Benefit of Cardiac Resynchronization Therapy in Patients with Heart Failure

VERONICA CALBOREAN[1], DANIELA CIOBANU[2], SORIN CECIL MIREA[3], OANA GALCEAVA[4], VICTOR GHEORMAN[5]*, VLAD PADUREANU[2], CATALIN MIRCEA FORTOFOIU[6], MARIA FORTOFOIU[7], ADRIAN MITA[6], SORIN NICOLAE DINESCU[8], SILVIA ALINA MISCOCI[2] , VENERA CRISTINA DINESCU[9]

[1] University of Medicine and Pharmacy of Craiova, Cardiology Department, County Hospital ofCraiova, 1 Tabaci Str., 200642,Craiova, Romania

[2] University of Medicine and Pharmacy of Craiova, Internal Medicine Department, County Hospital of Craiova, 1 Tabaci Str.,200642, Craiova, Romania

[3] University of Medicine and Pharmacy of Craiova, Surgery Department, County Hospital of Craiova, 1 Tabaci Str.,200642, Craiova, Romania

[4] University of Medicine and Pharmacy of Craiova, Neurology Department, Neuropsychiatry Hospital of Craiova, 99 Calea Bucuresti Str., 200473, Craiova, Romania

[5] University of Medicine and Pharmacy of Craiova, Psychiatry Department, Neuropsychiatry Hospital of Craiova, 99 Calea Bucuresti Str., 200473, Craiova, Romania

[6] University of Medicine and Pharmacy of Craiova, Internal Medicine Department, Filantropia Hospital of Craiova,1Filantropiei Str., 200143, Craiova, Romania

[7] University of Medicine and Pharmacy of Craiova, Emergency Department,County Hospital of Craiova, 2-4 Petru Rares Str., 200349, Craiova, Romania

[8] University of Medicine and Pharmacy of Craiova, Department of Epidemiology, County Hospital of Craiova, 2-4 PetruRares Str., 200349, Craiova, Romania

[9] University of Medicine and Pharmacy of Craiova, Department of Health Promotion and Ocupational Medicine, County Hospital of Craiova, 2-4 PetruRares Str., 200349, Craiova, Romania

Heart failure is a disease characterized by cardiac remodeling or progressive dilation of left ventricle and a consequent reduction in contraction. Ventricular remodeling has been shown to be a negative prognostic factor alone, and therefore the most beneficial drugs are those that prevent or reduce left ventricular dilation. The pharmacological therapy of heart failure, although maximal, has proven to be not fully effective. The aim of our research was to evaluate resynchronization therapy in a lot of patients, monitoring their cardiac performance before and after cardiac resynchronization therapy.

Keywords: cardiac resynchronization therapy, left ventricle, ejection fraction

Heart failure is a disease characterized by cardiac remodeling or progressive dilation of left ventricle and a consequent reduction in contraction. Ventricular remodeling has been shown to be a negative prognostic factor alone, and therefore the most beneficial drugs are those that prevent or reduce left ventricular dilation. The pharmacological therapy of heart failure, although maximal, has proven to be not fully effective [1-2].

According to the latest guideline in the field, in patients with symptoms of refractory heart failure symptoms under maximum treatment, cardiac resynchronization therapy is indicated. Hemodynamic studies performed in the period following implantation of the resynchronization device have shown that this therapy can improve the mechanical function of the left ventricle, increase cardiac output and decrease pulmonary artery pressure. These favorable effects are associated with decreased consumption myocardial oxygen and overall improvement of ventricular function [3-5].

The aim of this study was to evaluate the cardiac performance in patients resynchronized with heart failure NYHA III-IV class by conventional echocardiographic parameters: ejection fraction, volumes and diameters of the left ventricle and left atrium. We also evaluated the effectiveness of resynchronization therapy in patients with heart failure NYHA III-IV functional class, who have already received maximum treatment through the monitoring of natriuretic peptides (NT proBNP), and we also evaluated exercise capacity by maximal effort of oxygen to effort through the 6 min walk test.

Experimental part

Material and methods

We have performed a prospective study carried on 68 patients,aged 43 to 82, admitted to the County Emergency Clinical Hospital during February 2017 - February 2018.

The inclusion criteria for patients were: heart failure patients in NYHA III-IV functional class who remain symptomatic despite optimal pharmacological treatment with left ventricular ejection fraction ≤ 35% (normal men 59 ± 6%, women 58 ± 7%), left ventricletelediastolic diameter increased > 55-60 mm, left ventricle telesistolic diameter increased> 45mm, left atrial size> 40 mm, QRS complex ≥ 120 ms.

Exclusion criteria for patients in our study: Patients with heart failure in NYHA III-IV functional classes, FEVS ≤ 35%, left ventricular dilation, symptomatic despite optimal pharmacological treatment, permanent atrial fibrillation and indication for atrioventricular node ablation; heart failure in NYHA I-II functional class with left ventricle ejection fraction ≥ 35%; Significant valvulopathy, pericardial disease, congenital heart disease, atrial fibrillation, severe pulmonary arterial hypertension, chronic pulmonary disease with severe respiratory failure, stage V kidney disease, psychiatric patients, neoplasms, cirrhosis.

* email: gheormanv@gmail.com; Phone: 0768033526 *The authors contributed equally to the manuscript and share first authorship*

Results and discussions

We analyzed our cohort of 68 of patients with cardiac resynchronization therapy, female/men=24/44.

Table 1

DISTRIBUTION OF THE PATIENTS ACCORDING TO THE GENDER

	Number of patients	Percent
Men	44	65%
Woman	24	35%
Total	68	100%

Distribution of the studied lot according to the environment of origin divulge a number of 28 patients from rural areas and 40 patients from urban areas.

The gender distribution of the 68 patients included 24 women (35%) and 44 men (65%), as shown in table 1. The ratio between males and females in the study group was: M / W = 1.8.

From the point of view of the distribution of the patients according to environment area, 40 patients representing 59% of the studied group come from the urban environment, respectively 29 patients representing 41% of the studied group come from the rural area (table 2).

	Number of patients	Percent
Rural	28	41%
Urban	40	59%
Total	68	100%

Table 2

DISTRIBUTION OF THE PATIENTS ACCORDING TO ENVIRONMENTAL AREA

We classified our cohort in 6 groups of age and we separated the patients by sex.

Table 3 shows that the 70-79 age group predominates with 22 patients in the study group, followed by the age group of 60-69 years with 19 patients. The minimum age was 37 years, while the maximum age was 84 years. All men are predominant in all age groups.

It is noted that cardiac pathology(Heart Failure) is increased to over 60 years old with a close gender distribution, as opposed to younger ages where it is more common in males than in females, and due to ischemic etiology [6].

After the resynchronization procedure, an assessment was made from the first post-implant day (for post-implant complications), then the third post-implant day consisting of clinical examination, electrocardiography, thoracic

Table 3

DISTRIBUTION OF THE PATIENTS BY AGE AND SEX

Group of age	Women	Men	Total
<40 years old	1	2	3
40-49 years old	2	5	7
50-59 years old	4	10	14
60-69 years old	7	12	19
70-79 years old	9	13	22
>80 years old	1	2	3
Total	24	44	68

radiography, echocardiography and interrogation of the pacemaker using the programmer . Subsequent post-procedure complications were assess and followed and patients were evaluated at the 3,6,9 and 12-month visits to observed patients' clinical progression, ECG changes and echocardiographic parameters, the effort test for determining the benefit of this therapies in patients undergoing study. The series of correlations between the parameters followed and the post-implant clinical development were also made.

Postprocedural, functional capacity improved, most patients benefiting from the reduction of at least one NYHA class, as illustrated in table 4.

A percentage of 16% of patients experienced improvement in cardiac function, switching to the NYHA II functional class immediately after post-synchronization, with a progressive increase, at 3 months the percentage being 22% and at 12 months 31%. The percentage of patients with NYHA IV was 63% and immediately reduced post-resynchronization to 31%, continuing this improvement in the following months, so that at 6 months their percentage was 21% and at 12 months 12%. The percentages representing NYHA III functional class patients are apparently increasing compared to those included in inclusion; in fact, these include patients who have benefited from this therapy by switching from NYHA class IV to NYHA class III, in 12 months their percentage being 57%.

By making an average patient number based on the NYHA functional class, it is noted that the clinical severity of the NYHA class of post-echocardiography has been significantly reduced immediately.It is observed that clinical severity of post-syncronized heart rate assessed by the NYHA class has experienced a statistically significant

Table 4

RESULTS ON SEVERITY OF HEART FAILURE SEVERITY ESTIMATED BY NYHA FUNCTIONAL CLASS AFTER CARDIAC RESYNCHRONIZATION

NYHA CLASS	Before CRT	Immediately post CRT	At 3 months	At 6 months	At 9 months	At 12 months
NYHA IV	43 (63%)	21 (31%)	18 (27%)	14 (21%)	10 (15%)	8 (12%)
NYHA III	25 (37%)	36 (53%)	35 (51%)	37 (54%)	39 (57%)	39 (57%)
NYHA II	-	11 (16%)	15 (22%)	17 (25%)	19 (28%)	21 (31%)
TOTAL	68	68(100%)	68 (100%)	68(100%)	68(100%)	68(100%)

Table 5

EVOLUTION OF NTproBNP VALUES AFTER RESYNCHRONIZATION THERAPY

NT proBNP levels	<400 ng/L	400-2000 ng/L	> 2000
Before CRT	0	24 (35%)	44 (65%)
Soon after CRT	0	24 (35%)	44 (65%)
At 3 months	11 (16%)	19 (28%)	38 (56%)
At 6 months	31 (46%)	15 (22%)	22 (32%)
At 9 months	41 (60%)	11 (16%)	16 (24%)
At 12 months	54 (80%)	5 (7%)	9 (13%)

reduction immediately after 3 days, the curve being progressive in the following months from ±3.6 at the time of inclusion at 0.4 at 12 months (p=0.001).

In many studies is demonstrated that CRT improves hemodynamics and symptoms of heart failure by reducing ventricular asynchrony, the patients who performed cardiac resynchronization therapy, showed an improvement in the NYHA class from 3.1 to 2 ($p < 0.05$) [7-9].

NTproBNP was used for the non-invasive assessment of left ventricular function in patients undergoing study. Evolution of NT proBNP values after resynchronization therapy is shown in table 5.

6 minutes walk test (m)	<150 m	150-250 m	250-450 m	> 450 m
Before CRT	38 (56%)	19 (28%)	11 (16%)	0
At 3 months	26 (38%)	21 (31%)	15 (22%)	6 (9%)
At 6 months	17 (25%)	25 (37%)	18 (26%)	8 (12%)
At 9 months	9 (13%)	21 (31%)	23 (34%)	15 (22%)
At 12 months	9 (13%)	16 (24%)	22 (32%)	21 (31%)

Table 6
APPRECIATION OF EFFORT TOLERANCE THROUGH WALK TEST 6 MIN (M)

Ejection fraction%	At inclusion	Immediately after resynchronisation	At 3 months	At 6 months	At 9 months	At 12 months
> 35 %	0	9 13%	14 21%	17 25%	17 25%	19 28%
30-35 %	12 17%	25 37%	30 44%	29 43%	29 43%	31 45%
20-30 %	29 43%	24 35%	15 22%	14 20%	14 20%	12 18%
<20 %	27 40%	10 15%	9 13%	8 12%	8 12%	6 9%

Table 7
EJECTION FRACTION EVOLUTION OF LEFT VENTRICLE AFTER RESYNCHRONIZATION THERAPY

A 65% of the patients from our study had high NTproBNP values> 2000 ng / L, values that were maintained high immediately post-implant, then their levels began to drop and only 56% of the patients remained with high values.

It was noted that 6 months after the procedure, only 32% of the patients maintained NTproBNP> 2000 values, and at the end of the study, their percentage was 13%. At 6.9 and 12 months post-intervention, the number of patients with NTproBNP normalized progressively increased from 46, 60 and 80%.

The high levels of NT proBNP in the early post-implant days are correlated with the severity of heart failure,NYHA III-IV.

Patient evolution was further favorable in the following months after post-resynchronization, so that at the end of the study, the percentage of patients who maintained the NTproBNP level> 2000 ng / L decreased to 13%, NTproBNP> 400-2000ng / L to 7%. It was noted that a high percentage of 80% of patients with heart failure had low NTproBNP values <400 ng / L, with improvement in clinical symptomatology.

It is known that levels of natriuretic peptides are important markers of increased cardiovascular risk, resynchronization therapy substantially reduces NTproBNP which is known to be associated with a better prognosis[10].

Patients were initially evaluated under resting conditions and then after the 6-minute walk test at 3, 6, 9 and 12 months post-implant and we observed an increased exercise tolerance after cardiac resynchronization therapy (table 6).

The assessment of exercise tolerance through the 6-minute walk test at 3 months post-implantation showed a significant improvement, over more than half of patients with an effort tolerance of less than 150 m before the intervention, succeeded to perform a walk test of 150-250 m or between 250 to 450 m.

At 6 months postresynchronization more than 50% of patients performed a walk test of 150-250 m and between 250-450 m and 12% of patients managed to go even more than 450 m.

At the end of the test, 32% of the patients performed a walking test with values between 250 and 450 m, as the percentage of those who went> 450 m increased to 31%. Only 13% had no benefit after this therapy, their exercise tolerance remaining low at <150m.

The ejection fraction improved significantly after cardiac resynchronization therapy from the acute phase when the number of patients with EF<20% decreased from 40% to 15% by ejection fraction improvement and the number of patients between 30 and 35% increased from 17 to 37%.

In the following months, an increase in EF improvement was observed so that at the end of the study, the percentage of patients with EF between 30-35% was 45%, those with an ejection fraction of over 35% was 28% over time the number of patients with EF below 20% decreased to 9%.

The left atrium was reduced from 51 ± 0.4 mm before resynchronization at 49 ± 0.4 mm at 3 months, 46 ± 0.4 mm at 6 months and then at 45 ± 0.4 mm at 12 months post-implant (table 8).

The evaluation of the echocardiographic parameters evaluating the systolic function of left ventricle is illustrated in table 9.

An important objective in the treatment of heart failure is cardiac remodeling. The use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta-adrenergic blockers have improved parallel geometry and ventricular function and reduced mortality and morbidity. In patients with heart failure NYHA class III-IV who, while on maximum medical treatment, are not responding to therapy, CRT benefits from left ventricle remodeling, decreases the telediastolic and telesistolic volumes of left ventricle and increases ejection fraction. Evolution after the resynchronization therapy of the diameters and left ventricular volumes is a very good method of assessing the effectiveness of this therapy.Until at this moment, there are no formal contraindication to CRT. However, great caution should be taken in particular clinical settings[11-14].

A study by Hebert shows that only one-third of patients with heart failure is sufficient to evaluate the NYHA class, at the rest of the patients we need to perform an routine serial echocardiography [15].

The increased telediastolic diameter of the left ventricle at patients included in our study (mean 72 ± 1.4) did not recorded modifications post implantation immediately, but significant values (66 ± 1.2) (p = 0.001) at 6 and 9 months (53 ± 1.2) and 12 months (51 ± 1.2) was noticed.

The left ventricle telesistolic diameter with a mean value of 56 ± 1.2 at study inclusion is not significantly modified postresynchronization (55 ± 1.2), at 6 months it becomes significantly lower (45 ± 1.2), as in 12 months to 44 ± 1.2.

Table 8

EVOLUTION OF THE LEFT ATRIUM AFTER CARDIAC RESYNCHRONIZATION

Parameter studied	At inclusion	Immediately post resynchronization	At 3 months	At 6 months	At 9 months	At 12 months
AS diameter	51 ± 0,4 mm	50 ± 0,4 mm	49±0,4 mm	46±0,4 mm	46 ± 0,4 mm	45 ± 0,4 mm

Table 9

Parameter studied	At inclusion	Immediately postresynchronization	At 3 months	At 6 months	At 9 months	At 12 months
DTDVS (mm)	72±1.4	71±1.2 (p=NS)	66±1,2 (p=0.001)	53±1.2 (p=0.001)	53±1.2 (p=0.001)	51±1.2 (p=0.001)
DTSVS (mm)	56±1.2	55±1,2 (p=NS)	52±1.2 (p=0.001)	45±1.2 (p=0.001)	45±1.2 (p=0.001)	44±1.2 (p=0.001)
VTDVS (ml)	218±28.9	208±28.9 (p=0.001)	206±28.9 (p=0.001)	195±28.9 (p=0.001)	195±28.9 (p=0.001)	191±28.9 (p=0.001)
VTSVS (ml)	173±19.2	171±19.2 (p=NS)	168±19.2 (p=0.001)	155±19.2 (p=0.001)	155±19.2 (p=0.001)	152±19.2 (p=0.001)

Randomized studies over 6 months have demonstrated an absolute reduction of up to 15% of the left ventricletelesistolic diameter and an increase of up to 6% of the VS ejection fraction associated with cardiac resynchronization therapy [16].

The telediastolic volume of left ventricle (mL) at study inclusion of 218 ± 28.9 is statistically significantly reduced immediately postresynchronization (p = 0.001) at 208 ± 28.9. Continuing to be reduced to 3 months (206 ± 28.9) at 6.9 months (195 ± 28.9) and at 12 months (191 ± 28.9).

The telesistolic volume of left ventricle (ml) at enrollment was 173 ± 19.2 with a statistically significant decrease at 3 months (168 ± 19.2), at 6 months (155 ± 19.2), continuing to fall to 152 ± 19.2 at 12 months.

Conclusions

These changes provide consistent evidence of a pronounced, progressive and sustained reversion of cardiac remodeling after cardiac resynchronization therapy.

Cardiac resynchronization therapy (CRT) is a revolutionary interventional technique for patients with refractory heart failure at maximum medical treatment.

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