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RĪGAS STRADIŅA UNIVERSITĀTE

Nikolay Nesterovics

COMPARISON OF VARIOUS HEART PACING METHODS EFFECTIVENESS ON PATIENTS WITH HEART FAILURE AND PERMANENT ATRIAL FIBRILLATION

Dissertation summary
Speciality – Internal medicine, cardiology

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CONTENTS

ABREVIATIONS

AAL – antiarrhythmic agents

AFib – atrium fibrillation

ACC – American College of Cardiology

AFFIRM – Atrial Fibrillation Follow-up Investigation of Rhythm Management study

AH – arterial hypertension

AHA – American Heart Association

AVC – atrioventricular connection

AVJ – atrioventricular junction

AVN – atrioventricular node

BAB – beta adrenoblockers

BNP – brain natriuretic peptide

CFAE – Complex Fractionated Atrial electrogram

CHF – hronic heart failure

CRT – cardiac resynchronisation therapy

ECAS – European Cardiac Arrhythmias Society

ESC – European Society of Cardiology

EHRA – European Heart Rhythm Association

EDD – End Diastolic Diameter

ESD – End Systolic Diameter

HF – heart failure

HRS –Heart Rhythm Society

LV – left ventricle

LVEF – left ventricular ejection fraction

LA – left atrium

MILOS – Multicentre Longitudinal Observational study

MVP – mitral valve prothesis

NASPE – North American Society of Pacing and Electrophysiology

NYHA – New York Heart Assotiation

PAVE – Post A/V Nodal Ablation Evaluation study

QRS –ECG interval

RACE and RACE II – Rate Control versus Electrical cardioversion for AF ib study

RF – radio frequency

RFCA – radiofrequency catheter ablation

SR – sinus rhythm

TICMP – tachycardia induced cardiomyopathy

VVIR – ventricular pacemakers with ventricular rate response function

1. INTRODUCTION

The human heart contains a complex electric system, which provides coordinated blood circulation due to the various physiological mechanisms. Arrhythmia is a failure of this particular system – and none is as pronounced as atrial fibrillation (AFib). It is the most encountered arrhythmia and patients with AFib have a death rate double that of people with sinus rhythm. AFib probability increases with age, from 0.5% for young people to more than 6% for those who are older than 75. (1, 2, 4, 5, 10, 16, 20, 64).

AFib is characterized by fast and irregular atrial activation, usually 400 – 600 times, however with expressed structural change, even 800 times per minute. This kind of non-physiological frequency simply does not provide adequate hemodynamic support from the atrial side into overall heart output, therefore the loss of atrial contribution into systole volume occurs. The loss of atrial contraction increases the risk of stroke due to blood stasis in fibrillated atriums and the subsequent formation of thrombus (25, 26, 27, 28). During AFib the ventricular operating frequency is no longer physiologically controlled from the sinus node side. Instead, the atrioventricular connection (AVJ) filtering mechanism is used, which based on the atrial induced signals, regulates ventricular rhythm. Although AVJ is a lifesaving function (A-V retention) which ensures the transmission of frequencies from atriums to ventricles without pharmacotherapy or other kind of restriction, AFib can cause inadequately rapid and irregular activity of ventricular frequency (26, 27). This kind of condition on its own causes such symptoms as palpitations, heart failure (HF) development, discomfort in the thorax, headaches, as well as could cause syncope. Long lasting tachycardia, the result of uncontrolled ventricular frequency, leads to tachycardia induced cardiomyopathy (TICMP) (30), while adequate frequency control significantly reduces HF development (25, 26, 29, 35) Therefore one should ask the question: What exactly can be termed as

"sufficient" and what can be termed "insufficient" frequency control? Although the 2006 and 2010 AHA/ACC/ESC/HRS guidelines recommend a ventricular frequency of 60 – 85 times per minute as optimal for patients with AFib (25, 35, 37, 63), the data from 2010, and especially RACE II research results, urge taking a reserved look at this concept (63). In fact the expression "optimal ventricular frequency control" is not defined for the whole AFib patient cohort. If the relationship between the ventricular operating frequency and the cardiac output is chosen as evaluation criteria, then frequency control is evaluated as „sufficient" if the heart ejections/ventricular frequency relationship curve has a positive vector direction or positive dynamic, and respectively, if the curve is negative, then it is "insufficient". Another problem is TICMP with progressive HF, heart chambers dilatation, decrease ventricular systolic function and impossible pharmacological frequency control (30, 32, 33, 34, 39).

AFib complications are enough reason to try to retain sinus rhythm. Initially the main role within rhythm control belonged to antiarrhythmic drugs (14, 15). Patients were given more and more potent antiarrhythmic drugs in an ever increasingly doses until AFib had stopped or toxic effects developed (6, 7, 11, 12, 14, 15). The backers of rhythm control pointed out those patients who continued suffering from AFib, had more medical problems than those who had been treated with sinus rhythm maintaining drugs (68, 72). The second less attractive approach is ventricular frequency control. The initiators of this approach pointed out that rhythm control is achievable only for some of the patients (avoidance of antiarrhythmic medications is based on patient safety considerations), but the risk of stroke could be reduced with anticoagulant therapy (1, 2, 3, 5, 13, 16, 17, 65, 66, 70). Over time the low efficiency coefficient (~50% and lower, except Amiodarone) side effects and ventricular proarrhythmia damped antiarrhythmic drug use for patients with AFib and created the necessity to compare the two approaches. Both AFFIRM – "Atrial Fibrillation Follow-up Investigation of Rhythm Management" (1, 2, 72), and

RACE and RACE-II –"Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study", (3, 63, 72, 79) tested the hypothesis, that the maintenance of sinus rhythm with AFib could have similar results for ventricular frequency control. Although the primary objectives for both studies differ – general causes of death AFFIRM against total death rate and serious cardiovascular events in the RACE research, both studies support the fact, that rhythm control was not dominant over frequency control for the elderly population group (72). In both studies the analysis of primary objectives revealed a positive tendency in favour of frequency control. Therefore, both rhythm control and frequency control have their own defined place amongst AFib patients; however many questions remain and one of them – how to react when pharmacotherapeutic medications are no longer effective or their further use may endanger patients safety. The aim of this study is to answer this question.

2. TOPICALITY AND NOVELTY

The treatment of patients with permanent AFib is based on three primary points:

1. Thromboembolism prophylaxis,
2. Heart rate control,
3. HF/TICMP reduction.

All three points are closely interrelated and therefore any variation of these norm indicators positively affects both the rest negative dynamic, and improves the patient's overall forecast and decreases the risk of cardiovascular mortality (31). Since 1982, when Melvin Sheinmann performed the first ever AVJ catheter ablation followed with the implantation of a permanent pacemaker into a patient with permanent, pharmacotherapy uncontrolled AFib, AVJ ablation has been used as an alternative for ventricular frequency control for patients with permanent Afib, for whom pharmacotherapy is not effective or in cases where patients resist the intake of necessary doses of drugs or even when unwanted reaction occurs (25, 28, 34, 35, 37, 38). Because the AVJ is the only way to transfer AFib generated impulses to ventricles, one of the radical methods is to destruct the AVJ and create an AV blockade. This creates the necessity to implant a ventricular pacemaker, and thus the price for perfect rate control is a permanent pacemaker (33). Over time, this method became known as "Ablate and Pace", based on the same name as the research (36, 37). Various publications describe AVJ ablation and implantation of a permanent pacemaker as having a positive influence on the quality of a patient's life over a long time span, as well as load capacity and function of the right ventricle for patients with high symptomatic and pharmacotherapy resistant AFib. In the meantime there appears to be contradictory data on particular patient groups, on comparative data from different groups with systolic failure, on pacemaker

programme influence on load capacity, life quality, dynamics of heart failure development, and methodology associated with further choice of pharmacotherapy (36, 38),. Daoud (40) states that heart ejection increases, if there is constant stimulation, compared to irregular rate, while other authors state that irregular heart rate produces negative hemodynamic effects independently from average rate (40, 41). Nowadays there is one more problem acknowledged – according to some authors, under classical electro stimulation, inappropriate ventricular electrical activation creates a negative and harmful side effect on the top of the right ventricle (42).

Unfortunately, over time "Ablate and Pace" in its original demonstration developed many negative aspects and raised many unanswered questions:

1. „Ablate and Pace" with location of electrodes on the top of the right ventricle over time stimulated HF development, because it simulates the His bundle full left brunch block look, which according to many literature sources drastically worsens heart function and a patient's prognosis (47, 48).

2. Simultaneously performed AVJ catheter ablation and pacemaker implantation exposes the patient to elevated risk, because after AVJ ablation the patient is fully dependent on the functionality of the stimulator, and there is a probability (in centers with limited experience) of electrode dislocation or spontaneous increasing of the threshold (37, 49).

These facts have encouraged the search for a better solution. Although since 2000 there has been rapidly increased development of various catheter ablation technologies and increasingly more patients receiving AFib limiting invasive procedures (left atrium segmentation, CFAE potential ablation, AF-Nest identification, ganglion ablation etc.), there is still a significant patient group for whom these procedures are too late, or because of additional risk factors are not effective in the long run or they cannot be performed at all (35, 37). If the main principles behind the AVJ ablation have remained constant

since Sheinmanns's period (identification of AVJ through invasion with electrophysiological method and heat, cold or any other energy destructs tissues, interrupting conduction in AV node from atriums to ventricles, which results in complete AV block with AFib – Frederic syndrome), then the use of a pacemaker is optional and still debated (50, 51).

Firstly: Where to implant the ventricular electrode? One of the alternative places mentioned is the septal position, close to the His bundle (para-His position) and right ventricular ejection tract localization. Access was justified by close localization of the electrode to physiological transmission routes, normalized QRS interval and general improvement of the patient's clinical state (51, 52). Regrettably publications about these methods before 2006 were usually kept in register format without randomized comparison, before on various authoritative European and Asian congresses started to report about septal and high septal electrode localization benefits. Unfortunately these for a long time could only be attributed to patients with maintained systolic function, whose main problems were palpitations; tachycardia induced hemodynamic disturbances and decrease of life quality (51, 53, 54).

As a possible solution clinics provided cardiac resynchronization therapy CRT for patients with permanent AFib. Large randomized trials demonstrated CRT benefits in selected SM group of patients: following 2007 and 2008 AHA/ACC/ESC/EHRA/HRS guidelines, CRT therapy is indicated for patients with NYHA functional class II – III chronic heart failure, significantly reduced left ventricle systolic function (LVEF<35%), proven electric dysynchrony (QRS duration ≥120 ms), on optimal medical therapy and have sinus rhythm (11). In 2009 the European Society of Cardiology together with European Heart Rhythm association (EHRA) made a correction, which established that CRT can be used in patients with permanent AFib, if AVJ is done, but patients still have to comply with aforementioned guidelines – NYHA II – III, LVEF ≤35%, QRS ≥120 ms. The guidelines of associations in

USA up to the year 2010 connected the usage of CRT in patients with permanent AFib to aggressive control of frequency, retaining similar restrictions (37). This principles of treatment of groups of patients which are outside of restrictions of guidelines, was practically based on hypotheses found in publications and conceptions from universities.

In literature there were compared pharmacotherapy and different localization (septal, right ventricle outflow tract, biventricular) ventricle pacing, but comparison between different types of stimulation methodology was rarely found (54, 59). Comparison of usage of CRT in permanent AFib patients with groups using a combined approach – aggressive or less aggressive pharmacotherapy with or without CRT, after Gasparini and Khadjooi (46, 47, 48), confirmed that a significant CRT effect (hemodynamic, reduce of remodeling) appears only when frequency of stimulation is >85%, though a Multicentre Longitudinal Observational Study (MILOS by Gasparini and Auriccio confirms that CRT with aggressive, hemodynamic affecting frequency control is not superior to mild frequency controlling pharmacotherapy, which is likewise acknowledged by I. Van Gelder (RACE II) in 2010 (63).

A contradiction is encountered in that patients with moderated systolic dysfunction are omitted as they fall outside of the parameters of guideline restrictions (54, 55).

The OPSITE study "Ablate and Pace" approach confirmed significant benefits by reducing a patient's symptomatic and functional condition without substantial difference between right and left ventricle stimulation, though for these patients the left ventricle systolic function remained intact (54, 56). The PAVE (Post AV Nodal Ablation Evaluation) study confirmed "Ablate and Pace" and CRT benefits in patients with LVEF ≤45% and/or NYHA class III heart failure, however, its focusing only on ECHO parameter changes is considered as a shortcoming. There is no data in research literature about comparative analysis, using parameters of remodelation (like REVERSE, C.

Linde et al., classic CRT study about early efficiency in patients with moderated heart failure) or biochemical markers (55). Some smaller studies analyze acute results (6-12 month period) (58). AVERT-AF (Atrio-Ventricular Junction Ablation Followed by Resynchronization Therapy in patients with CHF and AFib) and An-Art focus more on analysis of a patient's functional condition in comparison with pharmacotherapy, thus remains an unexplained wide spectra of changes in the group of patients who are at risk of moderate or severe heart failure, but still doesn't fit classic indications, as described in guidelines (61).

The role of the biomarker atrium natriuretic peptide is significant in chronic heart failure. All four stages of heart failure (Chronic Heart Failure Classification (USA), Hearst etc.), from A to D, plasma BNP or NT-Pre-BNP provide prognostic information. A Val-HeFT substudy test determines that patients with plasma levels of BNP above 238 pg/mL have a 3 times higher risk of lethality in the first 2 years than patients with plasma levels of BNP less than 41 pg/mL. (32.4% against 9.7% of lethality).

If a patient is hospitalized with a diagnosis of heart failure and the plasma BNP level is measured before being released the chances of repeat hospitalization or lethality can be estimated.

In metha analyses from 19 studies, where BNP plasma was to assess lethality risk or cardiovascular system deterioration in patients with heart failure, it was established that elevation of BNP level for every 100 pg/mL is associated with a 35% higher relative risk of death. Furthermore plasma BNP level is superior in prognostication than traditional risk factors, such as heart failure functional classes (NYHA) and left ventricle ejection fraction (27, 62).

3. THE AIM OF STUDY, TASKS, HYPOTHESES

3.1. Aim of the study

The aim of this study is to compare the effectiveness of resynchronization therapy (CRT) against right ventricle top and ventricle high septal localization pacing in patients with permanent AFib, moderate heart failure, moderate left ventricular systolic dysfunction after AVJ catheter ablation over the long time period.

3.2. Tasks of the study

1. To evaluate the impact of procedures on symptomatology, using a variety of pacing localizations over a long period.
2. To evaluate the effectiveness of different approaches for left ventricular functional status over a long time period.
3. To evaluate the different approaches on cardiac cavity size over a long period.
4. To evaluate different approaches of the impact on biochemical markers of heart failure (BNP).
5. To evaluate the impact of different approaches to the heart's electrical synchronicity.
6. To develop a new method for AFib treatment with AVJ RFCA usage, where the patient's life-threatening complication probability is minimized or significantly reduced.

3.3. The hypothesis

The heart resynchronization technique and high septal localization heart ventricle stimulation in comparison with right ventricle apex stimulation are more physiological heart rate stabilization methods in patients with atrium fibrillation and heart failure after AVJ catheter ablation. Furthermore the heart resynchronization method not only improves left ventricle function, but supports the recurrent remodeling process, which has a substantial role in long-term heart failure treatment.

3.4. The structure of the study

The study is written in Latvian and consists of 127 pages. It has 10 parts: an introduction, literature review, aims and tasks of the study, material, methods, results, discussion, conclusion, practical recommendations, and bibliography. The study contains 19 tables, 16 figures and references 277 works.

4. MATERIAL AND METHODS

During the research 90 patients divided into three groups of 30 were analyzed. Since 1997 the Latvian Centre of Cardiology Arrhythmology Ward has performed AVJ Radiofrequency catheter ablation on 156 patients (RFCA) with subsequential implantation of a permanent pacemaker (106 patients) and CRT (46 patients). 90 patients out of this population were chosen, with various permanent pacemaker ventricular electrode localization, as well as patients with CRT implantation. The patients were distributed into 3 groups:

Group A: 30 patients with permanent VVIR type pacemaker with right ventricular apex stimulation;

Group B: 30 patients with permanent VVIR type pacemaker with electrode ventricular septum stimulation;

Group C: 30 patients with CRT implantation.

Group A was added for retrospective analysis due to the fact that from 2005 onwards the P. Stradins Clinical University Hospital Cardiology Center (Arrhythmology Ward) is no longer performing right ventricular apical pacing for patients with AVJ catheter ablation.

Entry criteria:

- Permanent, pharmacologically uncontrollable AFib with a strong subjective symptomatology,
- QRS interval ECG on average 100±30 ms, not exceeding 130 ms,
- left ventricular ejection fraction (LVEF) 43±8%,
- Echo-cg data of enlarged left ventricular diastolic volume>55 mm,
- heart failure functional class II-III NYHA

All patients were given specifically Center designed CRT/invasive arrhythmology procedure and life quality SF – 36 questionnaires (patients were given choice of Latvian or Russian language forms). The procedure methods

and scope was explained to the patients, as well as possible complications and risks. Patients who agreed to participate signed special release forms.

5. RESULTS

5.1. A, B, C group comparative data before the research:

When comparing results from groups A, B, C, it becomes evident that at the beginning of the research the demographic data relates to 90 patients. Minimum age in group A was 52, the oldest was 79 years old, the average age was 62.67 years, the standard deviation 6.39 years and standard statistical error was 1.16. In the B group minimum patient age was 49 years, the oldest patient was 74 years, the average age was 63.40 years, standard statistical deviation was 6.89 years and standard error was 1.25. In the C group minimum age was 52 years, the oldest patient was 77, average age was 66.63 years, standard deviation was 5.94 years, standard statistical error was 1.085. Patient distribution by age is shown in Table 5.1.

Table 5.1.

Distribution of patients by age

	N	Avg.	Std. Dev.	Std. error	95% probability		Min	Max
					Lowest decile	Highest decile		
A group	40	62,67	6,397	1,168	60,28	65,06	52	79
B group	40	63,40	6,896	1,259	60,82	65,98	49	74
C group	40	66,63	5,945	1,085	64,41	68,85	52	77
Sum	*120*	*64,23*	*6,584*	*,694*	*62,85*	*65,61*	*49*	*79*

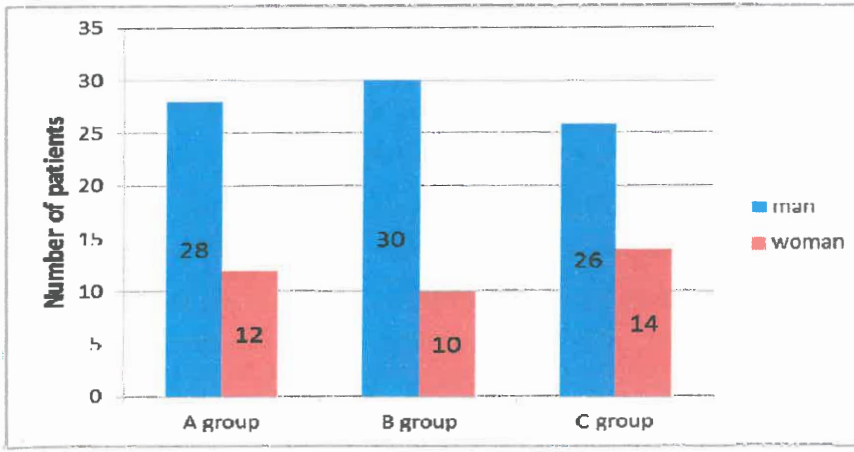

Figure 5.1. Patient distribution based on sex.

We analyzed data from groups A, B, and C and compared them using various criteria.

5.1.1. Patient distribution based on disease

As all 3 groups are dominated by arterial hypertension and coronary heart disease, whose occurrence is almost 90%, it can be stated that patient distribution based on basic pathology is similar. Arterial hypertension and coronary heart diseases are diagnosed based on guidelines and practical recommendations in accordance with ~~to~~ accepted classification of diseases in the country. Mitral valve pathology patients were marked with prosthetic operations after which they retained permanent AFib. For patients whose cause of AFib remained unknown and anamnesis lasted for more than 36 months, AFib caused serious disorder.

Table 5.2.

Patient distribution in groups based on disease symptomatology

Symptomatology	Group A		Group B		Group C	
	Number	%	Number	%	Number	%
Palpitations	30	75.0%	28	70.0%	29	72.5%
Breath Shortness	25	62.5%	23	57.5%	22	55.0%
Tiredness	8	20.0%	7	17.5%	6	15.0%
Coronary pain	4	10.0%	3	7.5%	3	7.5%
Asymptomatic	1	2.5%	1	2.5%	0	0.0%

Patients in all groups highlighted similar symptomatology: the dominant complaint was palpitations, however, no less important role is attributed to symptoms of heart failure, whose main features are shortness of breath and tiredness. Patient distribution based on their complaints is examined in Table 5.2.

5.1.2. Patient distribution in groups by atrial fibrillation duration

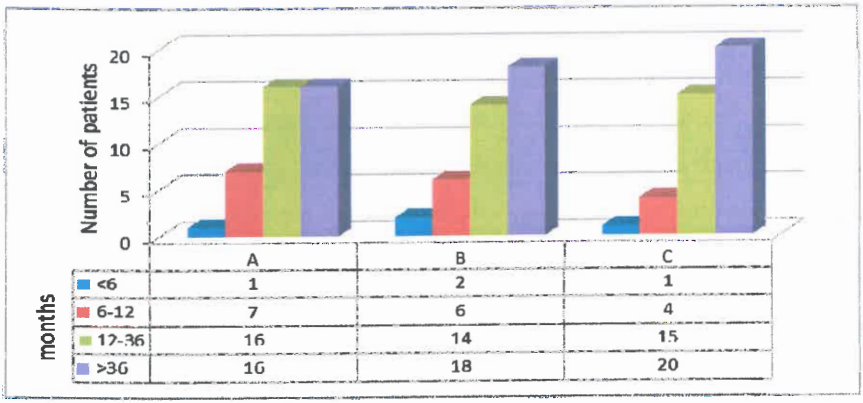

Figure 5.2. Patient distribution by atrium fibrillation duration and research group.

The length of the AFib corresponds to permanent AFib. Frequency control tactics were chosen for patients whose AFib duration was more than 12 months (76.1%), thus for a group for which it was impossible to restore and stabilize sinus rhythm or pose risks for patients based on AHA/ACC/HRS/ESC guidelines. Fig. 5.2. reveals AFib history length in group A, B and C. In group C the duration of AFib was longer than 36 months for 18 patients (60%). From 12 to 36 months the number of patients in the groups was equal. This data confirms that international criteria for permanent AFib, for which it is not possible to perform the rhythm conversion or it is not recommended, corresponds to 63.5% of patients.

Table 5.3.

Patient distribution by NYHA classes before the research

NYHAclass	Group A		Group B		Group C	
	quantity	%	quantity	%	quantity	%
I	2	5.0	1	2.5	1	2.5
II	25	62.5	29	72.5	26	65.0
III	13	32.5	10	25.0	13	32.5
IV	0	0.0	0	0.0	0	0.0
Sum	40	100	40	100	40	100

Heart failure connection with AFib is reflected by total patient distribution in groups A, B and C according to NYHA class (Table 5.3.), prevalent in patients with II and III heart failure class, based on NYHA.

We analyzed ECHO data on the cavity size of the heart: EDD/ESD, LVEF, LA sizes. Both descriptive and statistical methods were used. EDD/ESD measures confirms arrhythmogenic dilatation in all patient groups (A, B and C), meeting the specific criteria of cardiomyopathy. Left atrium size common in patients with permanent tachysystolic AFib, for whom restoration of sinus rhythm and its stabilization is connected by the frequent number of relapses and is problematic in the long run. This confirms rate control as the priority method of choice.

Table 5.4.

Patient distribution by (BNP) indicator.

BNP analysis (microg/ml)		
	B group	**C group**
Output data	340	320
Minimal	50	70
Maximal	570	505
Standard Deviation	202,38	132,18

B and C group patients were determined by a natriuretic peptide (BNP) indicator, which unfortunately was impossible to use in group A, because during this study this analysis was not performed in the hospital.

Before the start of the study, the BNP level was heightened with symmetrical numerical values in both observed groups. These values were analyzed for the completed study.

5.2. Overview of the results from groups A, B and C after 6, 12 and 24 month long observation

Procedure methodology differed for the groups, which was justified by change in concept, which was primarily based on patient safety. Before 2006 the procedure was as follows:

1. When using the transvenous approach, two electrodes were implanted:

- one temporary pacemaker electrode was implanted in order to ensure adequate heart activity rate for the period from AVJ ablation till permanent pacemaker implantation and
- a second, catheter ablation electrode that simultaneously served to recognize electrophysiological signs in the heart cavity.

2. After a successful AVJ catheter ablation, the patient was transferred to the pacemaker implantation hall, where a permanent pacemaker was implanted. In general, the duration of this procedure, where heart rhythm was leaded by a pacer, was 3 hours.

After 2006 the methodology changed:

1. The patient is hospitalized for permanent pacemaker (biventricular or septal localization) implantation. The implantation is performed, the AV node management affecting the pharmacological dose is increased and the patient is discharged from hospital.

2. After 30 days a checkup is required. If tachysystolic, symptomatic AFib remains and the systolic function hasn't improved and if pacemaker functionality (chamber stimulation) isn't approaching 85-90% per day, then the patient is hospitalized again. That same day, after carrying out the necessary exams, an AVJ catheter ablation is performed with one puncture and one electrode. The average duration of the procedure is 30 – 45 minutes, including control time after ablation. The next day, after reprogramming the pacemaker, the patient is discharged from hospital.

It is important to note that complications occurred in patients who were subjected to the earlier methodology. However, after shifting to the two stage method, while performing pacemaker/CRT implantation and AVJ catheter ablation, there were no complications recorded at the cardiology center.

5.2.1. Symptoms overview before and after procedure

Symptoms before and after the procedure – observation time span 24 months

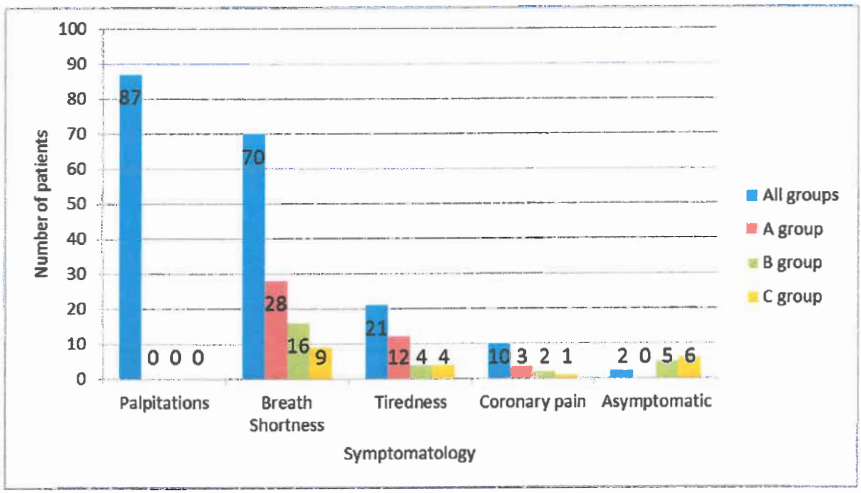

Figure 5.3. Patient complaints

When comparing patient complaints before and after the beginning of this study, the overall picture is totally different. If before the start of the research there were no substantial differences between groups A, B and C, then after 24 months the differences was notable. Heart palpitation symptoms disappeared in all groups. Interestingly, the next most frequent patient complaint was shortness of breath, followed by tiredness and coronary complaints, however overall the most frequent complaint was the combination of palpitations, breath shortness and stenocardic pain, which again shows that AFib is directly related to HF and impaired perfusion. After the procedure, practically asymptomatic during the 24 month period was only group A, relatively more stable felt group B while heart failure symptoms remained in some group C patients. Interestingly, this data applies to patients with

moderately impaired systolic function and changes in 2 years. Patient complaints distribution after 6, 12 and 24 months based on research group is shown in Figure 5.3.

5.2.2. Comparison of results based on NYHA classes

At the beginning of the research, the classification of patient HF corresponded to NYHA II and III functional classes. Comparatively rapid improvement took place in all 3 groups. After 12 and 24 months noticeable statistical differences between group A and C start to appear. Comparisons after examining NYHA classes in A, B and C groups after 6, 12 and 24 months are shown in Fig. 5.4.

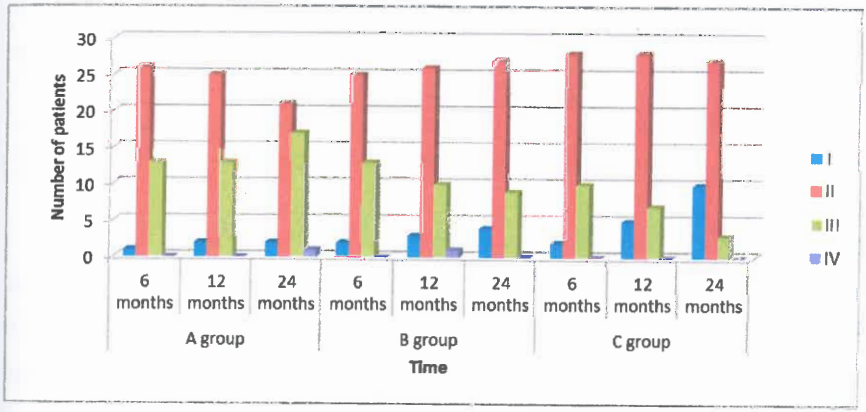

Figure 5.4. Patient groups compared by NYHA clases

5.2.3. Comparison of results after examining cardiac cavity size

Substantial proof of their effectiveness, both overall and individually, provides a comparison of various parameters in the dynamics. The cardiac cavity size is decreased in all patient groups at the beginning of the research, most notably in group C, whereas in group A (retrospective analysis) the observable tendency increases already after 12 months. When comparing LVEF dynamics of change it can be seen, that the advantage of group C does not appear instantly instead it develops gradually, which was something we were aiming to prove in our research.

Figures 5.5. and 5.6. describes the left ventricle end diastolic/systolic diameters dynamics (after data of ECHO ESD and EDD) 6, 12 and 24 months after the procedure. The most noticeable changes were observed in group C, although positive dynamics were also noted in group B. However, in the A group, following a retrospective analysis, a tendency for the left chamber dimensions to expand was observed over time.

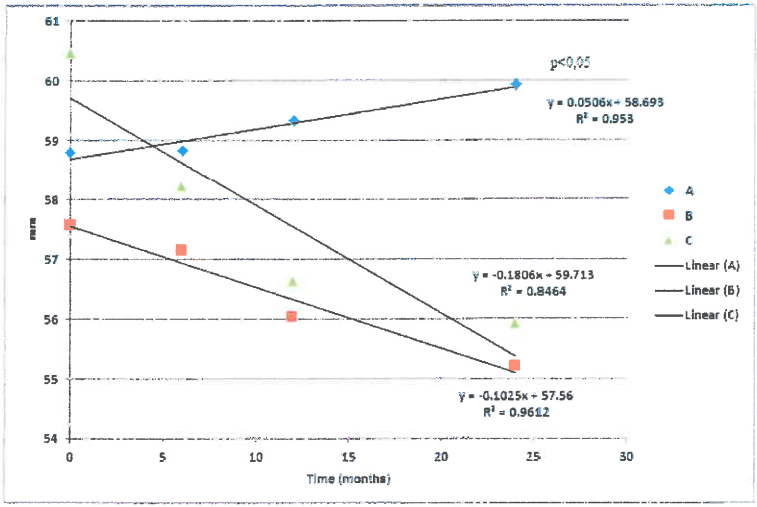

Figure 5.5. Heart left ventricle end diastolic diameter (EDD) in dynamics

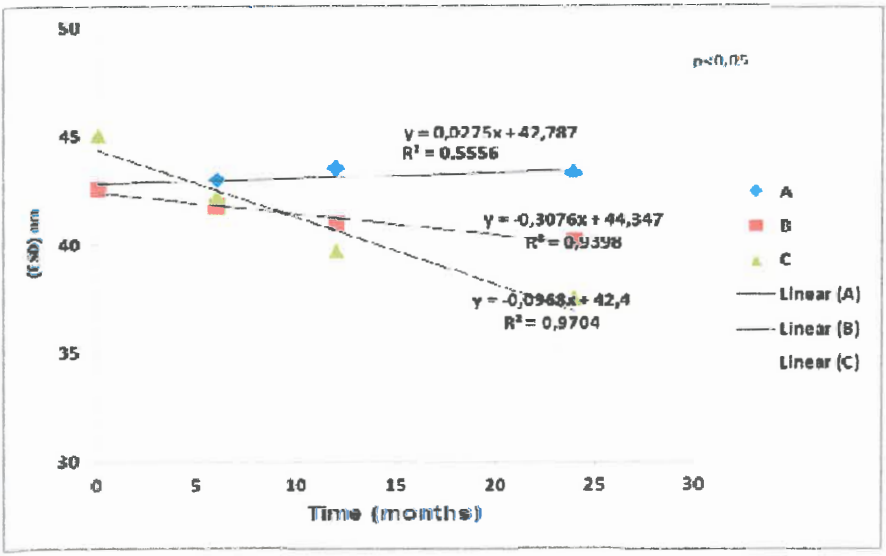

Figure 5.6. Heart left ventricle end systolic diameter (ESD) in dynamics

5.2.4. Comparison of groups A, B, C after LVEF measurement data in dynamics

When comparing LVEF changes, one can see that group C benefits don't appear immediately, but over a longer period of time, something that was a goal of our research. In comparing the graphic data in figure 4.7. it is possible to see how the overall picture in patient groups A, B, and C have changed after the start of the research.

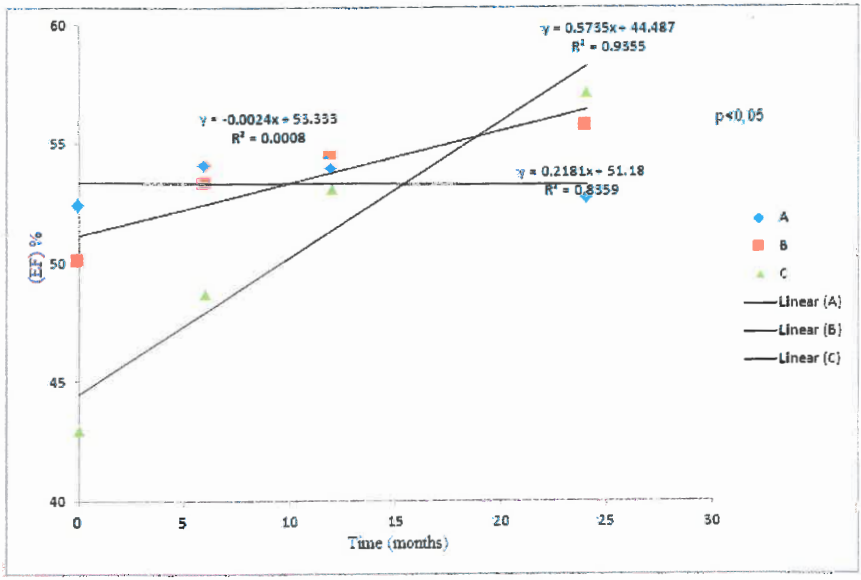

Figure 5.7. LVEF dynamics

5.2.5. Left atrium size dynamics in patient groups A, B, C during the study

As known from scientific literature, left atrium size is one of the most relevant risk markers for AFib and one of the measurements, which allows us predict sinus rhythm restoration and stabilization ability. We compared left atrium size in patients who were incorporated in research. As seen in the comparison, all groups exhibited left atrial enlargement. Statistical analysis shows that there is no statistical reliable difference between the groups.

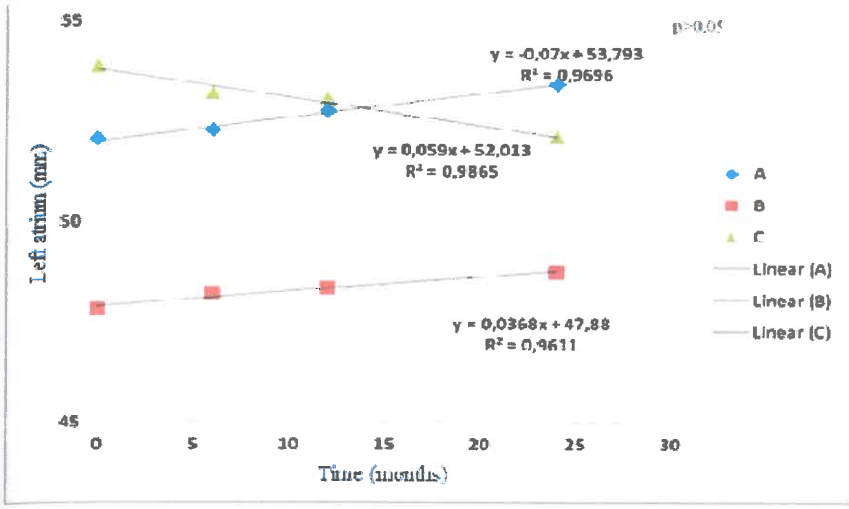

Figure 5.8. Size of left atrium in dynamics

5.2.6. Dynamics of changes in biomarker parameters, patient groups A, B, C

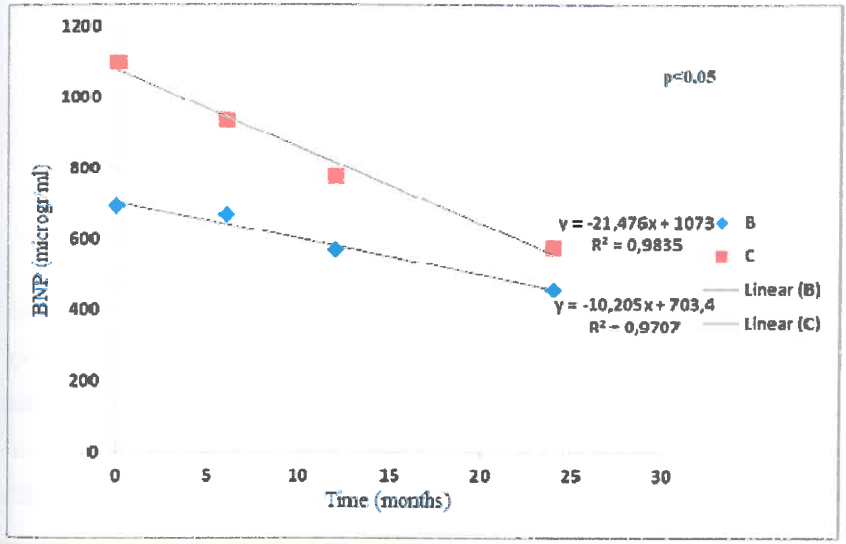

Figure 5.9. Dynamics of B-type Natriuretic Peptide levels (BNP) in patient groups B and C

After six months data of BNP (normal range of BNP <100 pg/ml, value that requires attention, begins from >166 g/ml) in groups B and C differs significantly, and after 12 months this particular marker shows convincing improvement in group C patients.

5.2.7. Dynamics of QRS in patient groups A, B, C

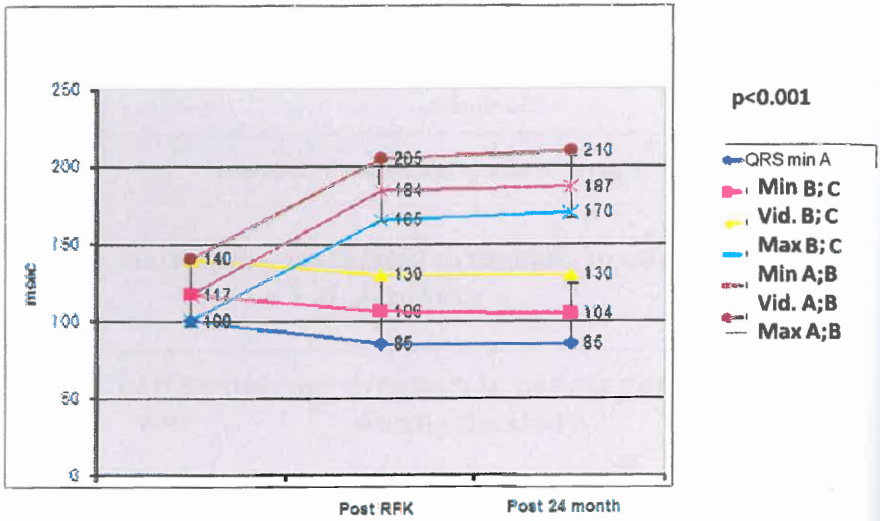

Figure 5.10. Dynamics of QRS in patient groups A, B, C

International guidelines note that QRS duration changes are a risk marker, and there is a direct correlation between QRS duration and mortality risk. The QRS width among group A patients after AVJ catheter ablation and pacemaker implantation in the right ventricle apex remained at 180±30 ms, compared to group B and C patients 110±30 ms ($p<0.001$). Changes of QRS duration in patient groups are shown in figure 5.10.

5.2.8. Comparison of groups A, B, C evaluating after a 6 minute walk test

Comparing groups A, B, C, the functional capacity in patients after CRT and AVJ catheter ablation improves more, which confirms improvement of both left the ventricle wall's synchronicity and biventricular pacing benefits, enhancing load tolerance. In group B there are also benefits, but they differ from data in group C. Load's tolerance in group A was significantly lower, which is shown in figure 5.11.

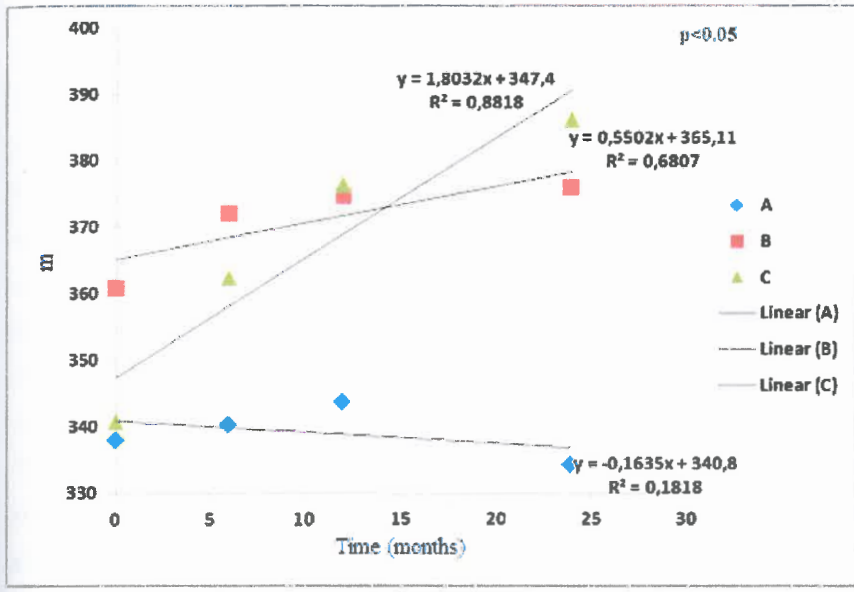

Figure 5.11. 6 minute Walk test parameter dynamics in groups A, B, C

6. DISCUSSION

The aim of this research was to look into the effects of cardiac resynchronization therapy CRT on the highly septal localization stimulation of the apex of the right chamber and the chamber itself for patients with permanent AFib, moderate heart failure and moderate systolic dysfunction of the left chamber after an AVJ catheter ablation in a longer period of time.

What characteristics do data on accessible "Ablate and Pace" share? The groups of patients are not large; the duration of observations rarely exceeds 20 months. To note the most prominent studies: the OPSITE research showed substantially positive results assuaging the symptoms and functional state without notably decreasing the differences between stimulation of the right and left chamber, however these patients still had retained systolic function of the left chamber (30, 32). The PAVE research confirmed "Ablate and Pace" + CRT benefits for patients with LVEF $\leq$45% and/or heart failure class III after NYHA, however the main downside of PAVE is that it focuses only on the variation of the ECHO parameter. There is no data in literature about comparative analysis using both remodulation parameters (such as REVERSE, C. Linde and co-authors, the classic CRT research on early effectuality to patients with moderate heart failure) and biochemical markers (31). AVERT-AF (Atrio-Ventricular Junction Ablation Followed by Resynchronization Therapy in patients with CHF and AFib) and An-Art research (AVJ ablation in CRT) (35, 36) focused on the analysis of functional states of patients in comparison to pharmacotherapy, so the issue still remains unclear on the larger scale differences in the group of problematic patients that do not correspond to the classic CRT indications that are described in most guidelines but retains a potentially high and serious risk of heart failure development without adequate treatment (37). In May 2011, the NASPE congress (M. Brignol) reported

results on a randomized APAF (Ablate and pace in atrial fibrillation) study that seems close to our task, although the research lasted 12-20 months. The research entailed comparison of results for patients with permanent atrial fibrillation after AVJ catheter ablation with the stimulation of the apex of the right chamber and biventricular (CRT) stimulation. The CRT implantation was carried out on patients without direct CRT indications (QRS <120ms, EF >35%, NYHA II-III functional class).

So it can be concluded that extended analysis of different data over a long period of time for different groups of patients is needed to evaluate the comparative effectuality of different approaches and analyze the advantages and disadvantages of different methods.

In order to evaluate the effectuality of different methods, gains and potential losses as well as different aspects need to be taken in consideration. Based on the initial data on groups of patients, all three groups (A, B and C) share common advantages:

1. patients with prominent symptomatics (palpitations of the heart, shortness of breath, coronary ache) share a common effect – the subsiding of palpitations;

2. based on poll data, the need to use medicine that impacts hemodynamics dwindles;

3. decreased risk of potential side-effects from bradycardic medicine.

The shared disadvantages are:

1. the RFCA method demands the implantation of a permanent cardio stimulator, which causes psychological discomfort to a number of patients;

2. The RFCA method has many notable advantages for the frequency control with pharmacotherapy, though it does not discount the use of pharmacotherapy altogether, anticoagulants included;

3. some patients are dependent on the pacemaker, although it retains the III level pacemaker cell rhythm of about 35-40 times a minute;

4. use of the RFCA method for younger patients can cause not only psychological problems but difficulties in workplaces as well. This statement is based on several incidents during the time of observation, although in the last number of years, due to intensive education and publications in medical press, these issues have lost their relevance;

5. the potential complication risk. Pacemaker implantations and AVJ RFCA are one of the least complication-inducing procedures in arrhythmology with the highest number of successful manipulations (close to 100% according to data), although potential risk still remains;

6. comparing the groups of patients whose LV function was retained (retrospective and literary data) the advantage was symptomatic, which can be interpreted differently if one takes objective examinations in consideration

When comparing different methods, procedural differences become noticeable. If RFCA and pacemaker implantation procedures for group A and a small part of group B were executed mostly in one stage, patients of group C and most patients of group B had it done in two stages.

Advantages of a two-stage procedure are:

1. the advantage of not doing RFCA for 100% if the stabilization of heart rate frequency with pharmacotherapy is successful after the CRT/pacemaker implantation, achieving 85-90% stimulation adequate control of the frequency is guaranteed without AVJ destruction (the forming of iatrogenic AV III level blockage) retaining normal AV control and the patient does not depend on a stimulator;

2. after the CRT/pacemaker implantation electrodes stabilize, during a period of 30 days the threshold of stimulation is constant, it cannot be changed as easily as when doing both stages simultaneously;

3. the ablation electrode for patients during RFKA is not located in near proximity of the stimulation, therefore the chance of interfering with the electrode because of heat energy and causing an AV blockage is decreased to

around 0% chance. This problem might occur with a high septal pacemaker electrode localization (figure 6.1.);

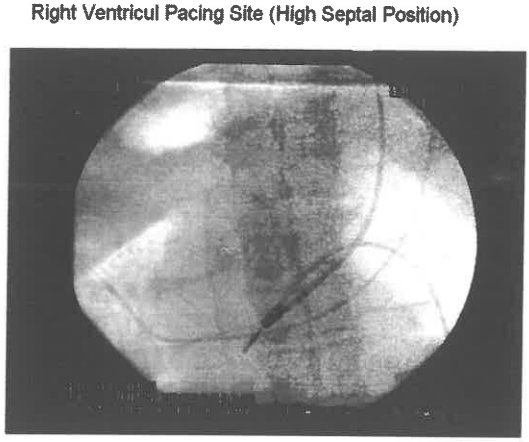

Figure 6.1. The formation of electrocardial electrodes

4. The overall length of procedures is shorter, hospitalization times don't differ substantially, but there is a financial advantage that varies individually;

5. Greatly reduced risk for complications, such cardiac tamponade, which can be caused by the perforation of the right chamber wall with a temporary pacemaker electrode either by transporting the patient or by interaction between electrodes, as well as the risk of hematoma in the spot of the puncture because in the second part of the two-stage procedure another puncture is needed (therefore, less traumatic), although all of these patients have a high risk of CHADS2 and they are on anticoagulants.

The differences in groups A, B and C demand a different analysis if the findings of ECHO are taken in consideration. Initially, the LVEF in all three groups improved, especially without substantial differences, however the

changes in groups B and C were respectively identical, although after 12 months, a division indicated a statistically believable ($p<0.05$) improvement in group C. The results of group B, after a period of initial improvement, started worsening and nearing the data of group A.

The findings correlate with literary data that indicate an acute effect after the "Ablate and Pace" approach to virtually all tachysystolic AFib patients. By reducing tachysystole and stabilizing the time of diastole, the filling of the heart improves, the minute volume as well as the systolic volume increases. Based on the principles of physiology (the Frank-Starling law of the heart), the contractility improves, however in the long term, consequences of TICMP appear, that are characterized by pathophysiological changes to long-term, permanent tachysystolic AFib. These changes are less common to patients with retained systolic function whose state can be improved with the prolonged use of the standard one electrode approach with "Ablate and Pace". Up to now, the analysis of literature has only entailed the comparison between pharmacotherapy and "Ablate and Pace" in the long term, to paraphrase, the stimulation of the apex of the right chamber and one of the left, also known as biventricular stimulation in a shorter period of time (up to 6 months), therefore our research allows to confirm the theses made by authorities in several medical congresses that biventricular stimulation is a choice method for any systolic function for patients issued the "Ablate and Pace" treatment method. This data is objectified both by the QRS interval as a marker of dissynchronia and the level of natriuretic peptide that affirms the advantages of CRT when choosing the "Ablate and pace" approach.

7. CONCLUSIONS

1. The technique of heart resynchronization and stimulation of a chamber with a highly septal localization in comparison to the stimulation of the apex of the right chamber entails more methods of stabilizing physiological heart activity for patients with permanent AFib and heart failure after the AVJ catheter ablation.
2. The technique of heart resynchronization not only improves the functions of the left chamber, but also stimulates the reflexive remodulation process which has a prominent role in the long term treatment of heart failure. This method does not change the size of the left atrium.
3. Both the biventricular (CRT) and the stimulation of the highly-septal chamber are safe and effectual methods which increase patients' quality of life and halt the development of heart failure.
4. The technique of heart resynchronization is superior to other current long term pacing methods if a long term stimulation of the chambers is needed.
5. The "Ablate and pace" strategy can be used for patients with permanent AFib whose heart rate frequencies cannot be controlled by medicaments. It does not replace medicaments, but enhances it when needed. The method substantially decreases the rate of emergency hospitalization and general hospitalization for cardiologic, heart failure and arrhythmia related problems.

8. PRACTICAL RECOMMENDATIONS

AVJ radiofrequency catheter ablation with follow-up CRT implantation is used as a method of choice in:

1. Patients with pharmacotherapy resistant, permanent tachysystolic AFib, which frequency control is impossible to maintain with medications.

2. Patients with tachy-bradisystolic but highly symptomatic permanent AFib, where the aim of the treatment is to control the symptoms.

3. Patients with a marked left chamber dilatation and intraventricular dissynchrony, with the provision that tachysystolic AFib prevails and pharmacotherapy provides an insignificant effect.

4. Patients with permanent, tachysystolic and pharmacologically uncontrollable AFib, with partial conduction disturbances through the bundle of the His or complete blockage of the left bundle branch of the His or where intraventricular conduction disturbances occur.

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