Original article:

A Profile of Heart Failure with Preserved Ejection Fraction in a Teaching Hospital

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Abstract:

Objective: Heart failure with preserved ejection fraction (HFPEF) is fast becoming an important public health issue. Nearly fifty percent of all heart failure cases are due to HFPEF. There are many associated comorbidities has been associated with this condition which may be pathophysiologically related. There is no specific treatment yet. The focus remains on symptomatic treatment of heart failure along with carefully managing the associated conditions. The present study was aimed at analyzing the comorbidities in HFPEF in a tertiary care centre. ***Method:*** Patient diagnosed with heart failure were echocardiographically analyzed. Those showing diastolic dysfunction on tissue Doppler imaging were diagnosed as HFPEF. Patients with chronic obstructive pulmonary disease, valvular heart disease, constrictive pericarditis, restrictive/ hypertrophic cardiomyopathy and sepsis related diastolic dysfunction were excluded. One hundred such patients fulfilling the inclusion and exclusion criteria were enrolled. Plasma B type natriuretic peptide(BNP) level was assayed in all participants. Institutional Ethics Committee approval was taken beforehand. Written informed consent was taken from each patient. ***Result:*** The mean age of the patients in the study group was 63.06yrs. HFPEF was more common in females(62%). The common comorbidities observed were hypertension(82%), high body mass index (80%),anaemia (76%), hyperlipidemia (30%) diabetes mellitus(28%). The plasma BNP was elevated in all except 2 patients. The BNP level was higher in those with higher left atrial size and those showing more severe diastolic dysfunction on tissue doppler imaging. Conclusion- HFPEF can be diagnosed clinically with the help of echocardiography. Plasma BNP level assay may be done when diagnosis is in doubt. The patients with HfpEf are heterogeneous and treatment need to be individualized depending on the associated comorbidities. Further studies with larger sample size are required to define the profile of this disease.

Keywords: Diastolic dysfunction; Tissue doppler imaging; heart failure with normal ejection fraction; BNP

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Introduction

Heart failure is a clinical syndrome that results from structural or functional dysfunction of the heart. The impaired ventricular filling or ejection of blood turn leads to the cardinal symptoms of heart failure e.g dyspnoea, fatigue, oedema and lung crepitations[1]. Heart failure is a problem worldwide especially in the elderly individuals with more than 26 million peoples

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affected[2].This is attributed to increased longevity of life, increasing incidence of diabetes, obesity, hypertension and heart disease[3]. It is becoming a significant public health issue as it carries a high economic burden especially due to hospitalization expenses. Heart failure once thought to arise primarily in patients of reduced ejection fraction but epidemiological studies in the community shows that heart failure with preserved ejection fraction (HFPEF) accounts for almost half of the cases[4].The prevalence of HFPEF has shown an increment in the last 15 years but mortality remains unchanged by this disorder. These patterns underscore the significance of this developing general medical issue and the pressing need to characterize particular treatment for this element[5].

Diastolic dysfunction (DD) on the basis of history, clinical examination, electrocardiography(ECG), chest radiography it is difficult to differentiate it from systolic dysfunction. It can be diagnosed invasively by cardiac catheterization, or noninvasively by Doppler echocardiography and supported by measurement of serum B-type natriuretic peptide(BNP) level. This study was undertaken to study the clinical profile of patients with HFPEF on the basis of signs-symptoms, trans-thoracic echocardiography and plasma brain natriuretic peptide level.

Methods

The study was conducted in the department of Medicine of a tertiary care hospital. All the patients presented with a clinical diagnosis of heart failure on basis of Framingham's criteria were taken up for the study. The patients with left ventricular ejection fraction (LVEF) ≥ 50% in absence of left ventricular dilatation were included. Patients with chronic obstructive pulmonary disease, valvular heart disease, constrictive pericarditis, restrictive/ hypertrophic cardiomyopathy, sepsis related diastolic dysfunctions were excluded. Such one hundred consecutive patients fulfilling the inclusion and exclusion criteria were the participants.

The informed written consent was taken from each participant before enrolment into the study. Apart from demographic details, detailed history, physical examination was done as per the approved pro-forma. Routine blood test, electrocardiography and X-ray chest was obtained. All the patients were subsequently submitted to detailed 2D/Doppler echocardiography study using EPIQ 7 Philips adult 4D Echo machine using sector probe of frequency range between 3-5 Hz. Ejection fraction was calculated by Modified Simpsons method[6]. Plasma BNP was estimated by automated quantitative ELFA (Enzyme-Linked Fluorescent Assay) technique. As per the European Society of Cardiology(ESC) guidelines plasma BNP level >35pg/ml is considered as elevated[7]. But a higher cut off level of 100pg/ ml increases the diagnostic accuracy substantially[8]. Hence the patients were subclassified into 2 groups i.e BNP level <100pg/ml and ≥100pg/ml. In the present study tissue doppler echocardiography was done to assess diastolic dysfunction. It is measured as a ratio between early mitral valve flow velocity(E) and early diastolic lengthening velocity(E'). In presence of diastolic dysfunction E will increase because of elevated filling pressure and E' will be low because of impaired relaxation. Normally E/E' is <8, left atrial pressure is normal and diastolic dysfunction is unlikely[9].

Ethical clearance: The protocol was approved by the Institutional Ethics Committee.

Results

The patients with clinical features of heart failure and an ejection fraction of ≥50% without ventricular dilatation were enrolled. Out of one hundred patient with HFPEF studied 44(44%) were in the age group <60 years and fifty six patients were 61 years or older. Majority (62%) patients were females. Body mass index (BMI) was within the normal range in 20 patients, whereas 80(80%) were overweight or obese (BMI graded according to WHO classification, <25kg/m^2 is normal weight, 25-29.9kg/m^2 is

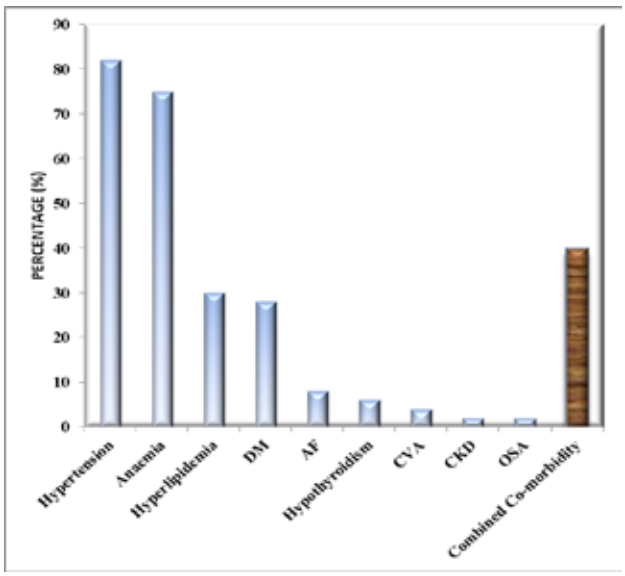

Figure1-Comorbidities in the patients studied

overweight, ≥30 kg/m^2 is obese). Besides obesity other comorbities analysed were as presented in the figure1. Most of the patients (82%) were hypertensive, 28% were diabetic, 76% were anaemic (anaemia was defined as per WHO classification, <13g/dL in men and <12g/dL in non-pregnant women), 8% had atrial fibrillation.

The Trans thoracic echocardiographic findings are given in table1. Left atrial enlargement was a common finding with a mean LA size of 39.86mm. The diastolic dysfunction was also measured by tissue Doppler echocardiographic imaging analysis of E/E'. This parameter is derived by mitral valve inflow velocity divided by early diastolic lengthening velocity(10). A normal E/E' of <8 suggests normal left atrial pressure.

Table1- Echocardiographic Findings

Echo parameters	Mean±SD
LA	39.86 ± 5.97 mm
Aorta	27.44 ± 4.67 mm
LVID d	42.72 ± 7.30 mm
LVID s	27.54 ± 5.2 mm
EF	58.78 ± 2.78 %
E/E'	15.49 ± 6.1

LA- Left atrium, LVID d- Left ventricular internal diameter in diastole, LVID s- LV internal diameter in end systole, EF- Ejection fraction, E/E'- ratio between early mitral valve flow velocity and early diastolic lengthening velocity

The BNP level >35 pg/ml is considered as elevated. All the patients had raised BNP level except two. The mean BNP level was 7420pg/mL. Eighty eight patients had BNP level ≥100pg/ml. The level<100pg/ml(Table 2). The plasma BNP level was analysed as per the different category of BMI. In present study majority of our patients were overweight with mean BMI of 27.7 kg/ m^2. The patients with BMI in normal range had mean BNP value of 3161.77 pg/mL, in overweight 2415.4 pg/mL, in obese 776.12 pg/mL and mean BNP was 778 pg/mL in very obese.

Table2- Correlation of BNP level withLA size and E/E' value

Echo parameter	BNP<100pg/ml(N-12)	BNP≥100pg/ml(N-88)
LA size	31.83 ± 7.4 mm	40.95 ± 4.9 mm
E/E'	13.50 ± 4.5	15.76 ± 6.2

BNP = Brain type Natriuretic Peptide

Discussion

Till recent times one of cardinal features of heart failure had been cardiomegaly and impaired systolic function. Many patients present with dyspnoea but with normal sized heart and normal ejection fraction. It was difficult to explain and remained undiagnosed till the concept of HFPEF came into vogue. The prevalence of HFPEF may be as high as 50% of all heart failure cases. The reason cited for such increasing prevalence is the increasing incidence of hypertension, obesity, atrial fibrillation[10]. Another reason probably is increasing awareness of such entity and increasing longevity. One of the common cause of breathlessness in elderly is HFPEF[11]. It is claimed that if this trend continues soon it would be the most common phenotype of heart failure. The morbidity and mortality is no different from those due to heart failure with reduced ejection fraction (HFREF)[12]. The various risk factors implicated in HFPEF are hypertension, obesity, diabetes mellitus, hyperlipidaemia, atrial fibrillation and obstructive sleep apnoea. The present study was conducted to study the clinical profile of patients with HFPEF in a tertiary care hospital.

In present study majority of our patients were overweight with mean BMI of 27.7 kg/ m^2. Obesity associated HFPEF was initially observed in African-American hypertensive women[13]. High body mass index is a proinflammatory state and seem to cause microvascular inflammation and endothelial dysfunction. Obesity has also been associated with left ventricular hypertrophy and diastolic dysfunction. Though obesity is a common comorbidity seen with HFPEF, plasma BNP level may not be raised in these patients. It has been proposed that in obesity lower BNP levels are because of increased number of natriuretic peptide clearance receptors which are present in adipose tissue which lead into increased clearance of BNP from the circulation[14]. In the current study the mean BNP was observed to be 3161.7pg/ml in patients with normal BMI, 2415.4pg/ml in overweight, 776.1pg/ml in obese and 778.0pg/ml in very obese category. The patients were from a tertiary care setting and all had high BNP level, but the value gradually declined with increasing BMI.

Besides obesity, hypertension has been attributed to the rising incidence of HFPEF. This study showed that 82 % of patients were hypertensive.76% were anaemic, 28% were diabetic, 30 % were having hyperlipidaemia, 8 % had AF, 6% hypothyroidism

and 2 % each had obstructive sleep apnoea(OSA) and chronic kidney disease(CKD). Hypertension brings left ventricular remodelling and has been traditionally implicated in pathophysiology of HFPEF. In an epidemiological study hyperlipidaemia was reported to be present in 15% of the population of HFPEF[15]. The present hospital based study showed hyperlipidaemia in 30% of cases and diabetes in 28%. Diastolic dysfunction has been reported in diabetes mellitus even before other complications develop.

Atrial fibrillation has been closely linked with HFPEF. Both atrial fibrillation and HFPEF lead to atrial remodelling[16]. It may antedate or occur concurrently or after the onset of heart failure[17]. The diastolic dysfunction of left ventricle will cause rise in left atrial afterload. It results in left atrial enlargement and increased atrial chamber tension. As a consequence there may be atrial arrhythmia and mechanical dysfunction. The BNP level may be elevated in AF even without heart failure[18] and it is expected to be much higher in heart failure. There were only 8 patients with AF in this study, the mean BNP was 7420pg/ml. Six of the patients (6%) in the study had hypothyroidism. A study reported hypothyroidism as comorbidity in 10% of patients. Sergio et al studied animal model of HfpEf and found thyroid hormone to be low in serum and myocardium[19]. Sleep-disordered breathing is common in heart failure and carries a worse prognosis[20,21]. In the present study cohort only two patients had OSA. Obstructive sleep apnea is a risk factor for hypertension and heart failure[22]. Dyspnea and fatigue are common symptom in both OSA and heart failure. It becomes imperative to focus on OSA as well while treating cardiac failure. Many patients had impaired renal function but only two patients had CKD. One of the presentation can be renal insufficiency in heart failure because of renal hypoperfusion[10]. It is important to screen for renal function in heart failure patients as the management may be altered because of associated hyperkalemia[23]. Angiotensin converting enzyme inhibitors, angiotensin receptor blocker, and spironolactone should be used more cautiously.

Anaemia is a bad prognostic marker in heart failure. In the present study 76% of patients were anaemic, identified using the WHO criteria. Limited data available in patients with HFPEF has shown that anaemia carries an increased mortality risk. However treating anemia with erythropoetin did not show any beneficial effect[24]

As per ESC criteria BNP level above 35pg/ml is considered as elevated. As per some guidelines diagnosis of heart failure is more likely if BNP is >100pg/ml. In the present study twelve patients had BNP<100pg/ml. This biomarker has also been correlated with LA size. In the present study LA size was increased in all the patients and mean LA size was 39.9mm. However it needs to be emphasised that BNP level in isolation cannot be considered to diagnose or exclude heart failure. It may be normal in nearly 30% cases of HFPEF and it may be elevated even without heart failure[25]. The patients who are symptomatic only on exertion or those who are obese, may have normal BNP.

One of the important parameter considered for the diagnosis of HFPEF is diastolic dysfunction of the heart. It can be assessed invasively by measuring pulmonary capillary wedge pressure and left ventricular end diastolic pressure. Noninvasively Various echocardiographic parameters can be analysed to study impaired relaxation of left ventricle e.g. prolonged deceleration time, left atrial enlargement, left ventricular hypertrophy. The E/E' ratio (mitral valve flow velocity to early diastolic lengthening velocity) is measured by tissue Doppler echocardiography. A value of E/E' >15 correlates with elevated left atrial pressure and is highly suggestive of HFPEF. Talreja et al in a small study found that this parameter corresponds to high pulmonary capillary wedge pressure[26]. While value <8 is considered normal, if it is in the range 8-15 a higher BNP level (>200pg/ml) is required to make the diagnosis[10]. We found mean value of E/E' to be 15.49 in this study. Subgroup analysis showed that the patients(n=12) with BNP<100pg/ml had a lower mean (13.50) E/E'.

There is no specific treatment of HFPEF. The CHARM-preserved trial had evaluated the role of candesartan and found that it reduced hospitalisation rate but showed no mortality benefit[27] However the inclusion criteria in this study had LVEF>40%(not 50%). The TOPCAT study showed that spironolactone has no mortality benefit[28]. However some authors believe that the role of spironolactone needs a relook[29]. The focus remains on symptomatic treatment like diuretics. The patients should be screened for various associated cardiovascular and noncardiovascular comorbidity. It has been seen

that in patients with HFPEF the cause of mortality is often noncardiovascular. Hence it is crucial that besides treating cardiac failure symptomatically, the comorbidities should also be managed meticulously.

Limitation of the study

The major limitation of the study is the small sample size and the sample is drawn from a tertiary care setting. Hence the participants may be in the advanced stage of heart failure. Some of the patients with HFPEF become symptomatic only on exertion and might have got excluded from the study. However this study would help to increase the awareness about this entity and make the clinician think of this possibility when the patient presents with unexplained dyspnoea.

Conclusion

The patients with the diagnosis of heart failure with preserved ejection fraction are heterogeneous and the treatment probably needs to be individualised. The diagnosis is based on symptoms and signs of heart failure with evidence of diastolic dysfunction. Echocardiographic features like left ventricular hypertrophy, left atrial enlargement and increased value of E/E' support will contribute to the diagnosis. The BNP level can be used as a biomarker when the diagnosis is in doubt. Various comorbities may be pathophysiologically related to this condition or may be prognostically implicated. The treatment is mostly symptomatic as no specific treatment available as yet. The associated comorbidities should be evaluated and managed adequately. However it is not known whether this approach would change the course of the disease. The present study was limited by its very small sample size. Further studies with larger sample size are required to define the profile of this disease.

Conflict of interest: None declare

Authors' contribution:

Concept, study design: Bimal K Agrawal, Gaurav Aggarwal, Robin Gahlawat, Suvarna Prasad

Data collection, writing of manuscript: Bimal K Agrawal, Gaurav Aggarwal, Usha Agrawal

Research question, proof reading of manuscript: Bimal K Agrawal, Barinder Kaur, Usha Agrawal

Data processing statistical analysis and proof reading: Bimal K Agrawal, Gaurav Aggarwal, Robin Gahlawat, Suvarna Prasad, Amit Saini, Barinder Kaur, Usha Agrawal.

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