

Shortening of paced QRS complex and clinical improvement following upgrading from apical right ventricular pacing to bifocal right ventricular or biventricular pacing in patients with permanent atrial fibrillation

Barbara Małecka, Andrzej Ząbek, Jacek Lelakowski

Department of Electrophysiology, Institute of Cardiology, Jagiellonian University *Collegium Medicum*, John Paul II Hospital, Krakow, Poland

Abstract

Background: Cardiac resynchronisation therapy (CRT) using biventricular pacing (BVP) has been shown to improve survival in patients with chronic heart failure (CHF). However, BVP cannot be achieved in all patients because of technical problems. In such patients, bifocal right ventricular pacing (BFP) may be an alternative.

Aim: To analyse the relationship between changes in paced QRS complex width and clinical responses in previously conventionally paced patients, who underwent upgrading to BFP or BVP.

Methods: A total of 34 patients (26 male, eight female) aged 53.4 to 84 years (mean age 70.3) with CHF, permanent atrial fibrillation and previous right ventricular apical pacing lasting 35.4–184.2 months (mean duration 92.2 months) due to primary or post-ablation (12 patients) atrioventricular block, were included in the study. The patients were split into two subgroups: in the first (ten patients), the cardiac pacing system was changed to BFP, whereas in the second (24 patients), BVP was performed. Over a 12-month period, the following changes were studied: NYHA classification, brain natriuretic peptide levels (BNP), distance covered in a six-minute walk test (6MWT) and left ventricular ejection fraction (LVEF). The observation period was divided into two stages: the first six months after the pacing system was changed, and the six months following that. All 34 patients finished the first observation period, and 27 of them completed the second period.

Results: Clinical improvement was observed in all the patients following the change of pacing system. The greatest clinical improvement occurred during the first stage of observation. At that time, a significant amelioration of HF, according to NYHA classification and improvement in LVEF and 6MWT were noted in both groups. Additionally, a significant improvement (reduction) of BNP level in the BVP subgroup was reported. In the second observation period, a further improvement in the LVEF value was observed in the BVP subgroup. A significant negative correlation between the relative shortening of QRS complex and relative change in LVEF was observed in the whole group, and in the BVP subgroup.

Conclusions: In patients with permanent AF the change of pacing site from right ventricular apex to BFP or BVP results in significant improvement in CHF symptoms. During long-term follow-up these changes are more pronounced in BVP than BFP patients. There is a correlation between shortened QRS complex duration and improvement of LVEF in BVP patients.

Key words: shortening QRS complex, upgraded pacing system, clinical improvement

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Address for correspondence:

Barbara Małecka, MD, Department of Electrophysiology, Institute of Cardiology, Jagiellonian University *Collegium Medicum*, John Paul II Hospital in Krakow, ul. Piłsudskiego 80, 31–202 Kraków, Poland, tel: +48 12 614 20 00, e-mail: barbara_malecka@go2.pl

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INTRODUCTION

Cardiac resynchronisation therapy (CRT) in patients with advanced heart failure (HF) with QRS widening, especially in cases of left bundle branch block (LBBB), has been used since 1994 [1]. Resolution of the signs of HF, as measured by clinical parameters, reduction in frequency of hospitalisations, and longer patient survival, have been reported [2–5]. However, the selection of patients for CRT has remained a significant problem, given the difficulty of finding a parameter that effectively characterises dyssynchronous ventricular contraction. Hopes have been raised by the echocardiographic observation of mechanical dyssynchrony and its regression following CRT. However, mechanical dyssynchrony and electrical dyssynchrony associated with prolonged duration of the QRS complex are not equivalent, and not all patients with QRS widening (electrical dyssynchrony) have mechanical dyssynchrony, and vice versa [6]. Out of many echocardiographic parameters that define mechanical dyssynchrony, none has been found to predict accurately the response to CRT [7]. Thus, despite numerous attempts to find such parameters, QRS widening remains the only dyssynchrony parameter that qualifies for CRT, according to recent guidelines [8].

A special form of electrical dyssynchrony is seen in ECG of patients with right ventricular apical pacing (RVAP). The deleterious consequences of RVAP have been known for many years. The DAVID trial showed that the percentage of RVAP was a major adverse prognostic factor [9]. Studies on the treatment effects achieved by changing from RVAP to CRT have borne out the clinical benefit of the latter procedure, including patients with permanent atrial fibrillation (AF) [10–15]. Patients with permanent AF, advanced atrioventricular block and RVAP have a high percentage of ventricular stimulation without fusion or pseudo-fusion. A high percentage of paced QRS complexes is a prerequisite for the success of CRT [16, 17]. In fact, patients with permanent AF undergoing chronic RVAP due to atrioventricular (AV) block provide a suitable model for the assessment of a pacing system upgraded to biventricular pacing (BVP) or bifocal RV pacing (BFP). In this case, AV synchrony does not overlap with the haemodynamic response, as it does in preserved sinus rhythm.

The aim of our study was to examine the relationship between the shortening of paced QRS complex and selected clinical parameters associated with HF following upgrading of the pacing system from RVAP to BVP or BFP.

METHODS

Patients

A total of 34 patients (26 male, eight female) aged 53.4 to 84 years (mean age 70.3) who had their pacing system upgraded were included in our study. Inclusion criteria were:

1. Advanced systolic left ventricular (LV) failure, NYHA class III or IV despite optimal medical treatment.
2. Permanent AF.
3. Idiopathic or post-ablation advanced AV block with a minimum 95% of effective RVAP. These criteria were

verified via pacemaker statistics and ambulatory ECG recordings during a six-minute walk test (6MWT).

4. Informed written consent for pacing system upgrade.

Exclusion criteria were:

1. Advanced HF with preserved LV ejection fraction (LVEF).
2. RV pacing electrode in non-apical position.
3. Low daily percentage of RV pacing.

Upgrading procedure

A procedure to upgrade the existing RVAP to a BFP system was performed in ten patients, while in the other 24 patients it was changed to a BVP system. Initially, all patients were selected for implantation of LV lead, i.e. upgrading of the RVAP to a BVP system. It was decided that the RV septal outflow tract stimulation would be performed in case of failed catheterisation of the coronary sinus or absence of a venous vessel, allowing for effective attachment of LV lead with acceptable electrical parameters, and (in the absence of patient consent for LV lead implantation) using a limited thoracotomy approach [18, 19].

In all patients, 12-lead ECG, echocardiogram, 6MWT, and serum brain natriuretic peptide (BNP) level measurements were performed.

Electrocardiogram

The ECG recording was taken with the patient lying down after several minutes of rest. A paper speed of 25 mm/s and an amplitude of 1 mV/cm were used. Prior to ECG, the pacemaker was reprogrammed to the VVI mode (by disabling the automatic frequency control), and the basic ventricular stimulation frequency was set at 70 beats per minute (bpm). For ECGs taken after the procedure, the interventricular delay was set at 0 ms (without myocardial pre-excitation from any of the leads). The duration of the paced QRS complex was measured from a standard 12-lead ECG manually from the pacemaker spike to J point using callipers, a ruler and a magnifying glass, and the results were rounded up to the nearest 20 ms. Two measurements were taken for each lead, and the average value was calculated. The maximum value from the 12-lead ECG was accepted as the final value for paced QRS duration.

Echocardiogram

The echocardiogram was taken during VVI mode pacing at 70 bpm with the patient lying on his or her left side, in standard parasternal and apical projections. The LVEF was assessed using Simpson's biplane equation for calculating volumes by an experienced echocardiographer.

Walk test

The 6MWT consisted of walking up and down a 20.6 m long corridor. The test result was the distance (in metres) covered by the patient in six min, rounded up to the nearest metre. Walking time was measured using a stopwatch accurate to

Table 1. Baseline characteristics of the study population

	BFP	BVP	P
Number of patients	10	24	–
Age [years]	72.2 ± 8.6	69.5 ± 8.5	NS
QRS duration during RVAP [ms]	194 ± 13	200 ± 23	NS
Percentage of RVAP [%]	98.0 ± 3	97.0 ± 4	NS
Duration of RVAP [months]	91.3 ± 63.3	92.5 ± 42.4	NS
Duration of AF [months]	96.5 ± 61.9	77.1 ± 53.1	NS
LVEF [%]	34 ± 9	29 ± 6	NS
NYHA class	3.1 ± 0.31	3.2 ± 0.41	NS
6MWT [m]	278 ± 94	281 ± 143	NS
BNP [pg/mL]	642 ± 520	938 ± 761	NS

BFP — bifocal pacing; BVP — biventricular pacing; AF — atrial fibrillation; LVEF — left ventricular ejection fraction; RVAP — right ventricular apical pacing; NYHA — New York Heart Association; 6MWT — six minute walking test; BNP — brain natriuretic peptide

one second. This test was not performed by patients who were incapable of performing exercise, or by patients with locomotor conditions that prevented them from walking. The BNP level was assessed from blood samples collected in the morning before the walking test.

Follow-up

These same tests were repeated throughout 12 months of observation. The observation period was divided into two stages: the first six months after the pacing system was changed, and the six months that followed. The statistical significance of changes in the parameters of clinical improvement and correlations were assessed only in those patients who completed the full 12 months of follow-up.

Calculations

The effects of shortened paced QRS complex duration on LVEF, 6MWT, and BNP measurements were analysed in both subgroups, the BFP and the BVP. To offset individual variations, the subsequent evaluations included only relative changes in these parameters.

Relative shortening of the QRS complex (ΔQRS) was calculated using the following formula: $\Delta QRS = \frac{QRS_0 - QRS_1}{QRS_0}$, where QRS_0 represents paced QRS complex duration during RVAP (baseline value), and QRS_1 represents QRS complex duration during six or 12-month periods of observation, during either BFP or BVP pacing. Similarly, relative change in LVEF ($\Delta LVEF$) was calculated using the formula: $\Delta LVEF = \frac{LVEF_1 - LVEF_0}{LVEF_0}$, relative change in six-minute walk distance ($\Delta 6MWD$) was calculated using the formula: $\Delta 6MWD = \frac{6MWD_1 - 6MWD_0}{6MWD_0}$, and the relative change in BNP level (ΔBNP) was calculated using the formula: $\Delta BNP = \frac{BNP_1 - BNP_0}{BNP_0}$.

Linear correlations between ΔQRS and $\Delta LVEF$, ΔQRS and $\Delta 6MWD$, as well as ΔQRS and ΔBNP , were subsequently calculated for the six and 12-month periods of observation.

Statistical analysis

Statistical analysis was performed using Statistica ver. 7.0 software package (StatSoft). Results are presented as minimum and maximum values, means, and standard deviations for all variables. A comparison between mean measured values was performed with rank sum test (Mann-Whitney U test). The two-variable relationships were tested using nonparametric correlation Spearman test. Statistical significance was set at $p < 0.05$.

RESULTS

The baseline characteristics of patients in the two subgroups, BVP and BFP, are presented in Table 1. The two groups did not differ significantly in terms of the study variables. Two patients did not take the 6MWT.

All patients finished the first observation period, and 27 patients completed the second period. The reasons for failure to complete the second stage of observation were: death (four patients in the BVP subgroup, including two sudden cardiac deaths); the declining neurological status of two patients (one from the BVP subgroup and one from the BFP subgroup); and the orthopaedic status of one patient in the BFP subgroup.

After the change of pacing system, a significant QRS complex shortening was observed in all patients (Fig. 1), which was significantly more pronounced in the BVP subgroup. In every patient, the width of paced QRS complex stayed at the same level over the whole observation period. The average QRS complex width tended to be longer in those patients who did not complete the second observation period than in those who did (170 ± 21 ms vs 157 ± 20 ms, NS).

The greatest clinical improvement occurred during the first stage of follow-up. At that time, a significant improvement in HF symptoms, according to NYHA classification, LVEF and 6MWT was observed. Additionally, a significant reduction of BNP level

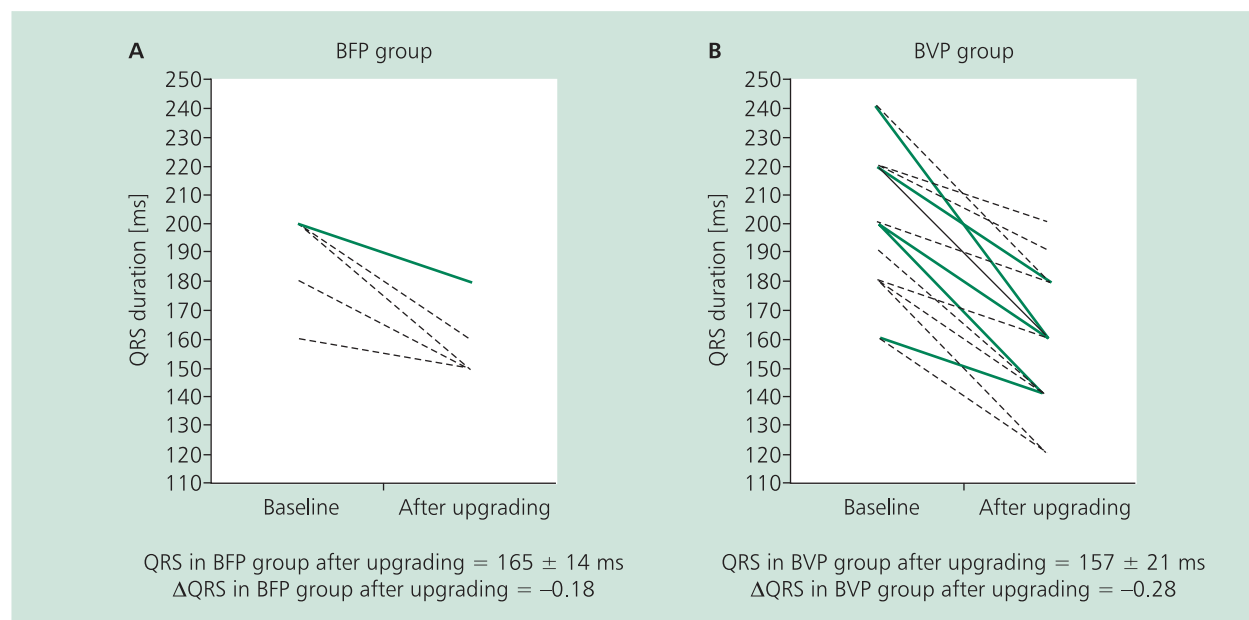


Figure 1. Changes of paced QRS width in the bifocal pacing (BFP) (**A**) and biventricular pacing (BVP) (**B**) subgroups. Data from one or more patients are presented by a single line in BFP and BVP groups. Solid lines represent patients who could not take part in the second observation period

in the BVP subgroup was documented. In the second follow-up period, a further improvement of LVEF was observed only in the BVP subgroup (Fig. 2). The obtained changes of parameters in both subgroups of patients after the 12-month observation period were compared (Table 2). Patients from the BFP subgroup differed significantly from the BVP subgroup by smaller shortening of paced QRS complex and by less pronounced LVEF improvement. The differences in the percentage of paced QRS complexes were not significant (Table 2).

Correlations between shortening of the QRS complex duration and changes in clinical parameters are presented in Table 3. A significant negative correlation between the relative shortening of the QRS complex and relative change in LVEF was observed in the BVP subgroup and in the whole group.

DISCUSSION

This study was conducted in a population with advanced cardiac disease. Old age and comorbidities made it necessary to cut the study's post-operative observation period to six months for seven (20.6%) of the study participants. Investigators studying the effect of CRT in patients with permanent AF have reported the need to reduce the follow-up period in a significant percentage of subjects. In the Mustic AF project, only 37 of the 64 patients included in the study completed the six-month observation period [11]. Despite the difficulties in the analysis of CRT effects, we were able to monitor the isolated effects of ventricular dyssynchrony. Electrical dyssynchrony may be recorded in the form of wide QRS complexes in a large proportion of the circadian rhythm, and subsequ-

ent dyssynchrony reduction following CRT is then reflected by QRS narrowing. This creates a point of reference for assessment of the relationship between electrical dyssynchrony and other parameters associated with HF.

In HF patients, a negative correlation between the prolonged QRS complex duration and LVEF was observed [20, 21]. The MADIT-CRT and REVERSE studies showed the relationship between prolonged initial/non-paced QRS complex duration (describing the electrical dyssynchrony before CRT) and the CRT therapeutic effects. Patients with QRS complex > 150 ms showed greater improvement after CRT [22, 23]. These findings were documented mainly in patients with sinus rhythm and LBBB. The importance of widening of paced QRS complex, especially as a result of RVAP, has not been studied so far, apart from data showing the disadvantageous clinical impact of RVAP in the DAVID trial [9]. This trial also documented the significance of percentage of paced QRS complexes during circadian rhythm.

Studies by Gasparini et al. [16, 17] also demonstrated a benefit of CRT in permanent AF over an extended period of follow-up, as long as a high percentage of ventricular pacing was ensured. In a study by Leon et al. [12], a high percentage of ventricular pacing was ensured by inclusion criteria for patients selected for pacing system change. The same approach was used in our study to ensure high pacing percentage levels. High percentage of QRS captures with recorded, long-existing electrical dyssynchrony, allowed us to relate the clinical effects to the consequences of the shortening of the paced QRS complex duration. Cardiac electrical dyssynchro-

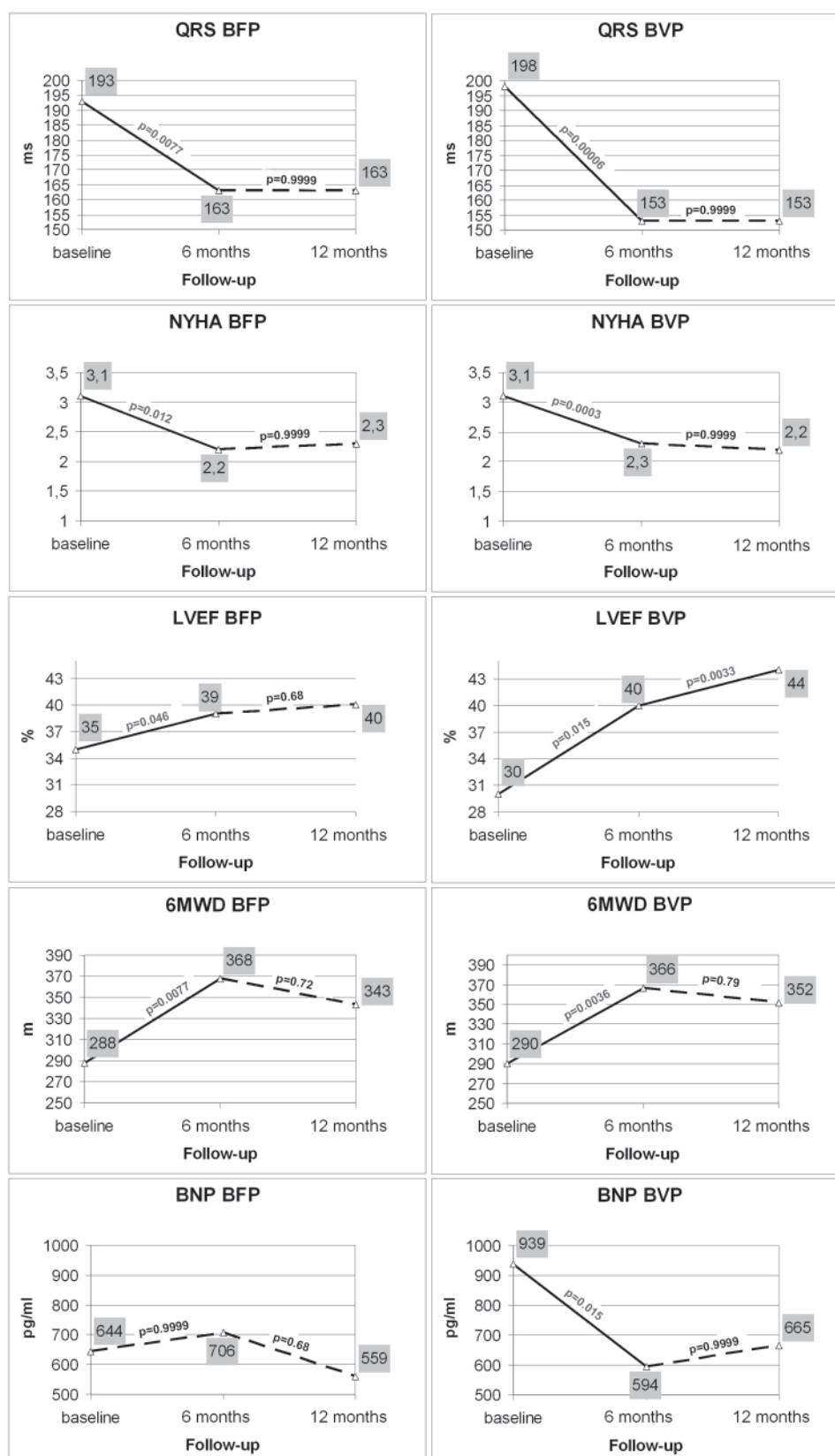


Figure 2. Changes in QRS duration, NYHA status, left ventricular ejection fraction (LVEF), six minute walking distance (6MWD) and brain natriuretic peptide (BNP) level in the bifocal pacing (BFP) and biventricular pacing (BVP) subgroups over a 12-month follow-up

Table 2. Comparison of examined parameters between BFP and BVP subgroups after 12 months of follow-up

	BFP (n = 9)	BVP (n = 18)	P
NYHA class	2.3 ± 0.5	2.2 ± 0.4	0.54
Paced QRS [%]	98.91 ± 0.93	99.09 ± 1.40	0.348
ΔQRS	−0.19 ± 0.09	−0.30 ± 0.12	0.018
ΔLVEF	0.10 ± 0.23	0.30 ± 0.15	0.010
Δ6MWT	0.03 ± 0.56	0.15 ± 0.17	0.83
ΔBNP	−1.12 ± 1.63	−2.46 ± 6.76	0.61

U Mann-Whitney test for independent groups. Abbreviations as in Table 1

Table 3. Linear correlation between relative QRS shortening and parameters of clinical improvement

Parameter	BFP (n = 9)	BVP (n = 18)	Whole group
ΔQRS and ΔNYHA	$R_s = 0.27$; $p = 0.49$	$R_s = 0.22$; $p = 0.39$	$R_s = 0.27$; $p = 0.17$
ΔQRS and ΔLVEF	$R_s = -0.26$; $p = 0.50$	$R_s = -0.52$; $p = 0.028$	$R_s = -0.55$; $p = 0.0031$
ΔQRS and Δ6MWT	$R_s = -0.45$; $p = 0.23$	$R_s = -0.30$; $p = 0.23$	$R_s = -0.35$; $p = 0.076$
ΔQRS and ΔBNP	$R_s = -0.38$; $p = 0.31$	$R_s = 0.12$; $p = 0.64$	$R_s = -0.060$; $p = 0.77$

Abbreviations as in Table 1

ny, expressed in the form of paced QRS complex widening followed by narrowing after upgrading of the pacing system, correlated with an improvement in LVEF during the long term (12 months) follow-up.

The length of the follow-up period after CRT implantation is an important factor in the assessment of therapeutic efficiency. The planned 12-month follow-up was completed by 80% of our patients. This is the longest observation period after upgrading from RVAP to BFP or BVP in patients with AF [11–15]. Various definitions of responders to CRT were proposed, with different variables of clinical improvement relative to the time period [16, 24]. The relationship between QRS shortening and responders' status after CRT was not assessed in this report, to avoid yet another controversial variable.

Moreover, our study is different from the majority of other CRT studies due to our focus on analysis of relative (and not absolute) changes in examined parameters. In the Kashani and Barold [20] meta-analysis, 34 reports assessing the impact of CRT on QRS complex narrowing were summarised. Most of these reports, however, did not study the relationship between QRS complex narrowing and clinical improvement. Only two studies examined an association between these parameters, showing no significant correlation. However, they were carried out in populations different from ours, i.e. predominantly in patients with sinus rhythm and native LBBB.

Our study also included patients with shortened QRS following BFP. The BFP was performed only in the case of unsuccessful implantation of the LV lead. A high percentage of failure of LV lead implantation was associated with a signi-

ficant widening of the right atrium and altered anatomy of the coronary sinus. To the best of our knowledge, there have been no reports comparing the CRT efficacy in patients with permanent AF versus sinus rhythm.

Numerous publications have documented the effectiveness of BFP [25–27]. However, it is not possess the status of BVP according to the recent guidelines of the European Society of Cardiology [8]. Pachon et al. [28] demonstrated the clinical efficacy of the BFP therapy, based on tests carried out one month after the procedure in a specific population of Chagas disease patients. Da Silva Menezes [29] showed that the BFP improvement was limited to six months as a natural result of chronic Chagas disease progression. O'Donnell et al. [30] compared subjects who underwent BFP and BVP procedures (six and 44 patients, respectively). In their study, a comparable QRS shortening and clinical improvement was achieved in both subgroups of patients with preserved sinus rhythm over a 12-month follow-up. However, in contrast to the report by O'Donnell et al. [30], our subjects had AF and initially RVAP.

Others have failed to document the positive effects of BFP treatment, including the randomised BRIGHT trial, which had however a short follow-up (three months) [26, 27]. One study was limited only to intra-operative investigations [25]. Our study presented a significant shortening of QRS duration highly correlating with a significant improvement in LVEF only in BVP patients. The improvement after BFP seemed highly promising in the first six months of the follow-up, while in the second observation period only the BVP patients continued to improve. Our results showed that BFP and BVP in patients with permanent AF are not equivalent.

The limitation of our study is a relatively small population of patients. Larger randomised studies are needed to compare BFP to BVP.

CONCLUSIONS

1. In patients with permanent AF, there is a shortening of QRS complex and clinical improvement following the pacing system being upgraded to BVP or BFP.
2. A significant correlation between shortened QRS complex duration and increased LVEF was shown only in BVP patients over a 12-month follow-up.

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Skrócenie czasu trwania wystymulowanego zespołu QRS a poprawa kliniczna w 12-miesięcznej obserwacji po rozbudowie systemu stymulacji z jednopunktowej wierzchołka prawej komory do dwupunktowej prawej komory lub dwukomorowej u chorych z utrwalonym migotaniem przedsionków

Barbara Małecka, Andrzej Ząbek, Jacek Lelakowski

Klinika Elektrokardiologii, Instytut Kardiologii, Uniwersytet Jagielloński *Collegium Medicum*, KSS im. Jana Pawła II, Kraków

Streszczenie

Wstęp: Stymulacja resynchronizująca (CRT) jest uznaną metodą leczenia przewlekłej skurczowej niewydolności serca (HF). Jej zastosowanie wpływa na szerokość zespołu QRS również u chorych poddawanych uprzednio przewlekłej prawokomorowej wierzchołkowej stymulacji serca.

Cel: Celem pracy była analiza związku zmian szerokości wystymulowanego zespołu QRS z odpowiedzią kliniczną w populacji chorych z utrwalonym migotaniem przedsionków (AF) i wysokim dobowym odsetkiem stymulacji serca.

Metody: Do badania zakwalifikowano 34 pacjentów (26 M, 8 K), w wieku 53,4–84 lat (śr. 70,3 roku), z przewlekłą HF i utrwalonym AF, którzy byli poprzednio stymulowani z wierzchołka prawej komory (RV) 35,4–184,2 miesiąca (śr. 92,2 miesiąca) z powodu bloku przedsionkowo-komorowego samoistnego lub poablacyjnego (12 osób). Pacjentów podzielono na dwie podgrupy. W pierwszej zmieniono system stymulacji serca na dwupunktowy RV (BFP; n = 10 chorych), w drugiej wprowadzono dwukomorową stymulację resynchronizującą (BVP; n = 24 chorych). Podczas 12-miesięcznej obserwacji porównano zmianę klasy NYHA, stężenie mózgowego peptydu natriuretycznego (BNP), pokonanego dystansu w teście 6-minutowego marszu (6MWT) i frakcji wyrzutowej lewej komory (LVEF) do skrócenia czasu trwania wystymulowanego zespołu QRS. Okres obserwacji podzielono na dwa etapy: pierwsze 6 miesięcy po rozbudowie i następne 6 miesięcy. Wszyscy chorzy ukończyli pierwszy etap obserwacji, a 27 pacjentów oba.

Wyniki: U wszystkich chorych zarejestrowano poprawę kliniczną po zmianie systemu stymulacji. Największą poprawę stwierdzono w pierwszym okresie obserwacji. W tym czasie istotną poprawę w zakresie HF mierzoną klasą NYHA, LVEF i 6MWT zanotowano w obu podgrupach. Dodatkowo istotne obniżenie BNP zaobserwowano u chorych z podgrupy BVP. W drugim okresie obserwacji dalsze istotne zwiększenie LVEF wystąpiło w podgrupie BVP. Zmiana szerokości QRS korelowała istotnie statystycznie z LVEF w całej grupie badanych i w podgrupie BVP.

Wnioski: U pacjentów z utrwalonym AF przewlekłe stymulowanych z wierzchołka RV zmiana systemu stymulacji na BFP i BVP prowadzi do istotnej poprawy parametrów klinicznych. Skrócenie czasu trwania zespołu QRS koreluje z poprawą LVEF w całej populacji chorych i w podgrupie BVP.

Słowa kluczowe: skrócenie wystymulowanego zespołu QRS, rozbudowa systemu stymulacji, poprawa kliniczna

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Adres do korespondencji:

dr n. med. Barbara Małecka, Klinika Elektrokardiologii, Instytut Kardiologii, Uniwersytet Jagielloński *Collegium Medicum*, KSS im. Jana Pawła II w Krakowie, ul. Prądnicka 80, 31–202 Kraków, tel: +48 12 614 20 00, e-mail: barbara_malecka@go2.pl

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