REZUMAT

Scop. Obiectivul nostru a fost studierea anumitor parametri ecocardiografici convenţionali, înainte şi după terapia de resincronizare cardiacă, pentru a stabili importanţa lor în evaluarea rezultatelor acestei terapii şi a întocmi un protocol eficient şi rapid de evaluare a pacientului. Material şi metode. Parametrii ecocardiografici standard care au fost evaluați într-un grup de șaptezeci și patru de pacienți suferind de insuficiență cardiacă, tratați prin resincronizare cardiacă, sunt: întârzierea mecanică interventriculară, întârzierea mecanică între septul interventricular și peretele posterior al ventriculului stâng, diametrul atriului stâng și diametrul telesistolic și telediastolic ale ventriculului stâng, regurgitarea mitrală și fracția de ejeție a ventriculului stâng. Am luat în considerare valorile acestor parametri precum și simptomele pacienților (clasa NYHA) și modificările ECG, înaintea implantului, imediat după, și la trei respectiv şase luni post-implant. Rezultate. Durata QRS, întârzierea de contractie interventriculară și întârzierea de contractie între septul interventricular și peretele posterior al ventriculului stâng s-au arătat semnificativ în faza acută (p= 0,001). La pacienții responsivi la terapie, fracția de ejeție s-a ameliorat semnificativ încă din faza acută (p= 0,001), iar diametrul atriului și ventriculului stâng s-au arătat semnificativ, dar abia la 3 luni postimplant (p=0,001, p=0,001, p=0,001). Gradul regurgitării mitrale s-a ameliorat semnificativ (p=0,001), dar nu la toți pacienții responsivi, iar clasa NYHA s-a ameliorat la majoritatea acestor pacienți. Concluzii. Parametrii ecocardiografici studiați s-au corelat cu modificările clinice și durata QRS și pot fi folosiți de rutină pentru evaluarea pacienților cu insuficiență cardiacă și disincronism.

Cuvinte cheie: insuficiență cardiacă, terapie de resincronizare cardiacă, disincronism, parametri ecocardiografici, remodelare, stimulare biventriculară.

ABSTRACT

Purpose. Our purpose was to study certain conventional echocardiographic parameters, before and after cardiac resynchronization therapy, in order to establish their importance in the evaluation of therapy results and to create an efficient and non time-consuming patient evaluation protocol. Materials and methods. The standard echocardiographic parameters evaluated in a group of seventy-four heart failure patients that underwent cardiac resynchronization therapy are: interventricular motion delay, septal to posterior wall motion delay, left atrium diameter, end-systolic and end-diastolic left ventricle diameter, mitral regurgitation and left ventricle ejection fraction. We considered the values of these parameters before the implant, immediately after the implant (the acute phase), at three and six months after the implant, and also the patients’ symptoms represented by the NYHA class at these specific points. Results. QRS duration, interventricular motion delay and septal to posterior wall motion delay reduced significantly immediately after the pace-maker was implanted (p= 0.001). In responder patients the value of the ejection fraction improved significantly in the acute faze (p= 0.001), and the left atrium’s diameter and left ventricle’s end-diastolic and end-systolic diameters (remodeling parameters) were significantly reduced, but only after three months (p=0.001, p=0.001, p=0.001). The degree of mitral regurgitation also significantly reduced, but not in all responsive patients (p= 0.001). NYHA class has improved in most of these patients. Conclusions. These conventional echocardiographic parameters correlated well with the clinical class and QRS duration, and can be routinely used for dysynchrony and heart failure patient evaluation.

Key Words: heart failure, cardiac resynchronization therapy, dysynchrony, echocardiographic parameters, remodeling, biventricular pacing.

INTRODUCTION

Cardiac resynchronization therapy is a new revolutionary interventional technique for patients with refractory heart failure. It recoordinates the electrical and mechanical activity of the failing heart, by biventricular, atrio-biventricular or left ventricular stimulation, and it has very important effects on cardiac structure and function, with obvious clinical benefits.1-3

The standard selection criteria recommended in the currently available guidelines for NYHA class III/IV are QRS complex duration ≥ 120ms, left ventricular ejection fraction ≤ 35%, sinus rhythm. Although the prolonged duration of the QRS complex is widely considered as a

1 Military Emergency Hospital Timisoara, 2 Cardiology Clinic, Timisoara Institute of Cardiovascular Diseases, 3 Victor Babes University of Medicine and Pharmacy Timisoara

Correspondence to:
Mihaela Nicolin, MD, Military Emergency Hospital Timisoara, Cardiology Clinic, Ghe. Lazar Street, nr.7, RO - 300041 Timisoara, Tel: 0722684128
Email: nicolominhaela@yahoo.com

marker of ventricular asynchronism, in a large number of studies it was observed that in 20 to 30% of patients undergoing cardiac resynchronization therapy based on this parameter, the therapy didn't show any benefit, meaning that the reverse remodeling of the left ventricle doesn't take place. Therefore, QRS complex duration is not a highly accurate parameter to be used in selecting the responder patients to this therapy. It describes only the epicardial synchronic activity and it's not related to the number of fibbers activated earlier or later (an example could be the prolonged QRS complex duration in Wolf-Parkinson-White syndrome). Therefore, determining the mechanical asynchronism is much more accurate.

Trans thoracic echocardiography can determine mechanical dyssynchronism and also its hemodynamic effects, in a qualitative matter, bringing more useful and exact informations. Conventional echocardiographic parameters (ventricular filling interval, interventricular motion delay, septal to posterior wall motion delay, haemodynamic and valvular parameters, cardiac chambers’ dimensions, etc) and modern echocardiographic techniques (tissue Doppler, displacement imaging, tissue tracking, strain imaging, strain rate imaging, tissue synchronization imaging, 3D echocardiography, etc) can be used.

It is not clearly established yet which of these parameters offers optimal information on cardiac dyssynchronism, nor which parameter could prospectively identify the responder patients to cardiac resynchronization therapy. That's why evaluating these parameters and establishing a proper investigation protocol is very important and useful.

**PURPOSE**

The aim of our study was to analyze certain conventional echocardiographic parameters, markers of heart failure and dyssynchronism, and to establish their importance and usefulness in patients' examination before and after cardiac resynchronization therapy. By determining these values, the way they modify, their relationship with NYHA class changing and the number of hospitalizations following cardiac resynchronization therapy, their importance in therapy results’ evaluation and patient selection can be described. Thus, we aim to establish an efficient and simple evaluation protocol for candidates for cardiac resynchronization therapy, a protocol that can be used in everyday examination.

**MATERIALS AND METHODS**

Seventy-four patients that underwent successful implantation of biventricular pacemaker for cardiac resynchronization therapy between 01.01.2004 - 01.01.2010 in the Cardiology Clinic of the Timisoara Institute of Cardiovascular Disease were included in the study. They were clinically, electrocardiographically and echocardiographically examined, before and after the device implantation. (Table 1)

All clinical investigations conformed to the principles expressed in the Helsinki declaration about “Ethical Principles of Medical Research involving Human Subjects”.

**Table 1. Parameters used in patient examination.**

<table>
<thead>
<tr>
<th>Clinical examination</th>
<th>Electrocardiographical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>- NYHA class</td>
<td>- ECG</td>
</tr>
<tr>
<td>- Number of hospitalizations</td>
<td>- QRS complex duration</td>
</tr>
</tbody>
</table>

**Interventricular dyssynchronism analysis**

- Interventricular motion delay
- Septal to posterior wall motion delay

**Structural changing analysis (remodeling)**

- Left atrial diameter
- End-systolic left ventricular diameter
- End-diastolic left ventricular diameter

**Other parameters**

- Mitral regurgitation severity
- Left ventricle’s ejection fraction

**Patients and study design**

The 74 patients included in the study, 63 men and 11 women, with ages ranging between 38 and 74 years old, were selected using the classical criteria for applying cardiac resynchronization therapy. These are: QRS complex duration ≥ 120 ms, left ventricular ejection fraction ≤ 35%, NYHA class III/IV and left ventricular dilation. Fifteen of the 74 patients presented ischemic dilated cardiomyopathy, and the rest presented idiopathic dilated cardiomyopathy. (Table 2)

Thirty five of the 74 patients, 28 men and 7 women, with a mean age of 60 ± 9 years, were implanted with biventricular VDD pacemaker. Biventricular DDD pacemaker was implanted in 25 of 74 patients, 21 men and 4 women, with a mean age of 58 ± 9 years, and 14 out of 74 patients, all men, with a mean age of 55 ± 8 years old, were implanted with biventricular defibrillator cardioverter. (Table 3)
The clinical, electrocardiographic and echocardiographic parameters mentioned before were considered for study. They were determined and analyzed before, immediately after (acute phase), and three months and six month after the implant. The changing in their values was compared, for patient evolution estimation.

**Implant procedure**

Based on the indications, VDD or DDD biventricular pacemakers were used for cardiac resynchronization therapy (CRT). The stimulating leads were implanted by transvenous approach, via the left cephalic vein or left subclavian vein. The left ventricular lead was implanted by passing through the coronary sinus, in a lateral or postero-lateral vein, as far as possible in the venous system. The right atrial and right ventricular leads were implanted conventionally. A fourth lead was implanted when needed, in the right ventricle on the interventricular septum. The implants were realized under radioscopic control. The atrio-ventricular and ventriculo-ventricular intervals were optimized considering the best Doppler echocardiographic profile. To visualize leads’ positions, chest postero-anterior radiographies were done after the procedure. (Fig. 1)

**Echocardiography**

Patients were echocardiographically examined in standard position. Images were obtained with a 3.5-MHz transducer at a depth of 16 cm. Parasternal and apical views were used to measure left atrial diameter, left ventricular end-systolic and end-diastolic diameters, and left ventricle’s ejection fraction (biplane Simpson technique).

The severity of mitral regurgitation was graded using bidimensional color-flow Doppler in the conventional parasternal long axis and apical 4 chamber views. Mitral regurgitation was characterized as follows: regurgitated flow area < 20% of the left atrial area - 1° degree, respectively 20- 40% - 2°, 40-60% - 3°, and > 60% - 4° degree.

Interventricular motion delay (IVMD) was determined by pulsed-wave Doppler. Right ventricle’s preejection interval (from the onset of QRS complex on the ECG to the onset of pulmonary outflow) was measured in parasternal short axis view at pulmonary valve level, and left ventricle’s preejection interval (from the onset of QRS complex on the ECG to the onset of aortic valve outflow) was measured in apical 5 chamber view at aortic valve level. The presence of interventricular dyssynchrony is considered with an IVMD value > 40 ms.

Septal to posterior wall motion delay (SPWMD) was calculated as the shortest interval between the maximal posterior displacement of the septum and the maximal displacement of the left posterior wall, using a mono-dimensional short-axis view at papillary muscle level. The presence of intraventricular dyssynchrony is considered with a SPWMD value> 130ms.

Patients with a shortening of left ventricle’s end-systolic diameter (or volume) of 10% or more at six month follow-up, and with shortening of end-diastolic diameter, left atrial diameter and improvement in mitral regurgitation severity, left ventricle’s ejection fraction and NYHA functional class were considered responders to therapy.

**Statistics**

This is a retrospective analytic study. The parameters are presented as mean value ± SD (standard deviation). Comparisons between the values
determined at certain moments during follow-up were done using student t test, a p value of < 0.05 being considered statistically significant.

RESULTS

Interventricular motion delay, calculated as the difference between left ventricle's and right ventricle's preejection interval, shortened from 70 ± 25 ms before CRT to 35 ± 12 ms (p = 0.001) in the acute phase. Three months after the pacemaker implantation, IVMD value was 32 ± 14 ms, and 29 ± 16.6 ms 6 months after implantation. (Figs. 2-4)

Figure 2. Inter and intraventricular dyssynchronism parameters before and after CRT. IVMD - interventricular motion delay; SPWMD - septal to posterior wall motion delay.

Figure 3. Interventricular motion delay of 59 ms in one patient, before CRT. Pulmonary preejection interval = 70 ms (first image), aortic preejection interval = 129 ms (second image)

Figure 4. Interventricular motion delay of 22 ms in the same patient after CRT. Pulmonary preejection interval = 89 ms (first image), aortic preejection interval = 111 ms (second image)

Septal to posterior wall motion delay mean value before the procedure was 200 ± 32 ms. In the acute phase, the interval shortened to 20 ± 15 ms (p = 0.001), without significant changes at 3 month (19 ± 13 ms) and 6 month (17 ± 16 ms) after implantation. (Fig. 2) Left ventricle's preejection interval before CRT was 165 ± 37 ms, 138 ± 18 ms immediately after CRT, 135 ± 19 ms at 3 months and 134 ± 17 ms at 6 months, respectively.

Left atrial diameter shortened from an initial mean value of 5.1 ± 0.6 cm before pace-maker implantation, to 5 ± 0.6 cm (p= NS) in the acute phase, to 4.8 ± 0.6 cm (p = 0.01) at 3 months follow-up, and to 4.8 ± 0.6 cm (p = 0.01) at 6 months, respectively. (Fig. 5)

Left ventricular end-diastolic diameter, marker of remodelation, shortened from a mean value of 7.3 ± 1.1 cm before CRT to 7 ± 1 cm (p = NS) in the acute phase, to 6.8 ± 1 cm (p = 0.001) at 3 months after CRT and to 6.5 ± 1 cm (p = 0.001) at 6 months, respectively. (Fig. 5)

Left ventricular end-systolic diameter, also marker of remodelation, shortened from an initial value of 5.7 ± 1.1 cm to 5.5 ± 1.1 cm (p = NS) immediately after pace-maker implantation, to 5.3 ± 1.1 cm (p = 0.001)
Concerning mitral regurgitation severity, that can be due either to atrioventricular, interventricular and intraventricular asynchronism, or to an organic affection of the mitral valve, it improved from a mean value of 2.7 ± 0.9 to 2.3 ± 0.7 (p = 0.001) after implantation, then to 2.1 ± 0.7 (p = 0.001) at 3 months and to 1.5 ± 0.6 (p = 0.001) at 6 months. (Fig. 6)

The left ventricle’s ejection fraction, indicating left ventricular dysfunction, improved from a mean value of 23 ± 6.3% to 25 ± 5.1% (p = 0.01) in the acute phase, than to 30 ± 4.5% (p = 0.001) after 3 months, and to 32 ± 4.2% (p = 0.001) after 6 months, respectively. (Fig. 7)

Clinically, heart failure severity is estimated by NYHA functional class. This parameter improved from 3.2 ± 0.4 before pace-maker implantation to 2.7 ± 0.5 (p = 0.001) immediately after the procedure, then to 2.5 ± 0.5 (p = 0.001) at 3 months and to 2.2 ± 0.6 (p = 0.001) at 6 months.

QRS complex duration, with a mean value of 142.9 ± 11.8 ms before CRT, shortened to a mean value of 129.6 ± 7.3 ms (p = 0.001) in the acute phase, and didn’t change during the 6 months follow-up. (Figs. 8-10)
In 15 out of the 74 patients (20%) the beneficial changes in the studied parameters were not observed, their clinical status didn't improve, or even worsened slightly, left ventricular performance didn't improve, and the reverse remodeling of the cardiac chambers didn't take place. They were considered non-responders to cardiac resynchronization therapy. The majority of these patients had lower dyssynchronism values than the responder patients.

Eighteen patients were rehospitalised (24%, 1-3 hospitalizations/patient), 14 of which with worsened symptoms of heart failure. Two of these 14 patients had coronary sinus lead displacement, and one had coronary sinus lead fracture, with loss of stimulation. One of the remaining 4 patients had post implantation hematoma, one had late decubitus lesion at the pacemaker's site, and 2 had post implantation infection.

**DISCUSSIONS**

The clinical, electrocardiographic and echocardiographic (conventional parameters) changes after cardiac resynchronization therapy were described in this study.

We used the same patient selection criterions as in the current guidelines. These were also used in the big randomized clinical studies concerning cardiac resynchronization therapy: MUSTIC (NYHA III, LVEF < 35%, LVEDD > 60mm, 6 min walk test < 450m, QRS > 150ms), PATH-CHF (NYHA III, IV, QRS > 120 ms), MIRACLE (NYHA III, IV, LVEF < 35%, LVEDD > 55 mm, QRS > 130 ms), MIRACLE-ICD (NYHA III, IV, LVEF < 35%, LVEDD > 55 mm, QRS > 130 ms, indication for ICD), CONTAK (NYHA II-IV, LVEF < 35%, QRS >120 ms, indication for ICD), COMPANION (NYHA III, IV, LVEF < 35%, QRS > 120 ms), CARE-HF (NYHA III, IV, LVEF < 35%, QRS > 150 ms or QRS = 120-150 with dyssynchronism).11

We observed that interventricular resynchronization, estimated by IMVD improvement and left ventricular resynchronization, estimated by SPWMD improvement, were statistically significant even in the acute phase. These changes were expected, given the fact that the atrio-biventricular stimulation was echocardiographically optimized for each patient. The improvement of left ventricular contraction continues during the six months follow-up, but less significant. Many other studies considered these parameters, like the CARE-HF study, on a subgroup of 735 de patients with left bundle branch block, where the mean value of IVMD was 49.2 ms, and the ones with values above the mean had the best response to cardiac resynchronization therapy. This didn't mean though that the ones with IVMD below the mean value should not undergo cardiac resynchronization therapy. Pitzalis et al. concluded in their studies that a SPWMD of more than 130 ms predicted the reverse remodeling after cardiac resynchronization therapy with a specificity of 63% and a positive predictive value of 80%. After CRT, SPWMD was shortened a lot, nearly reaching the value of 0, as we also demonstrated in our study.9,11,13

A statistically significant improvement was also observed regarding functional mitral regurgitation severity, starting from the acute phase and continuing during the entire 6 months follow-up. This can be due either to interventricular resynchronization (by resolving the preejectional posterior motion of the interventricular septum, that was modifying the posterior papillary muscle’s position) or to intraventricular resynchronization (which re-establishes the synchronic activation of the papillary muscles).13,14,15 The results were less significant in patients with a certain degree of organic mitral regurgitation.

Prevention of cardiac remodeling improves prognosis in heart failure. The present study confirms

---

Fig.10. The ECG of a patient after CRT. DDD biventricular stimulation
the previous observation that biventricular pacing can result in reverse remodeling, and the changes are associated with improvement in cardiac function. Improvement in studied remodeling parameters (left atrial diameter, left ventricular end-systolic and end-diastolic diameters) was statistically significant at 3 and 6 months follow-up, due to improved contractility and pump efficiency with a lower left ventricular end-diastolic volume.\textsuperscript{2,16} A significant improvement of these parameters was not observed in the acute phase, because reverse remodeling needs time, as it was demonstrated in several studies, like the one of Yu et al.\textsuperscript{16} They described in their study the changes in left ventricular end-diastolic volume after CRT, and the rate of pressure rise in systole (dP/dt) during 3 months follow-up.

Considering the reverse remodeling that developed over time in the cardiac chambers after CRT, the fact that left ventricle’s performance, described by the ejection fraction, improved significantly during the 6 month follow-up more than in the acute phase can be explained.

Echocardiographical findings correlated with clinical findings in therapy responsive patients, the NYHA functional class significantly improving after CRT. Hospitalizations’ number was also low, after applying this therapy. Besides the persistence or heart failure symptoms’ worsening, these were due to implantation complications like: lead disclosure or fracture with loss of stimulation, pain, infection, etc.

Our findings are concordant with the observations of Pitzalis et al, Yu et al, and Bleeker et al. in their studies.\textsuperscript{12,13,16,17} In this study we demonstrated that the parameters we used for patients’ examination are valuable, non-time consuming, and can be used in everyday examinations. Even so, the non-responder percent was $20\%$.

**STUDY LIMITATIONS**

Upcoming studies, on a larger number of patients, to establish the echocardiographic parameter that best describes dyssynchronism, for further lowering of the number of non-responders, are necessary. There are a lot of new studies that describe the importance of modern echocardiographic parameters. It is worth reminding the studies of Anasalone et al, which, by using tissue Doppler at the level of the lateral, inferior, posterior wall and interventricular septum, conclude that stimulating the wall with the longest regional contraction and isovolumic relaxation results in the highest rise in ejection fraction, and of Yu et al, which, by using tissue Doppler, conclude that standard deviation of the time to peak myocardial sustained systolic velocity (Ts-SD) is an independent predictor of left ventricle’s reverse remodeling.\textsuperscript{18,19} Also Bordachar et al demonstrated that the rise in cardiac outflow and the improvement of mitral regurgitation severity correlated with improvement of all tissue Doppler parameters and were superior to SPWMD or IVMD.\textsuperscript{20} Sogaard et al demonstrated, also using tissue Doppler and strain rate imaging, that the number of basal segments with delayed longitudinal contraction predicted the rise in ejection fraction at 12 months after CRT.\textsuperscript{21} Therefore these modern echocardiographic parameters seem to be more sensitive and specific, but they require special expensive hardware and/or software solutions, and they are also time-consuming.

**CONCLUSIONS**

1. The following echocardiographic parameters can be routinely used for heart failure and inter-and intraventricular dysynchronism patients: interventricular motion delay, septal to posterior wall motion delay, left atrial diameter, left ventricular end-systolic and end-diastolic diameters, mitral regurgitation severity and left ventricle’s ejection fraction.

2. The changes in these conventional echocardiographic parameters correlated with clinical and electrocardiographic changes.

3. These echocardiographic parameters can be determined with a medium technical equipped echocardiograph.

4. Echocardiographic evaluation of patients is mandatory before and after cardiac resynchronization therapy, with every periodical interrogation of the pacemaker, and with any change in the clinical status of the patient.

5. The new echocardiographic techniques (although more laborious), promise a more accurate estimation of dyssynchronism in this category of patients, addressing pre-eminently patients with changes that are hard to acquire with the usual techniques.

**REFERENCES**


