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Particularities of rhythm and conduction disorders in heart failure patients with preserved ejection fraction admitted to a rehabilitation hospital

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Abstract: (1) Background: The mortality and prognosis of patients with heart failure with preserved ejection fraction have shown minimal improvement over the past 20 years, possibly since this condition is often accompanied by various other cardiovascular risk factors and comorbidities, the correlation with various rhythm and conduction disorders being yet to be elucidated. (2) Methods: This study investigated 134 patients with heart failure with preserved and reduced ejection fraction, analyzing the presence and clinical impact of rhythm and conduction disorders in this groups of patients.; (3) Results: Atrial fibrillation is the most common arrhythmia in patients with heart failure with preserved ejection fraction and rhythm and conduction disturbances are significantly associated with essen-tial hypertension (p = 0,005) and chronic pulmonary heart disease (p = 0,016) in this pa-tients; (4) Conclusions: heart failure with preserved ejection fraction is an intensely ar-rhythmogenic condition that requires optimal treatment strategies which are adapted to the multiple possibly associated comorbidities.

Keywords: heart failure with preserved ejection fraction; atrial fibrillation; comorbidities; conduction disorders

1. Introduction

With a constant rise in prevalence, heart failure with preserved ejection fraction (HFpEF) is a major public health issue that associates high morbidity and mortality rates, thus being considered one of the greatest unsatisfied needs in modern cardiovascular medicine, given the lack of efficient treatment strategies.

The quality of life in HFpEF is most impaired in young, obese, and diabetic patients and is strongly related to the decline in functional capacity and daily activity levels rather than NT-proBNP elevation or prior hospitalization for heart failure [1]. A recent study [2] demonstrated severely symptomatic arrhythmic episodes that are usually associated with dizziness and exercise intolerance also significantly reduce the quality of life of these patients. Hence, it is important to know the most common characteristics of rhythm and conduction disorders that occur in HFpEF and establish their main differences compared to the population with reduced ejection fraction (EF).

On the other hand, there is unanimous recognition of the fact that HFpEF is a systemic, multiorganic disorder that requires a multidimensional investigative approach to improve understanding of its mechanisms and treatment. Therefore, it is necessary to describe the rhythm and conduction disorders of this patient population not only from an

intrinsic cardiovascular perspective but also to identify their main relationships both with the functional status of the other organ systems and with the general biological status of the patient and determine the differences existing compared to the heart failure (HF) population with reduced EF – differences whose acknowledgment could facilitate the establishment of an individualized therapeutic plan.

This study aimed to identify the main particularities in the context of rhythm and conduction disorders that occur in heart failure patients with preserved ejection fraction compared to patients with the reduced ejection fraction form of heart failure.

2. Results

134 heart failure patients were included in the study, using HF criteria defined according to the current guidelines published by the European Society of Cardiology [3]. The general characteristics of the patients are summarized in Table I. 41.04% % of the patients were women. 43.2% were diagnosed with HFpEF, and 57.61% had HFrEF. To verify the existence of an association between gender and the type of heart failure, the Chi-square test was applied, which resulted in a value of p = 0.001, which confirms the existence of this association, the female sex being significantly more frequently associated with HFpEF. The best-represented age group was between 71 and 75 years old, with 31 patients, and, in total, patients aged between 66 and 80 years represented 59.70% of the studied group. Regarding the two types of heart failure, the median age in the group of patients with preserved ejection fraction was 75 years, 2 years older than in the group with reduced ejection fraction (73 years).

Table I. General characteristics of the studied groups

Characteristic	Patient group		p-value
	HFpEF	HFrEF	
Median age	75	73	0,479
Gender (female)	35	20	0,001
Gender (male)	28	51	0,001
CAD	8	30	< 0,001
DCM	3	30	< 0,001
HCM	1	0	0,475
RCM	0	2	0,273
Mitral regurgitation	30	48	0,008
Mitral stenosis	6	4	0,311
Aortic regurgitation	11	10	0,625
Aortic stenosis	9	7	0,454
Pulmonary regurgitation	3	2	0,453
Tricuspid regurgitation	28	43	0,034
Pulmonary hypertension	26	41	0,033
Chronic pulmonary heart disease	15	6	0,016
Chronic venous insufficiency	13	11	0,468
Peripheral arteral disease	5	3	0,381*
T2DM	23	27	0,776
Arterial hypertension	48	38	0,005
Obesity	19	13	0.119
CKD	14	22	0,216
Asymptomatic hyperuricemia	14	16	0,912
COPD	18	13	0,13

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CAD, coronary artery disease; DCM, dilative cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

Regarding the rhythm and conduction disorders observed in the study, the frequency with which they were encountered in the two groups of patients is illustrated in Table II. It can be observed that, following the application of the Chi-square test, or, as the case may be, Fischer's exact test, no significant differences were revealed in the frequency of different types of arrhythmias between the two groups of patients, except for the left bundle branch block, which was significantly ($p = 0.03$) associated with HFrEF. 122 of the 134 patients included in the study presented rhythm and/or conduction disorders, and of these, 58 had a diagnosis of HFpEF, and 64 presented HFrEF, the p-value of the association between the category of heart failure and their presence being 0.697.

Table II. Rhythm and conduction disorders in the studied groups

Rhythm/conduction disorder	Patient group		p-value
	HFpEF	HFrEF	
AFib - total	45	51	0,777
Paroxysmal AFib	7	11	0.426
Persistent AFib	9	13	0,491
Permanent AFib	29	27	0,387
AFL	6	8	0,709
SVEa	5	6	0,884
VEa	15	16	0,913
Sinus node dysfunction	4	5	0,562
LBBB	4	18	0,002
RBBB	4	4	0,585
LAFB	1	2	0,537
AV block - total	8	10	0,776
I degree AV block	3	6	0,297
II degree AV block	1	0	0,475
III degree AV block	3	4	0,555
VT - total	3	3	0,612
NSVT	4	7	0,463
SVT	0	2	0,273*
VFib	0	3	0,141

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; AFib, atrial fibrillation; AFL, atrial flutter; SVEa, supraventricular extrasystolic arrhythmia; VEa, ventricular extrasystolic arrhythmia; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block; AV, atrioventricular; VT, ventricular tachycardia; NSVT, non-sustained ventricular tachycardia; SVT, sustained ventricular tachycardia; VFib, ventricular fibrillation

Statistically significant associations were found between patients with rhythm and/or conduction disorders and HFpEF and the presence of essential arterial hypertension and chronic pulmonary heart disease, while ischemic heart disease, dilated cardiomyopathy, mitral regurgitation, tricuspid regurgitation, and pulmonary hypertension were significantly associated with patients with arrhythmias and HFrEF - Table I. Regarding the main non-cardiovascular comorbidities, no significant differences were revealed, although type 2 diabetes and obesity were more frequently present in patients with HFpEF.

The biochemical parameters of the patients from the two groups are illustrated in Table III.

Table III. Biochemical parameters of the studied groups.

Parameter	Patient group					
	HFpEF			HFrEF		
	Median	Q 1	Q 3	Median	Q 1	Q 3
ESR (mm/h)	22	8	33,5	14	8	27,50
CRP (mg/dl)	0,90	0,30	2,75	0,90	0,30	1,85
RBC count (1012/L)	4,23	3,60	4,62	4,46	3,95	4,82
Hb (g/dl)	12,75	10,50	13,75	13	11,52	14,20
HCT (%)	38,70	32,25	41,60	39	35,27	42,17
WBC count (109/L)	7,27	5,48	8,90	6,91	5,42	8,83
Platelet count (109/L)	206	164,75	268,50	212,5	172,50	252
MCV (fL)	89,65	84,45	92,60	88,70	85,20	90,70
MCH (pg)	29,70	27,67	31,02	29,60	28,20	30,92
Ferritin (ng/ml)	120,50	42,03	213,50	92,30	48,50	178
TC (mg/dl)	133	107,50	165	133,50	107,25	166,75
LDL-C (mg/dl)	78,50	61	107,25	76	61	107
HDL-C (mg/dl)	37	32	42,5	39	31,25	46,75
TGL (mg/dl)	109,50	72	149	95,50	71	128,50
AST (U/L)	24	19	32	31	20,25	41
ALT (U/L)	17	13	27	20,50	15	32
Na^+ (mmol/L)	139	137	141,25	139,50	136,25	142
K^+ (mmol/L)	4,41	4,07	4,72	4,28	3,99	4,64
BG (mg/dl)	105	91,50	123,75	108	95	130
Urea (mg/dl)	56	36,75	85,25	64	42	101,50
Uric acid (mg/dl)	8,63	7,01	10,33	8,36	7,02	10,50
Creatinine (mg/dl)	1,02	0,82	1,48	1,20	0,97	1,64
NT-proBNP (pg/ml)	1381	861	2339	2383,50	1090	9000

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RBC, red blood cells; Hb, hemoglobin; HCT, hematocrit; WBC, white blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGL, triglyceride; AST, aspartate aminotransferase; ALT alanine aminotransferase; Na, sodium; K, potassium; BG, blood glucose; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

In this context, the correlation between the ejection fraction of patients presenting with rhythm and/or conduction disorders and the parameters for which the Mann-Withney-U test showed a statistically significant association, namely the number of red blood cells, aspartate-aminotransferase (AST), alanine aminotransferase (ALAT), and NT-proBNP was verified. Regarding the correlation between the ejection fraction and the number of red blood cells (Figure I), the Spearman correlation coefficient (rS) had the value -0.27 and p = 0.001. So, there is a statistically significant inverse relationship between the two variables. From the regression line of the correlation, it is revealed that R2 = 0.059, therefore, 5.9% of the variation in the number of red blood cells can be explained by its linear relationship with the ejection fraction and for each increase in the ejection fraction by 1%, the number of red blood cells decreases on average by 0.0145 x 1012/L.

Regarding the correlation between the ejection fraction and aspartate-aminotransferase (ALAT), the Spearman correlation coefficient (rS) has the value -0.19 and p = 0.001. So, there is a statistically significant inverse relationship between the two variables. The correlation regression line (Figure II) shows that R2 = 0.0453, therefore, 4.5% of the variation in the ASAT value can be explained by its linear relationship with the ejection fraction and for each increase in the ejection fraction by 1 %, the ASAT value decreases on average by 0.3531 U/L.

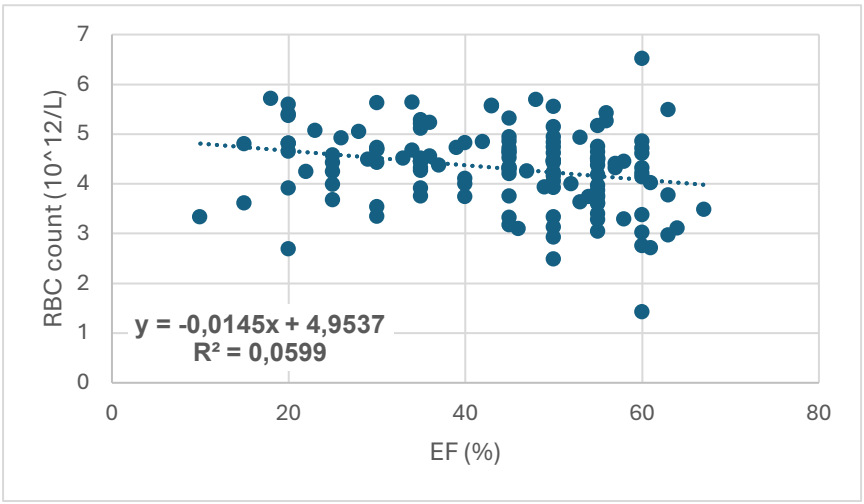
Similarly, the correlation between ejection fraction and alanine aminotransferase (ALAT) was evaluated, and the Spearman correlation coefficient (rS) has a value of -0.13 but p = 0.135. Therefore, there is no statistically significant inverse relationship between the two variables. The correlation regression line (Figure III) demonstrates that R2 = 0.026, therefore, only 2.6% of the ALAT value variation can be explained by its linear relationship with the ejection fraction and for each increase in the ejection fraction by 1%, the ALAT value decreases on average by 0.3456 U/L.

Analyzing the correlation between the ejection fraction and NT-proBNP (Figure IV), the Spearman correlation coefficient (rS) has the value -0.25 and p = 0.039. So, there is a statistically significant inverse relationship between the two variables. From the regression line of the correlation, it is revealed that R2 = 0.0685, so, 6.8% of the NT-proBNP variation can be explained by its linear relationship with the ejection fraction, and for each 1% increase in the ejection fraction, NT -proBNP decreases by an average of 64.689 pg/ml.

The frequency with which the different degrees of severity of heart failure, according to the NYHA (New York Heart Association) classification, were encountered in the group of patients with rhythm and/or conduction disorders was also checked (Figure V). A higher frequency of the lower severity classes (I, II) was observed among patients with arrhythmias and HFpEF, while the higher severity classes (III, IV) are more frequent in the group with HFrEF (p-value = 0.008).

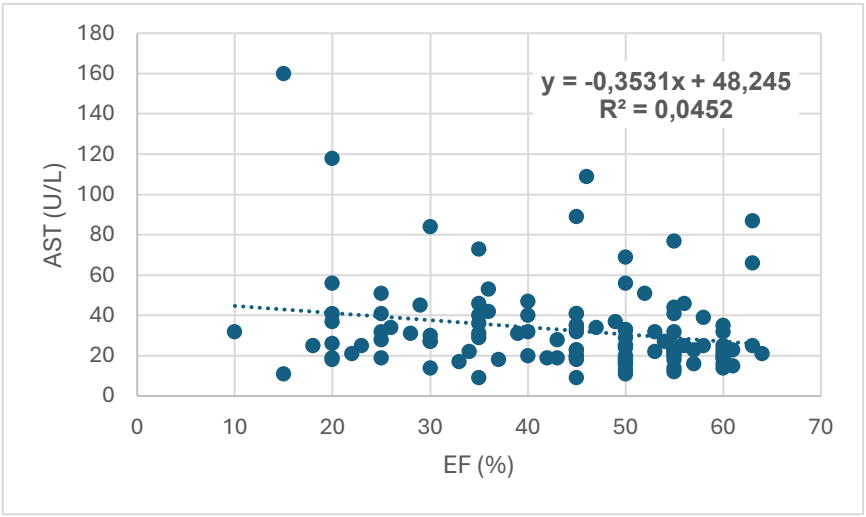
Finally, the treatment received by the two groups of patients during hospitalization was analyzed. To verify the existence of an association between the medication and a certain group of patients, the Chi-square test was used and it was highlighted that the therapy with the combination of sacubitril/valsartan (p = 0.014), digoxin (p = 0.008), and sodium-glucose transport protein 2 (SGLT2) inhibitors (p = 0.026) were significantly associated with the group of patients with arrhythmias and heart failure with reduced ejection fraction. There were no significant differences regarding the administration of the other medications indicated by the ESC guideline: angiotensin-converting enzyme inhibitors, sartans, beta-blockers, or diuretics.

Figure I. Correlation between ejection fraction and RBC count



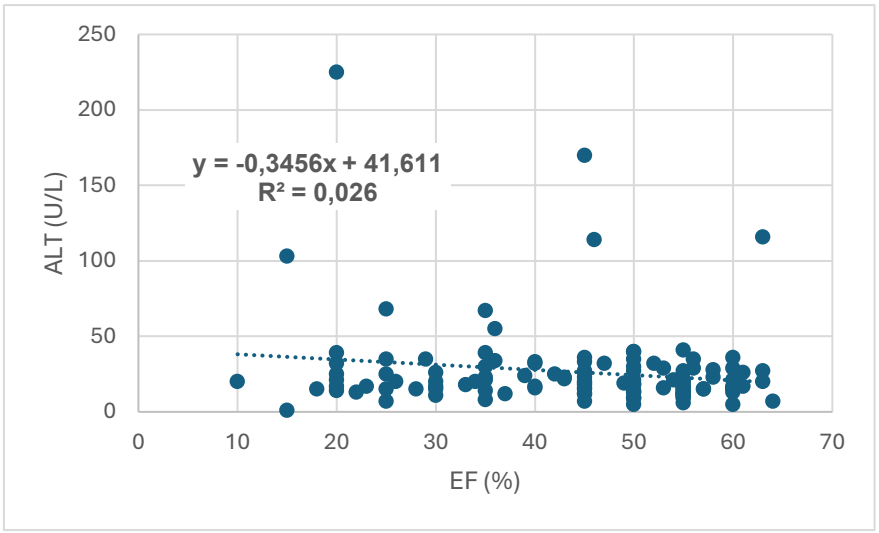
RBC, red blood cells; EF, ejection fraction

Figure II. Correlation between ejection fraction and AST



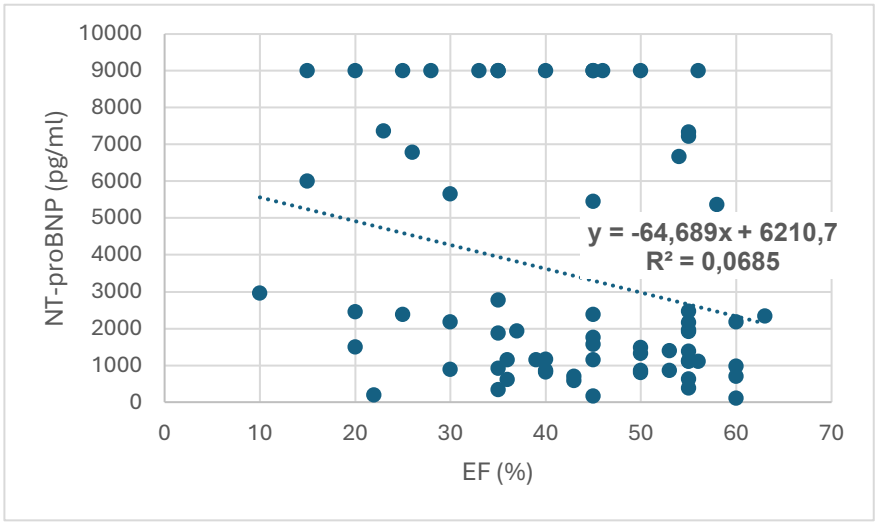
AST, aspartate aminotransferase; EF, ejection fraction

Figure III. Correlation between ejection fraction and ALT



ALT, alanine aminotransferase; EF, ejection fraction

Figure IV. Correlation between ejection fraction and NT-proBNP



NT-proBNP, N-terminal prohormone of brain natriuretic peptide; EF, ejection fraction

3. Discussion

The present research aimed to determine and evaluate the main peculiarities of rhythm and conduction disorders in the population of heart failure patients with preserved ejection fraction and, at the same time, to establish the existence and to evaluate the differences between them and patients with reduced ejection fraction.

Patients with HFpEF were older, consistent with data from the specialized literature, which presents senescence as one of the main risk factors for the development of HFpEF. A possible explanation for this association may be the fact that elderly patients usually

have a history of arterial hypertension and multiple other comorbidities also associated with HfpEF [4].

In terms of gender distribution, 55.55% of patients with HFpEF were female, while only 28.16% of patients with reduced ejection fraction were female. The association between female gender HFpEF was statistically significant. The high proportion of women with heart failure with preserved ejection fraction could partly be explained by their longer life expectancy and higher prevalence of comorbidities such as chronic kidney disease, hypertension, valvulopathies, and lung disease [5].

We also checked the severity of heart failure, according to the NYHA (New York Heart Association) classification in the two groups of patients and observed that patients with rhythm and conduction disorders and HFpEF presented with a significantly increased frequency lower severity classes of heart failure (65% of patients with NYHA classes I and II and only 39% of those with NYHA classes III and IV had preserved ejection fraction), the observed differences being statistically significant ($p = 0.008$). This fact was also found in a study on 849 patients which aimed to compare the quality of life of heart failure patients with preserved and reduced ejection fraction, respectively: 70% of HFpEF patients presented NYHA severity classes I or II, while the majority of HF patients with reduced EF (52%) presented NYHA severity classes III or IV [6].

Regarding the rhythm and conduction disorders observed in the study, the most common supraventricular rhythm disorder among patients with heart failure with preserved ejection fraction was atrial fibrillation, and the most common ventricular rhythm disorder was ventricular extrasystolic arrhythmia. Similar to these results, various other studies did not reveal significant differences in the association between rhythm and/or conduction disorders and the two types of heart failure: a meta-analysis [7] that analyzed supraventricular rhythm disorders showed that they were present in 40% of those with HF with reduced EF and in 32% of those with preserved EF, while a study [8] focused on ventricular rhythm disorders showed that the two categories of patients were similar in both in terms of incidence of ventricular tachycardia and ventricular fibrillation, as well as resuscitation outcomes and 30-day mortality.

Among conduction disorders, atrioventricular blocks were more common in HF patients with preserved EF than bundle branch blocks. However, no statistically significant differences could be revealed between the two groups of patients, except for left bundle branch block, which was significantly associated with heart failure with reduced ejection fraction. The predictive effect of arrhythmias on heart failure hospitalization, all-cause mortality, and sudden cardiac death in HF with preserved EF also remains unknown [9]. Identification of HFpEF phenotypes at higher risk of life-threatening arrhythmias could ease the development of interventions to reduce arrhythmia-induced morbidity and mortality in this category of patients [10].

Following the comparative analysis of the frequency of cardiovascular comorbidities in the two groups of patients, statistically significant associations were identified between patients with rhythm and/or conduction disorders and essential arterial hypertension and chronic pulmonary heart disease, while pulmonary hypertension, dilated cardiomyopathy, and coronary artery disease were significantly more common among dysrhythmic patients with reduced ejection fraction. Classic pathophysiology models of HF with preserved EF are centered on hypertension and other causes of increased left ventricular afterload leading to left ventricular hypertrophy and diastolic dysfunction. However, this type of HF is also linked to systemic proinflammatory changes secondary to common comorbidities that also include hypertension. Changes in ventricular stiffness, peripheral microvascular function, systolic reserve, and chronotropic response also occur. As a result, HF with preserved EF is complex, making it difficult to prescribe uniform therapies for all patients but the treatment of arterial hypertension remains a key step in

the management of this type of heart failure [11]. Unfortunately, no specific antihypertensive treatment has proven a major survival benefit in these high-risk patients. Until the efficacy results of the new valsartan/sacubitril combination are available, continuous monitoring and blood pressure lowering by pharmacological and non-pharmacological means should be considered the major prevention and treatment strategy in HFpEF [12].

Regarding the non-cardiovascular comorbidities, type 2 diabetes and obesity were most frequently associated with patients with rhythm and/or conduction disturbances and heart failure with preserved EF, but no statistically significant differences from the group with arrhythmias and HFrEF were observed. Diabetes is linked to numerous neurohormonal derangements that contribute to poor outcomes in patients with arrhythmias and HFpEF. By increasing angiotensinogen levels and the phenomenon of up-regulation of cardiac angiotensin II receptors, diabetes is associated with advanced hypertensive cardiomyopathy and diastolic dysfunction [13]. Central autonomic neuropathy and sodium retention are also linked to hyperinsulinemia, thus contributing to the deterioration of diastolic function [14]. At the same time, other studies described the link between obesity and HF with rhythm and conduction disorders [15]. Recent data emphasize that obesity is one of the most frequent comorbidities present in patients with HFpEF [16].

Following the analysis of the paraclinical data followed in the study, the existence of significantly lower values of the number of red blood cells, aspartate-aminotransferase, alanine-aminotransferase, and NT-proBNP were observed in the group of patients with rhythm and/or conduction disorders and heart failure with preserved ejection fraction compared to those with reduced ejection fraction. Although the patients included in the study did not have significantly reduced hemoglobin values, the negative prognostic effect of anemia on arrhythmic patients with HF with preserved EF is known: in these patients, anemia is associated with higher all-cause mortality and more frequent and longer all-cause hospitalization compared to non-anemic patients [17]. Treatment of anemia may improve clinical outcomes in these patients. Previous clinical trials have shown heterogeneity of treatment response depending on baseline NT-proBNP levels. However, a recent study has proven that dapagliflozin (a sodium and glucose cotransporter 2 inhibitor, one of the main classes of drugs currently used in the treatment of heart failure with preserved ejection fraction) is safe and improves outcomes, regardless of baseline NT-proBNP concentrations in HF with preserved and moderately reduced EF, the greatest absolute benefit being seen in patients with higher NT-proBNP concentrations [18]. The inverse correlation between the values of transaminases and the ejection fraction is explained by the fact that the worsening of HF leads to the establishment of liver stasis. At the same time, it is well known that the lower the ejection fraction, the higher the natriuretic peptide values.

The inclusion of these patients in cardiovascular recovery programs not only increases effort capacity, but also improves the risk factors, allows a better follow-up of the patient's lifestyle changes, and improves the the quality of life [3]. For this purpose, after compensation, they must perform a cardiopulmonary test and/or a 6-minute walking test, after which, depending on the particularities of each patient, they will be indicated a specific physical training program during hospitalization. At the end of this program, depending on the results obtained, a physical exercise program, that can be followed at the patient's home, will be prescribed. Telerecovery could play an important role in this long-term recovery.

Finally, the medication received by the patients from the two studied groups during hospitalization was comparatively evaluated and no statistically significant difference was demonstrated, except for digitalic therapy, the sacubitril/valsartan combination, and SGLT2 inhibitors, which were associated with heart failure with reduced ejection fraction.

Also, recent studies have shown that digoxin was associated with increased mortality and/or readmission in elderly HFpEF patients discharged after an episode of acute heart failure [19]. Recent guidelines indicate SGLT2 inhibitors as the first line of treatment in HFpEF [20].

Relevance of the study

Although much is yet to be understood about heart failure with preserved ejection fraction, a more detailed insight into the risk factors, epidemiology, prevention, diagnosis, pathophysiology, molecular mechanisms, treatment, and prognosis of this condition has been gained over the past 2 decades. Despite these advances, some barriers still exist. Apart from cardiac amyloidosis, therapies that successfully target the specific pathogenetic mechanisms of HFpEF have not yet been identified. Although the understanding of suitable animal models for the study of human heart failure with preserved ejection fraction syndrome has been improved, basic science studies are still far from truly mimicking the clinical syndrome. Phenotyping of HFpEF is still often done under resting conditions, although most dysfunctions in this type of heart failure only become obvious in stressful situations such as exercise. In these conditions, it is particularly useful to identify and characterize as thoroughly as possible the factors that could worsen the prognosis of these patients, such as rhythm and conduction disorders, which was also the purpose of this research.

Limitations

The limitations of this study are primarily represented by a relatively small number of cases, given the criteria for inclusion of patients in the study, with a relatively small number of patients with ventricular arrhythmias and Hiss-Purkinje system conduction disorders.

4. Materials and Methods

134 patients diagnosed with heart failure, admitted between December 2020 and August 2022 in the Cardiology Department of the Rehabilitation Hospital Cluj-Napoca, were included in the study. Heart failure criteria were defined according to the current guidelines published by the European Society of Cardiology [3]. The diagnosis of heart failure with reduced ejection fraction (HFrEF) was made if the ejection fraction was less than 50%, and of HFpEF when the ejection fraction was greater than or equal to 50%. All patients were evaluated from a clinical, biological, electrocardiographic, echocardiographic, and therapeutic point of view. The selected patients were informed about the study protocol and gave their signed informed consent. The study was carried out with the approval of the Ethics Commission of the Clinical Rehabilitation Hospital Cluj-Napoca (approval no. 29/27.11.2020) and in agreement with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Statistical Analysis

Data were added to Microsoft Excel 16.71 and processed using IBM SPSS Statistics 29. To verify the normality of the data distribution, the Shapiro-Wilk test was used and the homogeneity of the data was verified with the Lavene test. To compare the data, the tests used were chosen according to the type of variables: Student's test for independent samples – quantitative variables with normal distribution, Mann Whitney U test – quantitative variables with abnormal distribution, and the Chi-square test – qualitative variables. Pearson or Spearman tests were used to check correlations between variables, depending on their normal or abnormal distribution. The p-value < 0.05 was considered statistically significant. The description of the data was performed through pie charts and

histograms, and their analysis through contingency tables, column charts, and scatter diagrams.

5. Conclusions

In conclusion, the presence of rhythm and conduction disorders in patients with HFpEF can influence some parameters of the profile of patients with this pathology. Atrial fibrillation is the most common arrhythmia in these patients.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of The Clinical Rehabilitation Hospital Cluj-Napoca (protocol code 29/27.11.2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Conflicts of Interest: The authors declare no conflict of interest.

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