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Original Research Article

Clinical and echocardiographic features in patients with different phenotypes of heart failure

Dasani H. R. Dassanayake*, Mizna Fuward, Liudmila Kalatsei

Department of Internal Medicine, Grodno State Medical University, Grodno, Republic of Belarus

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***Correspondence:**
Dr. Dasani H. R. Dassanayake,
E-mail: ranulid24@gmail.com

ABSTRACT

Background: Despite the advancements in heart failure (HF) management, a gap remains in distinguishing the clinical and echocardiographic profiles among the different phenotypes of HF, particularly in HF with mid-range ejection fraction (HFmrEF). The aim of the current study was to establish clinical and echocardiographic differences in patients with HF with reduced and mid-range left ventricular ejection fraction (LVEF).
Methods: The study included 80 patients with chronic HF with LVEF less than 50% who were divided into two groups: HF with reduced ejection fraction (HFrEF) (n=45) and HFmrEF (n=35). All patients underwent clinical, laboratory, and instrumental studies, including transthoracic echocardiography. Statistical analysis was performed using «STATISTICA 12.0».
Results: Patients of both groups were predominantly male ($p>0.05$), comparable in age prevalence of atrial fibrillation and diabetes mellitus ($p>0.05$). Patients with HFmrEF more often suffered from hypertension ($p=0.04$) and stable angina class 3 ($p=0.010$). Laboratory markers in both groups had no significant differences except for NT-proBNP levels ($p=0.031$), which were higher in patients with HFrEF. Patients with HFrEF had higher linear and volumetric parameters of both atria and ventricles ($p<0.05$), which demonstrated undeniable correlation between LVEF and other heart diameters and volumes.
Conclusions: Our study showed that patients with HFmrEF have significant differences from HFrEF (higher incidence of hypertension, lower NYHA class and NT-proBNP levels). This highlights that the further study of clinical and laboratory characteristics of HFmrEF should be conducted.

Keywords: Heart failure with reduced ejection fraction, Heart failure with mid-range ejection fraction, Left ventricular ejection fraction, Hypertension, NT-proBNP

INTRODUCTION

Chronic heart failure (HF) is defined as "a complex clinical syndrome with symptoms and signs that results from any structural or functional impairment of ventricular filling or ejection of blood" as per the American Heart Association and the American College of Cardiology.[1] Studies have revealed that a multitude of factors are responsible for causing chronic HF as they cause a substantial loss of functioning cardiomyocytes.[2] Diseases such as chronic obstructive pulmonary disease, hypertensive cardiac disease, rheumatic heart disease, and ischemic heart disease (IHD) are cited to be the major causative diseases, amongst which IHD takes the lead.[3,4] IHD leads to poor perfusion of myocardium, resulting in decreased LVEF.

Rheumatic heart disease commonly affects the young adult and pediatric populations, leading to valvular disorders, aortic and mitral stenosis. In older individuals, valvular pathologies are usually due to age-related changes, and the aortic valve is affected often. Men mostly suffer from aortic stenosis or regurgitation, while women tend to experience mitral valve diseases. In addition, long standing hypertension leads to significantly high

mechanical stress and subsequent cardiac remodelling where the ventricular mass is increased as an adaptation to increased afterload.[4,6]

As a result of demographic shifts, the development of treatment modalities, and disparities in healthcare access, epidemiological data are progressively changing. During past 10 years, incidence of HF has stabilized or declined in developed countries; however, the prevalence continues to increase as a consequence of the ageing of the population, a surge in risk factors, the efficacy of emerging treatments, and increased life expectancy. An increase in prevalence is especially observed in younger generation, and this trend is progressing towards HF with preserved ejection fraction (HFpEF). Due to shortage of accurate data in developing countries, discrepancies are evident in understanding HF burden and progression in these regions.[7]

The 2016 European Society of Cardiology (ESC) guidelines have introduced a new classification of HF based on LVEF, which classifies patients with HF into HFpEF (LVEF≥50%), HFrEF (LVEF is<40%), and HFmrEF LVEF (40-49%).[8]

Despite the advancements in HF management, a gap remains in distinguishing the clinical, anamnestic, laboratory, and echocardiographic profiles among these subtypes, particularly in HFmrEF. Greater clarity in phenotypic presentations may facilitate diagnostic precision and guide targeted therapies. The aim of this study was to evaluate the clinical and anamnestic characteristics, laboratory and echocardiographic features in patients with HFmrEF.

Aim of the study was to establish clinical, anamnestic, laboratory and echocardiographic differences in patients with HF with reduced and mid-range LVEF.

METHODS

The study included 80 patients with HF and LVEF less than 50% who were admitted to the Grodno State Cardiological Centre for treatment from January to November 2024. Group 1 included 45 patients with HFrEF (LVEF<40%), while group 2 included 35 patients with HFmrEF (LVEF 41-50%).

Exclusion criteria from the study were: acute coronary syndrome, acute HF, infective endocarditis, myocarditis, hypertrophic cardiomyopathy, hereditary channelopathies, valvular pathology of the heart requiring surgical correction, oncological diseases and severe concomitant extracardiac pathology.

All patients underwent clinical, laboratory, and instrumental studies, including transthoracic echocardiography.

Echocardiography was performed on Phillips iE33 device with a multi-frequency sensor (frequency 2.5-5.0 MHz). The examination was performed with the patient lying on his left side with his back to the researcher or on his back. The study protocol included the following indicators: LA and right atrium (RA) diameter in 2-chamber and 4-chamber mode, end-systolic diameter and end-diastolic diameter (mm) of the left ventricle (LV), LVEF; assessment of the state of the valvular apparatus of the heart, degree of regurgitation on the valves.

Statistical analysis was performed using the STATISTICA 12.0 software package with a preliminary check for normal distribution using a distribution histogram. Quantitative data, the distribution of which was not normal, were given as a median, 25% and 75% quartiles. Since most of the quantitative characteristics did not obey the normal distribution law, non-parametric methods were used for comparison. The Mann-Whitney test was used to assess differences in quantitative traits between two independent groups. At a significance level of p less than 0.05, it was believed that the studied indicator in the compared groups had statistically significant differences.

The study was performed in accordance with good clinical practice standards and the principles of the declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

RESULTS

Patients with HFrEF and HFmrEF were predominantly male (29 (64.4%) vs 25 (71.4%), p>0.05), comparable in age (63 [56; 71] vs 64 [59; 71] years, p>0.05), prevalence of obesity (22 (49%) vs 15 (43%), p>0.05), prior myocardial infarction (24 (53%) vs 19 (54%), p>0.05) and diabetes mellitus (13 (28%) vs 7 (20%), p>0.05) (Table 1).

Patients with HFmrEF more often suffered from hypertension (33 (73%) vs 32 (91%), p=0.04) than patients with HFpEF. In both groups there was rather high number of patients with stable angina (20 (44%) vs 14 (40%), p>0.05), but patients with HFrEF more often had CCS class 3 (10 (22%) vs 1 (3%), p=0.010). Also, patients with HFrEF were characterized by higher class of HF (NYHA Class IV in 13 (28%) vs 1 (3%), p<0.001), while in HFmrEF patients NYHA class II was more common (15 (43%) vs 4 (9%), p<0.001).

Laboratory markers of patients in both groups had no significant differences except for urea level (8.1 [6.2; 9.1] vs 6.9 [5.5; 7.7] mmol/L, p=0.026) and NTproBNP level (6155 [1549; 6256] vs 2495 [1716; 2661] pg/mL, p=0.031), which were significantly higher in patients with HFrEF (Table 2). Interesting to say, that creatinine and estimated GFR levels were comparable (p>0.05).

Clinical blood test values and hemostatic screening tests did not show significant intergroup differences.

Echocardiographic parameters of patients are presented in Table 3.

Table 1: Clinical characteristics of patients.

Parameters	Group 1, HFrEF (n=45)	Group 2, HFmrEF (n=35)	P
Male gender	29 (64.4%)	25 (71.4%)	>0.05
Age (in years, Me [25%;75%])	62.5 [56; 71]	64.4 [58.7; 70.8]	>0.05
Body mass index, kg/m^2, (Me [25%;75%])	30.8 [24.5; 33.45]	28.9 [25.7; 31.8]	>0.05
Obesity	22 (48.9%)	15 (42.8%)	>0.05
Class 1	13 (28.9%)	13 (37.1%)	>0.05
Class 2	3 (6.7%)	2 (5.7%)	>0.05
Class 3	6 (13.33%)	-	0.022
Hypertension	33 (73.3%)	32 (91.4%)	0.040
Stage 1	7 (15.6%)	5 (14.3%)	>0.05
Stage 2	24 (53.3%)	26 (74.3%)	0.046
Stage 3	2 (4.4%)	1 (2.9%)	>0.05
Stable angina	20 (44.4 %)	14 (40%)	>0.05
Class 1	-	-	>0.05
Class 2	10 (22.2%)	13 (37.1%)	>0.05
Class 3	10 (22.2%)	1 (2.9 %)	0.010
Myocardial infarction history	24 (53.3%)	19 (54.3%)	>0.05
Diabetes mellitus	13 (28.9%)	7 (20%)	>0.05
Atrial fibrillation	29 (64.4%)	19 (54.3%)	>0.05
Paroxysmal AF	4 (8.9%)	4 (11.4%)	>0.05
Persistent AF	25 (55.5%)	15 (42.9%)	0.049
Atrial flutter	4 (8.9%)	3 (8.6%)	>0.05
HF NYHA class	-	-	
Class 1	-	-	>0.05
Class 2	4 (8.9%)	15 (42.8%)	<0.001
Class 3	28 (62.2%)	19 (54.3%)	>0.05
Class 4	13 (28.9%)	1 (2.9%)	<0.001

Table 2: Laboratory parameters of patients (Me [25%;75%]).

Parameters	Group 1, HFrEF (n=45)	Group 2, HFmrEF (n=35)	P
RBC (10^{12}/l)	4.6 [4.2; 5.0]	4.8 [4.4; 5.2]	>0.05
Hemoglobin, (g/l)	135.8 [122.5; 149]	146.4 [133.5; 160.5]	>0.05
WBC, (10^9/l)	8.0 [6.05; 8.5]	7.6 [5.345; 8.65]	>0.05
ESR, (mm/h)	9.1 [3; 12]	11.3 [5; 11]	>0.05
Urea, (mmol/l)	8.1 [6.2; 9.1]	6.9 [5.5; 7.7]	0.026
Creatinine, (µmol/l)	102.8 [85.2; 110]	97.2 [77.2; 115.3]	>0.05
eGFR, (ml/min/1.73 m^2)	63.9 [53.5; 72.5]	71.2 [58.75; 81]	>0.05
Cholesterol, (mmol/l)	4.7 [2.9; 5.3]	4.67 [3.6; 5.16]	>0.05
Glucose, (mmol/l)	6.5 [5.28; 7.45]	6.1 [5.3; 7.225]	>0.05
Sodium, (mEq/l)	140.5 [138.4; 143]	135.6 [137; 143]	>0.05
Potassium, (mEq/l)	4.65 [4.2; 5.1]	4.59 [4.3; 4.8]	>0.05
NTproBNP, (pg/ml)	6155 [1549; 6256]	2495 [1716; 2661]	0.031

*Note: RBC-red blood cells; WBC-white blood cells; ESR-erythrocyte sedimentation rate; eGFR-estimated glomerular filtration rate; NT-proBNP-N-terminal pro b-type natriuretic peptide.

Table 3: Echocardiographic parameters of patients (Me [25%;75%]).

Parameters	Group 1, HfrEF, (n=45)	Group 2, HfmrEF, (n=35)	P
LA diameter (2 chamber), (mm)	48.4 [44; 52]	43.9 [41; 47]	0.007
LA diameter (medial to lateral), (mm)	47.8 [45; 51]	43.5 [41; 46]	<0.001
LA diameter (front to back), (mm)	66.1 [60; 70]	59.6 [54; 64]	0.002
RA diameter (medial to lateral), (mm)	44.6 [42; 48]	41.1 [36.5; 45.5]	0.007
RA diameter (front to back), (mm)	62.3 [57; 68]	56.6 [49; 62]	0.011
LV ESD, (mm)	51.6 [46; 57]	41.9 [39; 46]	<0.001
LV EDD, (mm)	62.6 [57; 66]	55.7 [52; 60]	<0.001

Continued.

Parameters	Group 1, HfrEF, (n=45)	Group 2, HfmrEF, (n=35)	P
M-mode	-	-	-
LV ESV, (ml)	140.6 [110; 168]	86.2 [69; 106]	<0.001
LV EDV, (ml)	210.1 [167; 235]	160.8 [130; 185]	<0.001
LVEF, (%)	33.7 [29; 39]	46.9 [43; 51.5]	<0.001
B-mode	-	-	-
LV ESV, (ml)	145.1 [93; 155]	79.9 [64; 91]	<0.001
LV EDV, (ml)	191.3 [149; 216]	148.1 [117; 170]	<0.001
LVEF, (%)	33.6 [30; 38]	46.3 [45; 49]	<0.001
Septal thickness (systolic), (mm)	14.3 [12; 16]	17.3 [15; 18]	<0.001
Septal thickness (diastolic), (mm)	11.9 [11; 13]	13.2 [12; 14]	0.003
Posterior wall thickness (systolic), (mm)	14.6 [13; 16]	14.8 [13.5; 16]	>0.05
Posterior wall thickness (diastolic), (mm)	11.2 [10; 12]	11.5 [10; 12]	>0.05
Right ventricle diameter, (mm)	32.1 [28; 34.5]	28.1 [26; 30]	0.008
Contractility index	1.81 [1.48; 2.13]	1.52 [1.06; 1.56]	<0.001

*Note: LA-left atrium; RA-right atrium; LV-left ventricle; ESD-end-systolic diameter; EDD-end-diastolic diameter; ESV-end-systolic volume; EDV-end-diastolic volume; LVEF-left ventricular ejection fraction.

According to results of transthorasic echocardiography, patients of the studied groups had significant differences in the linear and volumetric parameters of both atria and ventricles ($p<0.05$), which demonstrated undeniable correlation between LVEF and other heart diameters and volumes. It is interesting that patients with HFrEF had lower systolic and diastolic septal thickness ($p<0.05$), indicating formation of dilated cardiomyopathy in patients with HFrEF, in comparison with patients with HFmrEF. Systolic and diastolic thickness of LV posterior wall didn't show significant intergroup differences ($p>0.05$).

DISCUSSION

According to the different authors, prevalence of HFmrEF among patients with HF ranges from 14-24%.[5] According to majority of scientific studies, this group occupies an intermediate position between patients with HFrEF and HFpEF in terms of a number of parameters (gender, age, presence of comorbidities). CHARM study demonstrated that patients with HFrEF were more likely to have HFrEF than HFpEF based on gender and age.[6] Meta-analysis conducted by Lauristen et al in 2018 identified several characteristics of patients with HFmrEF (73.6±9.8 years): they were older than patients with HFrEF (72.6±9.8 years) and younger than patients with HFpEF (77.6±7.2 years). HFrEF and HFpEF were more commonly recorded in men (68.5 and 59%), while HFpEF was more common in women (60%).[5] In our study patients of both groups were predominantly male (64.4 vs 71.4%, $p>0.05$) and comparable in age (63 [56; 71] vs 64 [59; 71] years, $p>0.05$). It should be noted that IHD is considered as common in HFmrEF as in HF with HFrEF, and according to some meta-analyses, proportion of IHD in study group is even higher.[5,6] However, in our study patients with HFrEF had higher class of stable angina than HFmrEF patients.

The American PINNACLE registry noted that AF was more common in patients with HFmrEF than in patients with reduced EF, however in our study patient of both groups were comparable in prevalence in AF and atrial flutter.[7] According to data from the Swedish HF Registry, the prevalence of diabetes mellitus, coronary artery disease, valvular heart disease, and the frequency of statin and antiplatelet drug use in patients with CHFmrEF were similar to those in patients with HFrEF, which is confirmed by our data.[8]

Streng et al analyzed the prevalence of non-cardiac comorbidities in 3,499 patients from the BIOSTAT-CHF registry. The prevalence of diabetes mellitus, thyroid dysfunction, stroke, chronic obstructive pulmonary disease, chronic kidney disease, anemia, obesity, and peripheral arterial disease in patients with HFmrEF was also intermediate compared to the incidence of these conditions in patients with HFrEF and HFpEF.[9]

Of interest is the study of BNP and NT-proBNP levels in patients with CHFrEF and CHFmrEF. A study by Ageyev et al demonstrated a close correlation between LV filling pressure, which characterizes LV diastolic function, and increased serum BNP and NT-proBNP levels.[10] The authors noted an increase in NT-proBNP levels, primarily with an increase in LVDP, regardless of LVEF. Later studies, including patients with reduced LVEF (less than 50%), found a correlation between NT-proBNP levels and LVEF.[11] Elevated NT-proBNP levels were observed in both HFmrEF and HFrEF patients. However, in HFrEF, it was statistically significantly higher than in HFmrEF (433.05 pg/ml compared to 289.97 pg/ml, $p<0.05$).[11] In our study NTproBNP levels also were significantly higher in patients with HFrEF (6155 [1549; 6256] vs 2495 [1716; 2661] pg/mL, $p=0.031$).

Rickenbacher et al used echocardiographic parameters to characterize all classes of HF (TIME-CHF). According to their data, LV cavity size increased, and systolic function worsened from HFpEF to HFmrEF and then to HFrEF. In all three cohorts, patients showed increased LV end-diastolic pressure and LV hypertrophy (LVH). However, patients with HFpEF and HFprEF were more likely to have concentric LVH, while those with HFrEF were more likely

to have eccentric LVH.[12] Tsuji et al observed patients with HFmrEF for more than 3 years and concluded that HFmrEF represents a transitional status between HFrEF and HFpEF, and is not an independent syndrome.[13] However, it should be noted that this primarily affected patients with ischemic HF. With ongoing therapy, improvement in patient condition and a decrease in the severity of HF is logical.[1,6] On the other hand, in patients with HF with increased EF, primarily of non-ischemic etiology (dilated cardiomyopathy), patient transitions from one category to another were recorded significantly less frequently. It is more likely that patients with HFmrEF represent a heterogeneous category, including patients with different clinical profiles who can be classified as HF with improving, stable, and deteriorating LVEF.

Limitations

The main limitation of this study is the small sample size, from single hospital. Additionally, other important factors that may play a role in these findings, including genetic polymorphisms and patient's adherence to treatment were not assessed. Nonetheless, our results must be interpreted with caution and larger studies with higher patient numbers should be carried out to confirm our findings.

CONCLUSION

Patients with HFmrEF for many years belonged to so-called gray zone; they were excluded from most clinical studies or were put in same category as patients with HFrEF. After being grouped in separate phenotype of HFmrEF, this group of patients was analyzed in detail. However, the results of studies conducted to date remain controversial. Our study has showed that group of patients with mid-range LVEF has significant differences from HFrEF (lower incidence of hypertension, higher NYHA Class, higher NT-proBNP levels). This highlights that further study of clinical, morphological and laboratory characteristics of HFmrEF should be conducted, and factors that cause a decrease or contribute to the restoration of LV systolic function should be determined. Further prospective studies will possibly allow developing an effective treatment strategy for this poorly studied group of patients.

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