BMI, CAD and male sex has strongest prediction potential for development of RVD. In the present study it was observed that there was no improvement in the study parameters with the use of medications like RAAS blockers, beta blockers, diuretics and on mineralocorticoid receptor antagonists. Other studies have also made a similar observation.[7,9,12] 11 patients developed atrial fibrillation after enrollment in the study. The LVEF fraction was significantly reduced in some patients with as many as nine patients has LVEF less than 50% at the end of study indicating a transition towards HFrEF. There was some improvement in NYHA class IV symptoms which is likely due to the use of diuretics and control of other co-morbidities. Mean NYHA class in patients with no RVD was 1.5 in opposed to 3.6 in patients with RVD (p value <0.001). Progression of MR and TR occurred in significant number of patients and significantly more patients had severe MR and TR at the end of study. Mean pulmonary artery pressure was calculated from RVSP and it was found that patients with mPAP of > 40 mm Hg indicating moderate pulmonary hypertension increased from 16 to 19 suggesting that though predominant cause of RVD is indeed development of pulmonary hypertension but it does not explain all cases of RVD. Larger studies need to be done to find out the contribution of intrinsic RV abnormalities or other factors for development of RVD in HFpEF patients. There was statistically significant impact on number of hospitalizations for heart failure, the data was obtained based on clinical history and past hospital records during one year follow up period. It was observed that patients who ultimately developed RV dysfunction had more frequent hospitalizations for heart failure (HHF). Mean HHF for patients without RV dysfunction was 0.7 per patient as opposed to 3.5 per patient in patients with RV dysfunction (p value < 0.001). In our study the presence of AF, higher body weight (BMI), CAD, adverse haemodynamics including higher LV filling pressures and PA pressures, RV dilation (inferred by echocardiographic parameters) at baseline were independently associated with development of RVD. This leads to the conclusion that, HFpEF patients with more advanced disease are more likely to develop incident RVD over time. Moreover, RVD can be considered to be an indicator of greater disease progression in the HFpEF syndrome. Pulmonary hypertension is commonly associated with HFpEF and associated with worse symptoms and deterioration of HF. The right ventricle is highly sensitive to afterload, RVD in HFpEF may be due to associated PH. Obesity is highly prevalent in HFpEF. It is considered to be one of the important causative factors for development of RVD. In our study we have evaluated impact of BMI on development of RVD. In this study it was observed that greater BMI is associated with incident RVD in HFpEF. Obesity and increased adiposity worsens RV function, possibly through expansion of plasma volume, RV remodelling, inflammation, or by enhancing ventricular interdependence.[14] Coronary disease is also associated with poor outcomes in HFpEF. It is observed to be associated

with prevalent RVD in cross sectional HFpEF studies.[15] In our study we observed that CAD is a predictor of the development of RVD in HFpEF, even in the absence of clinically-evident myocardial infarction. This data suggests that ischemia, whether due to epicardial or microvascular coronary disease, might also contribute to RVD and LV dysfunction as well which was seen as some patients at the end of study had LVEF less than 50%. Revascularization may preserve LV function in such cases and transition from HFpEF to HFrEF can be prevented or at least delayed.

One of the important causes for high left sided filling pressures in HFpEF is presence of atrial fibrillation and it is independently associated with exercise intolerance, and increased mortality. Prevalent AF at baseline was associated with incident RVD in HFpEF This finding confirms and extends upon the data from other cross-sectional studies.[16] Elevation in left heart filling pressure in AF adversely affect the RV structure and function by increasing the pulsatile load to the right ventricle, inducing pulmonary vascular disease. In the present study, AF was associated with incident RVD independent of RVSP. This suggests that the effects of AF on RV function are due to a loading dependent mechanism. An observation in this was that the development of new persistent AF was strongly associated with incident RVD in patients with HFpEF. Rhythm irregularity, tachycardia, neurohormonal activation, and microvascular dysfunction, annular dilation secondary to AF might decrease basal RV contractile performance independent of PH. More trials to evaluate whether restoring and maintaining sinus rhythm can prevent RVD or improve RV function in people with HFpEF are essential. This will provide insights to new treatment strategies, particularly when no drugs to date have shown any promising benefits.

Apart from smaller sample size and short follow up period for a prospective study the most important limitation of our study is not using the hemodynamic data which could have introduced objectivity in our findings. Another limitation is not using the recently published ESC HFA-PEFF 2019 criteria for diagnosis of HFpEF. As when this algorithm was published participants had already been enrolled. Because of very few mortality events the initially planned objective to evaluate the impact of RV dysfunction on mortality could not be achieved. Some referral bias might have influenced the selection of patients, as study was conducted at tertiary care institute where only highly symptomatic were referred.

5. Conclusion

In HFpEF focus has been on LV structure and function, more so on LV diastolic dysfunction, our study in consonance with recent studies support the notion that right ventricular dysfunction is an important pathophysiological aspect in patients with HFpEF. There occurs significant deterioration of parameters related to right ventricular structure and function. Evaluating and monitoring of echocardiographic parameters for assessment of RV structure and function and attempts at restoration of sinus rhythm in AF patients may benefit HFpEF patients.

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7. Conflicts of Interest

No conflicts of interest.

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