

THE EFFICACY OF BIFOCAL RIGHT VENTRICULAR PACING IN CARDIAC RESYNCHRONIZATION THERAPY FOR THE TREATMENT OF HEART FAILURE

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Abstract

Background: It has been reported that bifocal pacing (BiFP) in the right ventricle (RV) may be an alternative to unsuccessful left ventricular (LV) lead implantation.

Aim: This study seeks to assess the improvement in the clinical and hemodynamic parameters after long term BiFP in patients eligible for cardiac resynchronization therapy (CRT), in whom conventional biventricular (BiV) implantation was not feasible or failed.

Methods: The three leads (right atrial appendage, RV apex and RV outflow tract) of a BiFP were implanted in 46 patients, among whom 16 lost follow up within one month of BiFP implantation, so 30 patients (19 male/11 female) were enrolled in the study with the mean follow up period of 8.7 (\pm 6.7) months. All patients had heart failure refractory to medical therapy, New York Heart Association (NYHA) functional class of II, III and IV, ejection fraction (EF) \leq 35 %, left bundle branch block (LBBB) with QRS duration \geq 130 milliseconds and functional mitral regurgitation. The parameters (QRS duration, NYHA class, EF, and cardiomegaly) were evaluated before and 1, 3, 6, 12 and 24 months after BiFP implantation. A six minute walk test (6MWT) was performed on 7 patients, before and after implantation.

Results: The results showed significant improvement in whole parameters, after both acute and long term BiFP. The improvement increased during subsequent follow up.

Conclusions: The study concluded that BiFP is a feasible type of CRT in patients with refractory HF and can be used as an alternative to biventricular pacing when LV lead implantation is infeasible.

Keywords: Bifocal right ventricular pacing, cardiac resynchronization therapy, heart failure

Introduction

Heart failure (HF) is an increasingly common condition in the developed world, which causes significant morbidity and mortality (Cleland *et al.*, 2001). The treatment of congestive HF has improved with the great therapeutic advances of the past two decades, with clear reductions in the morbidity and mortality of these patients. However, many patients remain with significant symptoms and incur a high number of hospital admissions (Rocha *et al.*, 2007). This is why an electromechanical approach (through pacing) is acceptable in certain patients as a useful adjunct to optimal medical therapy (Cazeau *et al.*, 2001; Abraham *et al.*, 2002).

Dyssynchrony; atrioventricular (AV) delay, inter- and intra-ventricular delay (VD); which are common in patients with HF (Paisey & Morgan, 2004), are a consequence of progressive global or focal degradation of the myocardium, caused by the heterogenous propagation of cardiac electrical activity (Cazeau *et al.*, 1998). First-degree heart block is common in, and contributes to HF (Panidis *et al.*, 1986), and is a reliable indicator of AV conduction delay. Inter- VD defined as the time interval between RV and LV depolarization (mostly LV delay as the common conduction defect in ischaemic and cardiomyopathic ventricles) resembles LBBB both electrically and mechanically (Haber & Leatham, 1965). Prolonged AV intervals result in the loss of cardiac output (C.O) due to reduced ventricular filling time and pressure and increased mitral regurgitation (MR) (Panidis *et al.*, 1986).

CRT with biventricular (BiV) pacing is recommended in patients with advanced HF, severe systolic dysfunction (LVEF \leq 35%) and intra-ventricular conduction delay -intra-VCD- (QRS \geq 120ms).

Resynchronization may improve pump performance and reverse the deleterious process of ventricular remodeling (Saxon *et al.*, 2010). CRT with BiV (in which the left lead implantation is achieved by transvenous insertion into tributaries of the coronary sinus) (Paisey & Morgan, 2004) can restore cardiac synchrony in some patients and is associated with improved systolic function and clinical outcomes (Abraham *et al.*, 2002). Although a

substantial hemodynamic effect is evident from many studies, the technique used for LV lead implantation is associated with many limitations, including a definite learning curve, failure to implant, a relatively high dislocation rate, and additional complications such as phrenic nerve stimulation (Vlay 2004, 2006).

BiFP, using two pacing sites in the RV: RV apex (RVA) and RV outflow tract (RVOT), has been developed as an alternative way to achieve cardiac resynchronization in special situations (Barold *et al.*, 2008b). In contrast to that of CRT, the technique used for placing an RVOT lead is associated with a short learning curve, no special delivery tools are involved and the technical success rate is very high. Several non-randomized long-term studies of CRT candidates, including single case reports, suggest that bifocal RV pacing may yield a sustained hemodynamic benefit with improvement in LV function (da Silva, 2004; O'Donnell *et al.*, 2005). In two studies (Saxon *et al.*, 2003; Res *et al.*, 2007), clinical and echocardiographic parameters have demonstrated significant improvement in a NYHA class, 6MWT, EF, and grade of MR at three months compared to baseline.

The aim of the present study is to assess the long-term benefit and effectiveness of bifocal right ventricular pacing implantation (as an alternative to the standard method) through assessing the clinical and echocardiographic parameters of heart failure patients who do not respond to optimal pharmacological therapy.

Methods

This study is a simple descriptive design. It includes the consecutive patients who were referred to the Sulaimanyah Center for Heart Disease (SCHD) and Nasriah Heart Center (NHC) for CRT implantation, from 2005 to 2011. Bifocal pacing was chosen for the following reasons: failed implantation using the conventional technique, whole facilities of conventional CRT implantation (coronary sinus entrance) being unavailable, and, lastly physician's choice. The inclusion criteria were as follows: a) Heart failure patients with NYHA class II, III and IV despite optimal medical therapy; b) LVEF \leq 35%; c) LBBB with QRSd \geq 130; and d) Functional MR. 46 patients fulfilled the inclusion criteria, 16 of them lost follow up for more than one month, so the number of patients included in the study was 30.

Patients were kept on the following medications: ACE-inhibitors, Beta-blockers, loop diuretics and spironolactone, for at least six weeks prior to implantation; all patients were in sinus rhythm. The study was approved by the local ethical committee and informed consent was obtained from each patient.

Implantation procedure

The implantation was done under local anesthesia, the subclavian vein was accessed through three separate punctures and a pulse generator pocket was formed.

Two or three guide wires were introduced and a peelaway introducer sheath, size 7, 8 or 9 French was used to introduce the leads. Leads from *St Jude Medical* (Tendril™ ST, AV PLUS™ DX), *Medtronic* (CAPSUREFIX^R), and *Biotronic* (Selox SR, JT) were used. The leads were introduced under fluoroscopic guidance. The first lead was positioned at the right ventricular apex, R wave sensing was done and the pacing threshold was measured. The accepted threshold was around 0.5-1.5 volts. The second lead (the active fixation lead) was positioned at the RVOT by making a wide curve in the stylus in the pacing lead to attain a position at the RVOT. The third lead, a J shaped passive or active fixation lead, was positioned either in the RAA or in the lateral atrial wall. A P wave sensing measurement was made, and a sensing threshold > 2 mA was accepted.

Eight patients (26.7 %) who were eligible for CRT also met the criteria for ICD implantation (had resuscitated VT /VF or suspected VT induced syncope), so CRT-D (CRT with defibrillator) implanted in them, while the other 22 (73.3 %) were implanted with CRT alone (CRT-P). Then ICD testing of defibrillation thresholds including arrhythmia induction was conducted. R-wave of more than 6 mA were accepted.

The pacemaker boxes of *ST JUDE Medical* (Frontier I, Frontier II 5596, Epic HF, Atlas HF) in 26 patients, *Medtronic* (InSync Sentry 8040, 7272) in 3 patients, and *BIOTRONIC* (Talos DR) with the Y-connector for the two RV leads in 1 patient were implanted subcutaneously in the left prepectoral region. The RVA lead was connected to the pacemaker's RV port, the RVOT lead to the LV port and the RA lead was connected to the atrial port. Then the leads and device were secured, and the pulse generator pocket closed. Appropriate post-operative antibiotics were given to the patients. The estimated procedural time was 2 hours. No in-hospital death occurred during the procedure. Three patients developed complete heart block (CHB) during the procedure, but were recovered after RV pacing, two developed arrest and one ventricular tachycardia (VT), but they were resuscitated and returned to sinus rhythm.

Optimization of the device was carried out 10 days post implantation, when most (26) of the pacemaker boxes used for bifocal CRT were SJM Frontier I and Frontier II with the facility of Quick Optimization software for AV optimization. AV delay was set short to avoid native ventricular activation.

Patient follow-up approaches:

The patients were clinically followed up by using the following approaches:

- 1) A 12-lead surface ECG for measuring QRSd in milliseconds (ms).
- 2) Echocardiography: by using a 2-dimensional (2-D) Doppler, M-mode, to assess the LVEF.
- 3) Assessment of NYHA functional class.
- 4) 6MWT was done in 7 patients; according to the American Thoracic Society (ATS) guidelines (2002) [20].
- 5) CXR was undertaken for the degree of cardiomegaly. Cardiomegaly is divided into mild, moderate and severe, according to the cardiothoracic ratio (CTR). CTR above 50% is regarded as cardiomegaly, CTR of (51%-55 %) as mild, (56%-60 %) as moderate and > 60% as severe cardiomegaly.

All the above clinical data were obtained at baseline and were repeated after implantation (during 1, 3, 6, 12 and 24 months follow up in all the patients who completed their follow up), except the 6MWT which was performed in 7 patients and was done at base line and 1 and 3 months of follow up. The mean follow up periods were 8.7 (1-24) months. Pacemaker programming was performed at 10 days, at the first and second month follow ups and bimonthly thereafter. During each visit the patients were examined for any other complications.

Statistical analysis:

Statistical analysis was performed using SPSS version 13. Descriptive statistics were calculated for all variables; statistical analysis was done to find the relations between variables by using Chi-square, t-test, and analysis of variance (ANOVA). All numerical variables were recorded as mean \pm standard deviation. A P-value < 0.05 was considered significant.

Results

Thirty patients were included in the study, their ages ranging between (23 and 74) years with the mean age of 55.63 ± 10.14 years, 19 of the patients (69.3 %) were male. The mean NYHA class was (3.2 ± 0.6); the mean LVEF was (33.2 ± 6.0) %; the mean QRSd was (160 ± 16.8) ms; and the mean 6MWD was (195.8 ± 91.2) m. All the patients had chronic HF refractory to medical therapy. The causes of HF were: coronary artery disease (ischemic CMP) in 6 (18.4 %) of the patients and idiopathic (non-ischemic) DCMP in 24 (81.6 %) of the patients.

Remarkable improvements in clinical status, NYHS class, LVEF and a shortening in QRS duration were noticed acutely after BiFP. The improvement was maintained and increased progressively during long-term follow up as shown in the figures below (Figures 1, 2, 3, 4, 5, 6 & 7). These improvement were statistically significant, except for the 6MWT (P-value = 0.123).

Only three patients (10%) showed no changing or worsening after BiFP in most parameters and they were regarded as non-responders. There were two patients with no changes at the beginning in any of the parameters except for QRS narrowing, but later on (after 6 months in one of them and 9 months in the other) they began to improve; these patients are regarded as late-responders.

Complications during follow up

Complications include: Hematoma (1 case), infection (1 case), pulmonary edema (1 case), non-sustained ventricular tachycardia (VT) (2 cases), supraventricular tachycardia (SVT) (1 case) and AF (5 cases). No lead dislodgement or fracture occurred during the study period.

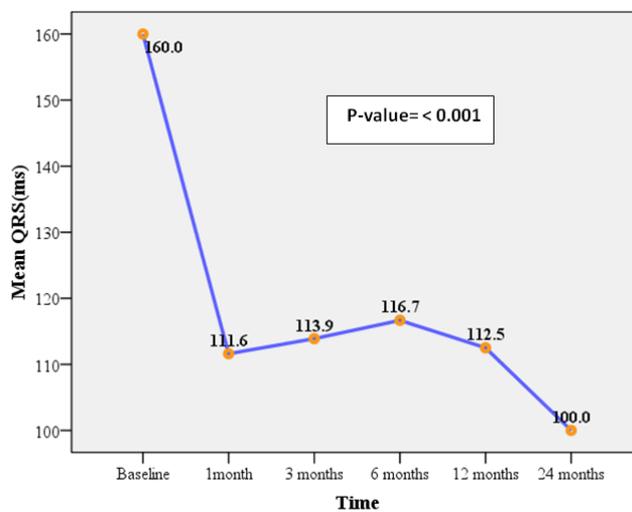


Figure 1. Mean QRS duration, before and after BiFP during different follow up periods (at 1, 3, 6, 12 and 24 months post-implantation).

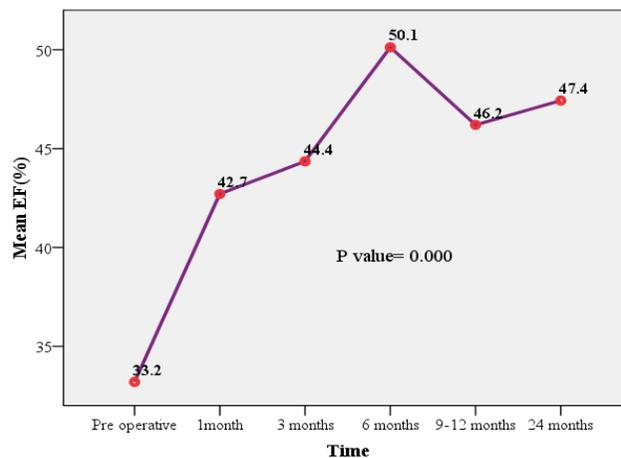


Figure 2. Mean LVEF (%) at baseline and after 1, 3, 6, 12 and 24 months of follow up.

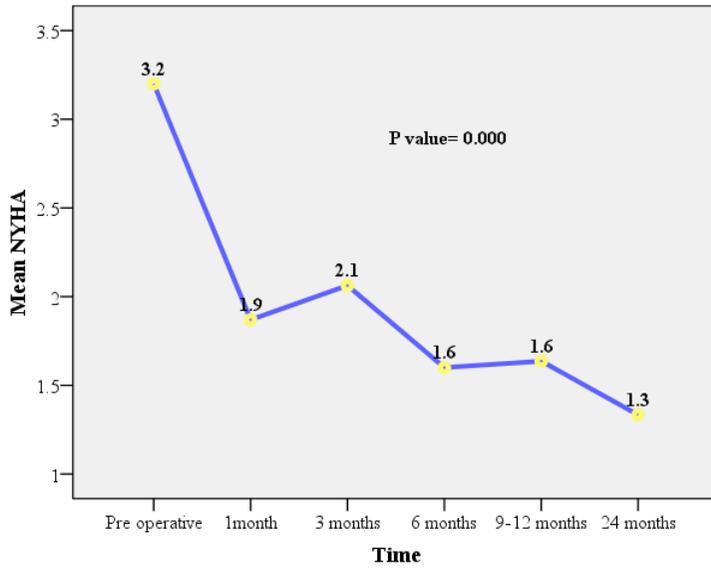


Figure 3. Mean NYHA class at baseline and at different months in the follow up period.

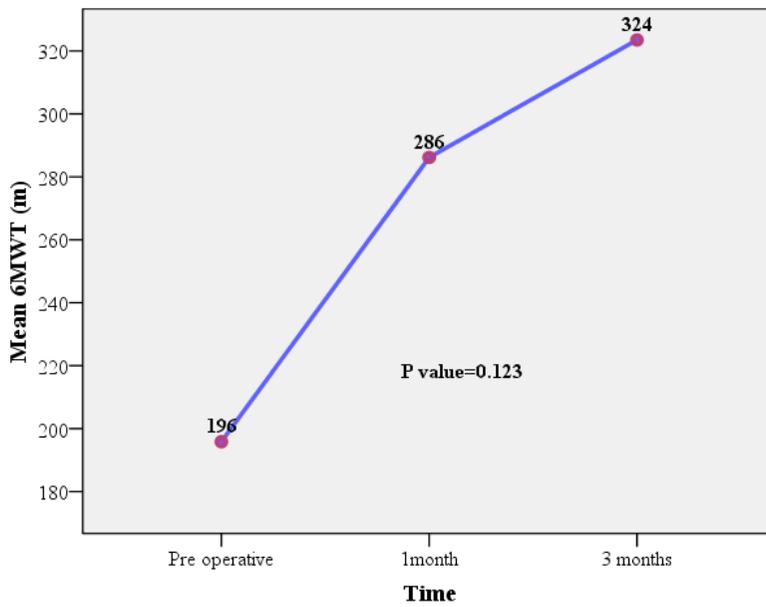


Figure 4. Mean 6MWT at baseline and at 1 and 3 months post- implantation.

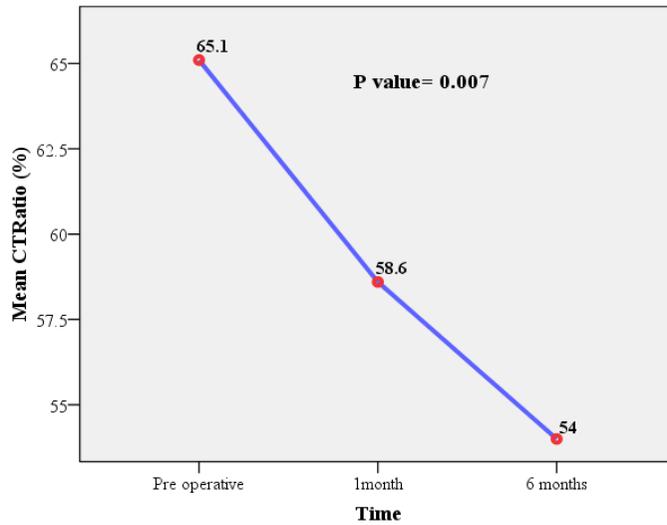


Figure 5. Mean cardiothoracic ratio at baseline and after 1 and 3 months of BiFP.

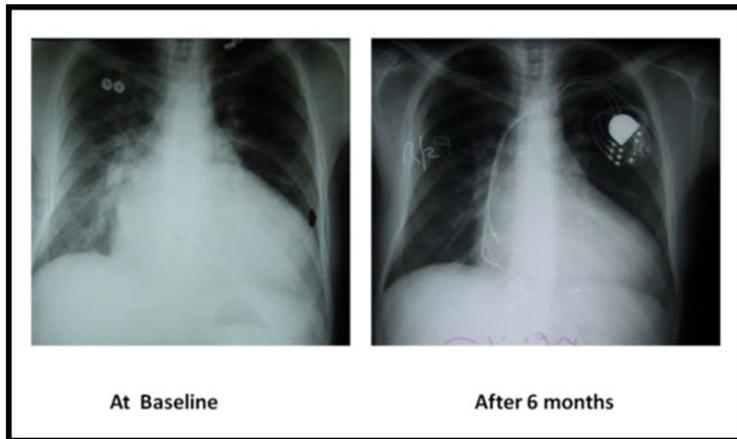


Figure 6. CXR of a patient, showing decrease in cardiac size after 6 months of BiFP

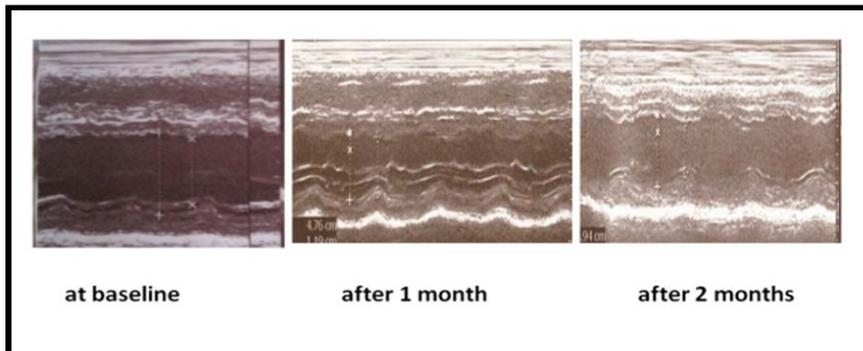


Figure 7. LVEF before (35%) and after 1 (49%) and 2 months (53%) of BiFP

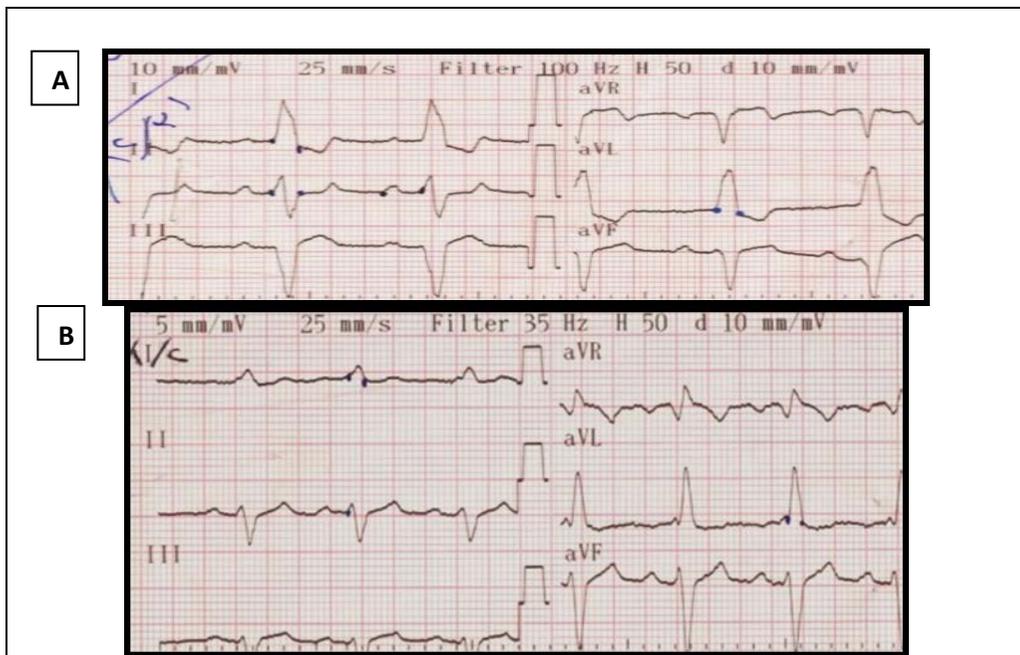


Figure 8. ECG before (A) and directly after (B) BiFP.

Discussion

CRT through LV implantation via C.S cannulation is a widely used method; it causes a great improvement in the hemodynamic and functional status of patients with refractory HF. However, this technique is sometimes unsuccessful because of failure to cannulate C.S or enter its branch veins due to anatomical factors or severe scarring. Stimulation through cardiac veins, in addition to the difficulty of access, causes additional problems such as: the need for a special lead, long-term stability of the lead, inability to obtain an adequate pacing threshold, cardiac vein phlebitis, and problems with removing chronicle leads (Pachón *et al.*, 2001, Chudzik *et al.*, 2009). The only endocardial solution for those patients in whom CRT is not feasible is an attempt to pace an additional site in the RV (choosing RVOT instead of LV) (Vlay, 2003).

Restoring the origin of depolarization to the high ventricular septum, with BiFP through RVOT pacing, restores a more favorable contraction pattern. In addition, RVOT pacing is usually associated with good sensing and low thresholds due to viable myocardium in the proximal septum in which the blood supply is usually preserved. Low pacing thresholds also improve battery longevity in contrast to LV pacing when myocardium is sometimes so scarred that it cannot sense or pace (Vlay, 2004). LV pacing also needs prolonged time in the laboratory, which has medical and financial

consequences. Long fluoroscopy time results in radiation exposure to the patient and physician. Implanting an RVOT electrode, in contrast, takes only a few minutes (Vlay, 2004).

The present study shows clearly the significant improvement in both the hemodynamic and functional status of patients treated with BiFP with an indication for CRT, who are not feasible for CRT implantation (either due to failure of the procedure or inaccessibility of the tools for C.S cannulation).

Acute effect of BiFP

There are several studies and case reports on the acute effect of BiFP: Early in 1997, Buckingham *et al.* tested different RV pacing sites, but the authors failed to show any significant change in the LVEF, C.O and peak LV dp/dt during intrinsic rhythm, atrial pacing and DVI pacing at the RVA, the RVOT, and both RV sites. However, the highest absolute values of dp/dt were observed during sinus rhythm and the lowest with RVA pacing. This parameter tended to improve progressively with pacing in the RVOT and at both sites (i.e. bifocal pacing).

Pachón *et al.* (2001) showed the advantages of BiFP over both RVA and RVOT pacing in a heterogeneous group of 39 DCM patients. They report a significant (12%) increase in LVEF during BiF stimulation compared with RVA stimulation, and a decrease in QRS duration by 51.5 ms, together with a 50.1% reduction in QoL score. The total follow up period was only 30 days. In the present study, the acute improvement in hemodynamic status was about the same as the study by Pachón *et al.* (2001).

In a case report by Vlay (2003), BiF was implanted in two patients after failure to secure C.S cannulation. He also showed that BiFP decreased QRS duration in one of the cases by 40 ms after 2 months of follow up. NYHA improved, but he did not report any improvement in hemodynamics.

There are studies which used Tissue Doppler Imaging (TDI) to assess the level of dyssynchrony in patients with BiFP (Matsushita *et al.* 2005, Martiniello *et al.* 2005, Lane *et al.* 2007). The results showed that BiFP was effective in reducing LV dyssynchrony. It was concluded that BiF improves LV hemodynamic by decreasing inter- and intra-VCDs. Unfortunately, inter and intra ventricular mechanical delay was not assessed in the present study, though it is important in the course of following up patients and in choosing patients for CRT implantation.

Chudzik *et al.* (2009), in their study, which is the most recently published study of BiFP, assess BiFP in 8 patients with severe HF. It is shown that BiFP provided an improvement in HF class in all patients after 3 months of follow up. Echocardiography revealed a significant increase in CO and LVEF but the only discrepancy in the results from the present study is that, among the 8 patients, only 3 showed a reduction in QRSd, where as in

the remaining patients QRS otherwise widened. This may be due to the small size of the study group.

Long term effect of BiFP

A number of studies and reports have been written on the long term effect of BiFP: Vlay (2004) evaluates NYHA class in 22 patients after unsuccessful CRT implantation followed by using a BiFP type. During a seven-month follow-up period, the NYHA class improved. Most of them became NYHA I and II after 7 months of follow up. Significant improvement was achieved in the NYHA functional class in the present study also, for 60% of the patients became NYHA I by the sixth month of follow up. Malinowski& Jacob (2003), in their study assessing clinical outcomes in CRT, find that 6 of the 49 patients had BiF implants. BiF patients improved in NYHA class and LVEF, and so did BiV patients after 20 months. QRS duration remained unchanged; results were statistically insignificant, due to the small number of BiF patients.

The first published long-term (12 months), non-randomized study of BiF was performed by O'Donnell *et al.* (2005). He reports 6 patients in whom BiF increased LVEF, and resulted in the reduction in MR and in the NYHA functional class. The mean NYHA showed improvement from 3.1 to 1.4. Additionally, these results were similar to changes observed in 44 patients with conventional BiV. The present study is consistent with the study of O'Donnell. It was observed that the mean NYHA Class improved from 3.2 to 1.6 by the twelfth month of follow up. A decrease in QRSD and NYHA class with an increase in LVEF is also found in a study published by Riedlbuchora (2005), who investigated 19 patients with a mean follow up period of 12 months.

Zamparelli (2005), studied 25 patients with a mean follow up period of 18 months. He reports a QRS narrowing from 157 to 115 ms, increase in EF from 32% to 41%, lower degree of MR and improvement in NYHA class from 3.5 to 2.0. These results are about the same as in the study published by Diotallevi (2006), who implanted BiFP in 27 patients but placed the lead in the parahisian region instead of the RVOT site. The patients were followed up for 20 months, QRS showed a significant narrowing from 190 to 152 ms, EF increased (1-29%), NYHA class showed significant improvement (3.4-1.9). The results from these two studies are very near to those of the present study during a long term follow up of more than 12 months.

In the BRIGHT study which was the first randomized, long term cross over study [16], the patients were followed up for 6 months. BiFP significantly improved LVEF, decreased the NYHA class from 2.8 to 2.3 and decreased the QoL score. There was also a small but significant decrease in QRS width from 180 to 171 ms.

Wojciuk *et al.* (2007), in their case report, mention an improvement in LVEF from 23% to 43.4% after 4 months of BiFP and after switching off the BiF device, EF was 32.6%. The findings were supportive of a sustained effect of RVOT pacing on EF and beneficial results on cardiac remodeling.

In the present study, 3 patients (10%) did not respond to the BiFP. In one of the cases there was an improvement in most of the parameters in the first month following BiF but later the EF and NYHA class of this patient declined to that of the baseline. The other 2 patients following BiF, had their EF and NYHA class decreased or remaining about the same, so they were regarded as non-responders. The explanation of these non-responders is mostly due to the AV optimization problem, or may be due to the absence of re-synchrony despite QRS narrowing, or to such extensive scarring in myocardium due to IHD that the pacing was ineffective, or that the exact RVOT site had not been secured, for the same reason.

There was significant improvement acutely following implantation (mostly after one month) in 25 patients, in particular a large reduction in QRSd was noticed directly or within a month of BiFP (48.8 ms) while at the twenty-fourth month follow up there was only minor change (11.1 ms) compared to the 1st month. This QRS narrowing reflects the concomitant activation of the left lateral wall and the septum, abating any delay between them, and reflecting that on the QRS width. With chronic pacing, there was progressive improvement of parameters and more improvement in the patient's functional class. Parameters which show great improvement after long term BiF are the cardiothoracic ratio and LVEF, both of which may be due to LV remodeling following BiFP.

Another parameter tested in this study, is 6MWD. There was a marked increase in the mean walking distance from 196 m to 286m, after 1 month and to 324 m, after 3 months of BiFP; however the increase was not statistically significant. Only in a few studies was 6MWD tested, but they all show an increase in the mean walking distance after BiFP (Res *et al.* 2007, O' Donnel *et al.* 2005, Chudzik *et al.*, 2009, Diotallevi *et al.*, 2006).

This study is the first study on BiFP conducted in Iraq and there has been only one study on CRT performed in Iraq (Basheer and Al-Hamdi, 2004). The writers implanted a BiV device in 21 patients, and a BiF in 1 patient (because of BiV failure). Significant improvement was seen in clinical and echocardiographic parameters after the 1 month follow up. They state that the results for this patient were similar to those with BiV CRT implantation.

Limitations of the study

This study included also a retrospective patient group in whom a BiF was implanted before the start of the study because the number of patients

having a BiF device implanted was not quite sufficient and the time of the study was limited, to allow for this long follow up period.

Not all the patients included in the study completed the 24 months of follow up, so it would have been better to take a larger sample size.

Only in 7 patients was 6MWT tested. This is because they were either in a retrospective group or they had a contraindication about doing this test; sometimes the patients were unable or unwilling to be tested.

Conclusion

Bifocal right ventricular pacing is a feasible type of cardiac resynchronization therapy. It can improve a patient's functional status and hemodynamic parameters significantly and can be used as a treatment in CHF patients who are indicated for BiV CRT in the following situations: when the attempts of LV lead implantation are unsuccessful, when they are at high risk of prolonged procedural time or thoracotomy for epicardial lead implantation and when the LV lead implantation, and C.S cannulation tools are unavailable.

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