PROGNOSTIC FACTORS IN PREDICTING THE SHORT TERM RESPONSE IN THE PATIENTS WITH CARDIAC RESYNCHRONIZATION THERAPY

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Abstract: *We assess the potential benefit of cardiac resynchronization therapy in the patients with normal sinus rhythm, drug refractory chronic heart failure related to dilated cardiomyopathy and prolonged QRS duration. 31 consecutive patients were included with NYHA class II (n=4), class III (n=12) or class IV (n=15) heart failure, LV ejection fraction <30%, and prolonged QRS ≥ 150 ms received biventricular pacing therapy. The 6-minute walk distance was also increased early after the pacing therapy (3 months) and improved additionally by 9 months (all P<0.05). The LV fractional shortening and ejection fraction improved progressively during the resynchronization therapy and were significantly higher than the baseline values after 3 (p<0.05) and 9 months (p<0.01). Cardiac resynchronization therapy reverses LV remodelling and improves cardiac function. The patients with longer QRS duration and longer mitral regurgitation duration are more likely to benefit from atrio-biventricular stimulation.*

Cuvinte cheie: *insuficienţă cardiacă, ecocardiografie, stimulare biventriculară*

Rezumat: *Am urmărit beneficiul terapiei de resincronizare la pacienţii în ritm sinusal, cu insuficienţă cardiacă datorată cardiomiopatiei dilatative refractară la terapia medicamentoasă şi cu durată crescută a complexului QRS. Am studiat 31 de pacienţi consecutivi cu insuficienţă cardiacă clasa II (n=4), clasa III (n=12) şi clasa IV (n=15), cu fracţie de ejecţie < 30% şi QRS ≥ 150 ms care au fost implantaţi cu stimulatoare biventriculare. Testul de mers de 6 minute a crescut precoce după stimulare (3 luni) şi s-a îmbunătăţit suplimentar după 9 luni de urmărire (P<0.05). Fracţia de scurtare şi fracţia de ejecţie s-au ameliorat în timpul stimulării biventriculare şi au fost semnificativ mai mari după 3 (p<0.05), respectiv 9 luni (p<0.01) de urmărire. Terapia de resincronizare cardiacă poate inversa remodelarea ventriculară ameliorând funcţia cardiacă. Pacienţii cu durata complexului QRS mai mare şi cu regurgitare mitrală prelungită au cea mai mare probabilitate de a răspunde pozitiv la stimularea atrio-biventriculară.*

INTRODUCTION

Heart failure is a progressive disease that is characterized by progressive left ventricular (LV) dilatation and loss of contractile function, a condition referred to as remodelling. The severity of LV remodelling has been shown to carry independent prognostic importance. Therefore, treatments that are able to prevent or even regress LV remodelling are potentially beneficial. Despite remarkable advances, the pharmacological treatment of heart failure suffers serious limitations.(1)

According to the most recent guidelines for pacing, cardiac resynchronization therapy (CRT) is indicated when drug therapy has failed (i.e., for the patients who have refractory symptoms despite the optimal drug therapy for heart failure).(2)

Acute hemodynamic studies demonstrated that CRT could improve left ventricular mechanical function, increase cardiac index, and decrease pulmonary artery pressures.(3) These favourable effects were associated with a decrease in myocardial oxygen consumption, indicating a reorganization of the segmental left ventricular contraction sequence and ultimately, an improved global ventricular function, instead of an increase in contractility at cellular level.(4)

Cardiac resynchronization therapy is currently approved for the patients with mild and advanced heart failure (New York Heart Association (NYHA) (class II, III and IV) and a wide QRS complex. These patients derive significant benefits from this therapy, which result in a reduction of the risk of heart failure hospitalization and death, in addition to the improvement of the patients' functional status.

PURPOSE

The aim of this study was to assess the potential benefit of biventricular pacing by comparison with no ventricular pacing in the patients with normal sinus rhythm, drug refractory chronic heart failure related to dilated cardiomyopathy and surface ECG evidence of major intraventricular conduction block.

METHODS

The major inclusion criteria required for the inclusion in the study were : age between 18 and 75 years old, stable sinus rhythm, mild and severe chronic heart failure as defined by NYHA class II, III or IV (in a stable condition for at least 4 weeks despite maximal medical treatment including at least β-blockers, diuretics and ACE inhibitors at doses individually optimized for each patient), left bundle branch block defined by QRS duration more than 150 milliseconds (ms), as measured from three leads at least on surface ECG in spontaneous sinus rhythm, left ventricular ejection fraction (LVEF) assessed by echocardiography less than 30%, left

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ventricular dilatation defined by an echocardiographic end-diastole diameter more than 60 mm.

The major exclusion criteria from our research were: acute coronary syndrome less than 3 months before the procedure, suspected acute myocarditis, significant and correctable valvular heart disease, percutaneous coronary angioplasty or coronary artery bypass grafts within the preceding 12 months. Written informed consent approved by our institutional Ethics Committee was signed by all the individuals included in our research project.

There were included in our study 31 consecutive patients (mean age, 62±7 years old, 19 males) with New York Heart Association (NYHA) class II (n=4), class III (n=12) or class IV (n=15) heart failure, LV ejection fraction < 30%, and electrocardiographic evidence of prolonged QRS ≥ 150 ms received biventricular pacing therapy. The etiologies of heart failure were idiopathic dilated cardiomyopathy in 7 patients, ischemic heart disease in 16 cases and alcoholic cardiomyopathy in 8 subjects. Pharmacological management included diuretics, angiotensin converting enzyme inhibitors, beta-blockers in all patients and digoxin in 25 patients. Serial investigations were performed before the pacemaker implantation as well as 3 and 9 months after cardiac resynchronization therapy was delivered. Studies included echocardiography and 6 minutes walk test (6 MWT).

Atriosynchronized biventricular pacemakers were implanted by a left subclavian approach. The LV pacing lead was inserted through the coronary sinus into the lateral or posterolateral cardiac vein. The biventricular devices used were InSync (model 8040, Medtronic Inc) in all the patients. The AV interval was optimized by Doppler echocardiography.

Echocardiograms were obtained according to a study protocol at baseline, just prior to device implantation, after 3 months and after 9 months. Standard echocardiography, including Doppler studies, was performed using a HP Sonos 5500 machine equipped with a 2.5-MHz phased array transducer. The LV dimensions and ejection fraction were measured by two-dimension guided M-mode method. Change in LV volume was assessed by Simpson's equation using the apical 4-chamber view. LV diastolic function and cardiac output were assessed by pulse-wave Doppler echocardiography. At least 3 consecutive beats of sinus rhythm were measured, and the average value was taken.

Data are presented as mean ± SD. Mann_Whitney *U* test was used to compare the independent variables between the groups. Wilcoxon test was used to assess post-implant differences. Repeated measurement procedure providing analysis of variance when the same measurement is made several times on each subject, was used to compare acute changes of QRS duration, mitral regurgitation between groups by biventricular pacing. Statistical analysis was performed by using SPSS 17 software. $P < 0.05$ was considered statistically significant.

RESULTS

All the patients included in our study were successfully implanted and were receiving ≥ 90% biventricular pacing at follow-up.

There was no change in heart failure medications. The NYHA functional class decreased by at least one class in all subjects except for 5 patients.

The 6-minute walk distance was also increased early after the pacing therapy (3 months) and improved additionally by 9 months (all P<0.05) (table no. 1 and figures no. 1 and 2).

Table no. 1. The results of the 6-minute walk test at 3 and 9 months

Parameter	Baseline	3 months	9 months
NYHA class	3.2±0.4	2.9±0.5	2.4±0.3
6 MWT	307±92	342±86	365±104
EF	25.2±4.2	32.2±8.5	39.4±10.3
LVSD (mm)	67±13	62±10	56±12
LVDD (mm)	72±16	65±10	62±12
dMR (ms)	387±56	348±62	322±56

6 MWT = 6 minutes walk test; EF = left ventricular ejection fraction; LVSD = left ventricular end-systolic diameter in millimetres; LVDD = left ventricular end-diastolic diameter in millimetres; dMR = duration of mitral regurgitation.

Figure no. 1. Changes in 6-minute walk distance before and after 3 and 9 months of biventricular pacing

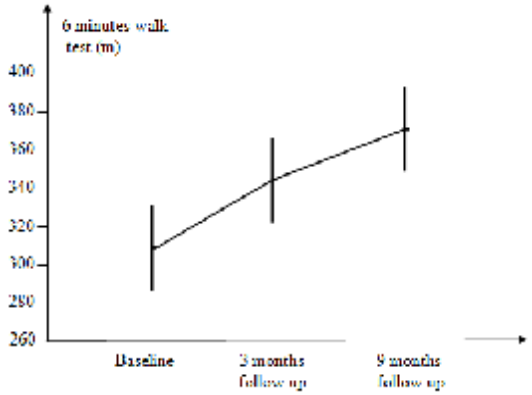
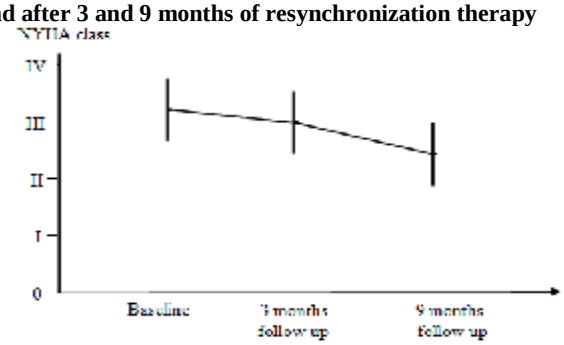


Figure no. 2. Changes in NYHA class of heart failure before and after 3 and 9 months of resynchronization therapy



The LV fractional shortening and ejection fraction improved progressively during biventricular pacing and were significantly higher than the baseline values after 3 (p<0.05) and 9 months (p<0.01), (table no. 1 and figure no. 3). When pacing was stopped, repeating echocardiogram immediately showed a decrease in these parameters, although they were still significantly higher than the prepacing values. The change in cardiac output followed a similar pattern to that of the ejection fraction.

The LV end-systolic diameter was also reduced significantly 3 and 9 months after the pacing therapy (both p<0.05), (table no. 1 and figure no. 4). The mid-systolic mitral regurgitation reduced immediately after pacing (p<0.05) and was sustained throughout the pacing period. For the diastolic function, the LV filling time was significantly increased after the optimization of the atrioventricular interval (p<0.05). Cessation of biventricular pacing was associated with immediate loss of such benefit.

Figure no. 3. Mean differences in the ejection fraction between subgroups after 3 and 9 months of follow-up (FU)

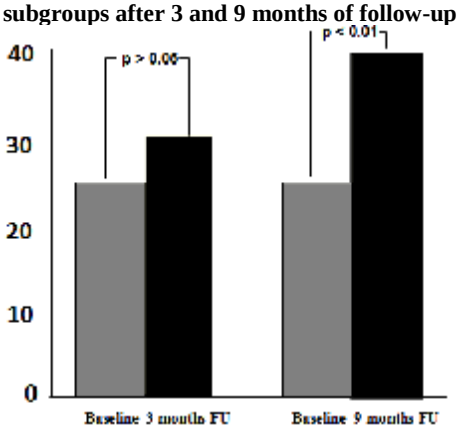
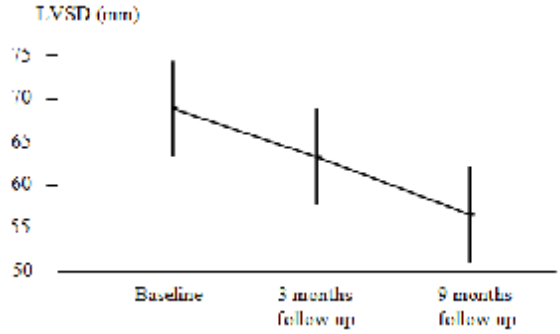
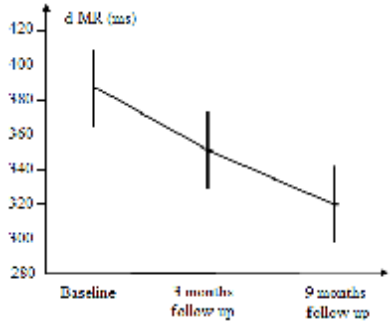


Figure no. 4. Changes in the left ventricular end systolic diameter (LVSD) in millimetres before and after 3 and 9 months of biventricular pacing



There was no change in the isovolumic relaxation time, ejection time, and deceleration time attributable to biventricular pacing. In our population, we did not observe a significant change of the duration of mitral regurgitation (dMR) in the overall population between biventricular pacing turned off and turned on after 3 months of follow up: MR duration 387±56 ms vs. 348±62 ms (p= 0.34), (table no. 1 and figure no. 5).

Figure no. 5. Changes in the duration of mitral regurgitation (dMR) in milliseconds before and after 3 and 9 months of biventricular pacing



This change became statistically significant only after 9 months of follow up: 387±56 ms vs. 322±56 ms (p<0.05).

DISCUSSIONS

This study underlines the effectiveness of cardiac resynchronization therapy to induce LV reverse remodelling in the patients with mild and advanced heart failure. Our study demonstrated that this subgroup of heart failure patients has a clear benefit from biventricular stimulation as shown by: a decrease of QRS duration; improvement of symptoms and exercise capacity; enhanced systolic function and decreased LV dimensions. Mechanistically, the benefits are attributable to an improvement in the intraventricular and interventricular synchrony as well as to a shortening of the isovolumic contraction time.(5)

In our study population, the responder group had longer baseline duration of QRS and mitral regurgitation consistent with the hypothesis that patients with relatively more impaired ventricular synchronization would be more likely to benefit from biventricular pacemakers.

Although previous works have indicated that biventricular stimulation can provide a great benefit to the patients with both ischemic and non-ischemic cardiomyopathy, a greater benefit from CRT in the non-ischemics has been suggested.(6) Our results demonstrate that the resynchronization therapy can improve haemodynamics in both ischemic and non-ischemic cardiomyopathy, and that this is predictive for the clinical outcome in both subgroups and is consistent with the other data.(7)

Some of the limitations of our study are the fact that our research was conducted on a small number of patients and these findings need to be confirmed in larger groups.

CONCLUSIONS

Cardiac resynchronization therapy reverses LV remodelling and improves cardiac function. The patients with longer QRS duration and longer mitral regurgitation duration are more likely to benefit from atrio-biventricular stimulation.

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