Initial Experience of Biventricular Pacing in Patients with Chronic Severe Heart Failure

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Key words:
Resynchronization therapy.

Introduction: Biventricular pacing is a new method for the treatment of patients with severe chronic heart failure, especially in cases of intraventricular conduction disturbances.

Patients and Methods: Biventricular pacing devices were implanted in 32 patients with chronic severe heart failure (10 pacemakers, 22 defibrillators). Initially, patients remained in their previous intrinsic rhythm (device set to VVI 40 bpm) for 1 month after implantation, following which baseline evaluation was conducted, including NYHA class assessment and quality of life estimation. A six minute walking test, cardiopulmonary treadmill test and echo study were also conducted at that time point. Following a subsequent 3-month period of biventricular pacing, patients were evaluated again in the same way.

Results: Following device implantation, a significant decrease was observed in QRS duration (170±13 from 185±18 msec before implantation, $p<0.05$). In 20 patients who uneventfully completed a 3-month period of biventricular pacing, an improvement was observed in NYHA class (1.7±0.5 from 3.0±0.4 before implantation, $p<0.0001$), Minnesota quality of life score (24±8 from 45±16 respectively, $p<0.001$) as well as in the six minute walking distance achieved (464±81 from 424±24 m, $p<0.001$). Treadmill exercise duration was increased (9.5±3.0 from 8.2±3.0 min, $p<0.005$) without any significant improvement in VO_2 max (15.9±3.2 from 15.3±3.8 ml/kgr/min, p: NS). Cardiac output was increased (4.9±1.2 from 4.3±1.2 lit/min, $p<0.05$), while LVEF was not significantly elevated (26.5±7.1 from 25.0±8.1 %, p: NS).

Conclusions: Permanent biventricular pacing is a safe method which improves the functional status and quality of life in patients with severe heart failure and intraventricular conduction disturbances. Following biventricular pacing, an improvement is also observed in exercise capacity and indexes of left ventricular performance.

Manuscript received:
September 3, 2002;
Accepted:
August 13, 2003.

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The number of patients with chronic heart failure has increased substantially during the last few decades[1]. The use of drugs such as the converting enzyme inhibitors[2], angiotensin II receptor blockers[3], β-blockers[4] and spironolactone[5] has led to significant reduction of the mortality and morbidity associated with this disabling syndrome. Despite this, the prognosis of patients with drug-resistant heart failure remains disappointing.

The first attempts of pacing these patients date from the early years of the previous decade. Atrioventricular pacing in various positions of the right ventricle was initially attempted, but results regarding its effectiveness were conflicting[6-9].

A number of acute studies assessing the potential of biventricular pacing in patients with heart failure and intraventricular conduction disturbances in improving certain indexes of left ventricular performance has shown promising results[10-13].

These findings have gained clinical importance after the achievement of permanent transvenous left ventricular pacing through branches of the coronary sinus[14].

Following this, a number of chronic studies[15-20] showed the beneficial influence of chronic biventricular pacing on chronic,

Table 1. Clinical characteristics of patients included in the study.

Total number of patients	36
Male / Female	29/7
Age (years)	64±7
Ischemic cardiomyopathy	22 (61%)
Dilated cardiomyopathy	14 (39%)
Sinus rhythm	35
Atrial fibrillation	1
Left bundle branch block	15 (42%)
Non-specific intraventricular conduction disturbances	21 (58%)
NYHA class	3.1±0.6
Indication for defibrillator implantation	23 (64%)
Preexisting pacemaker	4 (11%)
PR duration (msec)	195±21
QRS duration (msec)	186±23
Left ventricular ejection fraction	22±5%
Medical treatment	
Diuretics	36 (100%)
ACE inhibitor	34 (94%)
B-blocker	26 (72%)
Spironolactone	31 (86%)

severe heart failure. In particular, significant improvement was observed in patients' quality of life, functional capacity, morbidity, and recently - mortality[39,40].

In this report, we present our initial experience on chronic biventricular pacing in chronic, severe heart failure.

Patients

During a 3-year period (February 2000 until January 2003), 36 patients (29 male, 7 female) with chronic, severe heart failure met the criteria for the implantation of a biventricular pacing device. All were under maximally tolerated drug treatment (Table 1) and exhibited intraventricular conduction disturbances. Twenty-two of them had a cardiomyopathy of ischemic origin (6 with a history of by-pass grafting), while the remaining 14 had idiopathic dilated cardiomyopathy. Implantation of a biventricular defibrillator or pacemaker was attempted in all these patients.

Twenty-three of the above mentioned patients fulfilled the indications of the American College of Cardiology for implantation of a cardioverter-defibrillator and, therefore, we attempted to implant a biventricular defibrillator.

In 4 patients, with a functional class of 3.1±0.6, upgrading of a pre-implanted pacemaker device was conducted. The mean QRS duration was 186±23 msec, while the mean PR duration 195±21 msec.

Thirty-five patients were in sinus rhythm, while one had atrial fibrillation. The mean left ventricular ejection fraction, as assessed echocardiographically, was 24±7%.

Implantation data

For the insertion of the pacemaker electrode in the branches of the coronary sinus we used the Easytrak (Guidant, St Paul, MN)[21] or the IncSync (Medtronic, Inv., MN) implantation systems[22].

The electrode was inserted in the coronary sinus through the left subclavian vein, under regional anesthesia. Initially, the coronary sinus ostium was cannulated by a 6 Fr guiding catheter, through which contrast material was injected to delineate cardiac venous anatomy (Figure 1). The optimal branch was chosen for electrode insertion. The middle cardiac vein was avoided, so as not to pace the right ven-

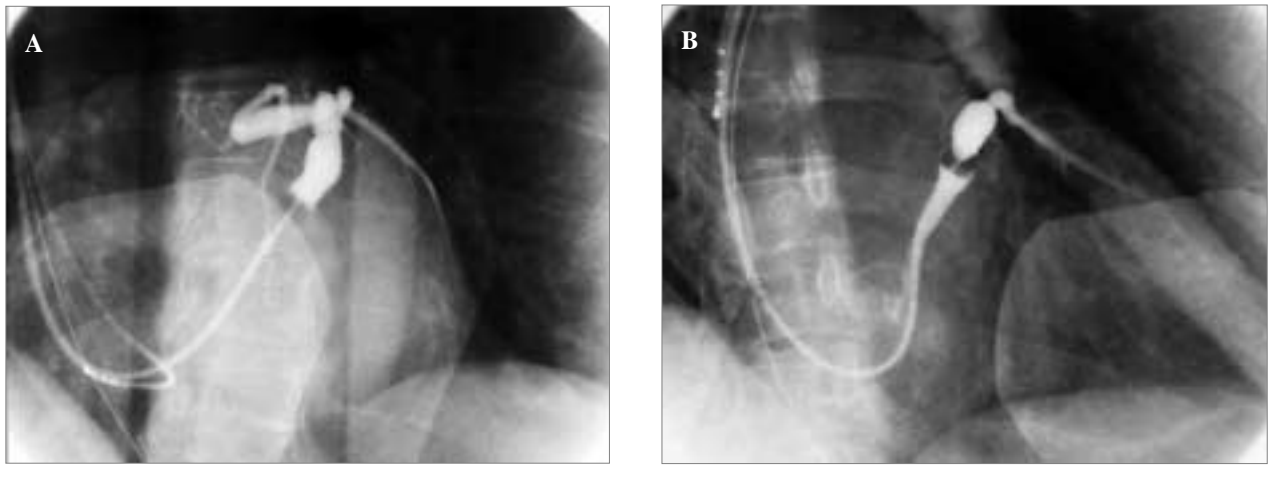

Figure 1. Coronary sinus branches before implantation of the biventricular pacing device (A left anterior oblique view, B right anterior oblique view).

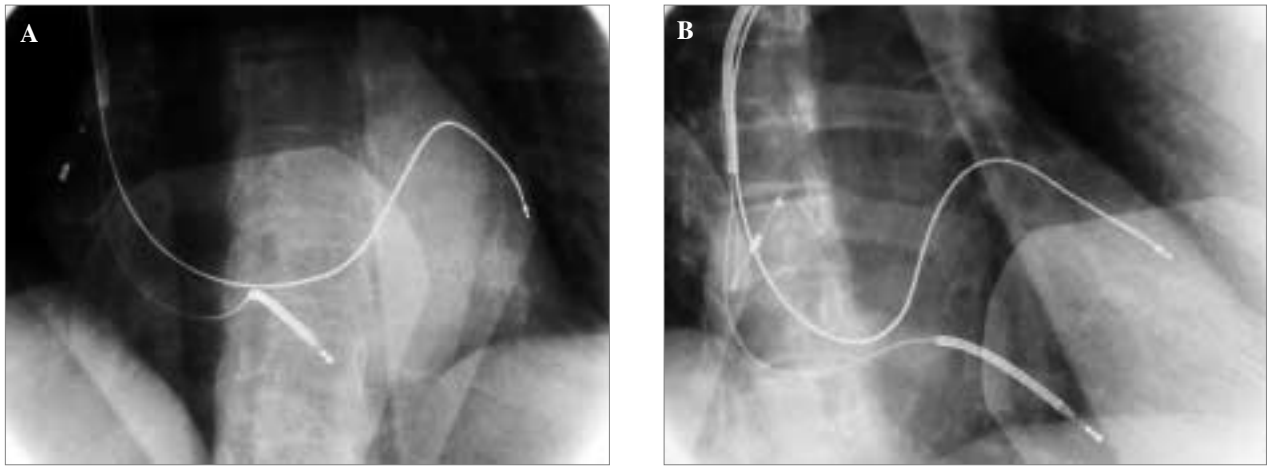

Figure 2. The three system electrodes after their fixation in the right atrial appendage, right ventricular apex and a lateral coronary sinus branch (A left anterior oblique view, B right anterior oblique view).

tricle. We preferred to insert the electrode into lateral or posterolateral branches, provided the electrode was adequately stabilized at these sites and satisfactory pacing/sensing thresholds were feasible.

Then, a guidewire (0.014-inch) was inserted through the Easytrak system to the coronary sinus branch. The Easytrack electrode has a lumen which permits its insertion over a guidewire.

On the contrary, the Medtronic 2187 electrode was inserted directly into the coronary sinus through the IncSync guiding catheter. This electrode can be stabilized into the coronary sinus branches. Following left ventricular electrode stabilization, implantation of electrodes in the right ventricular apex and right atrial appendage was performed (Figure 2).

Methods

For at least 1 month before device implantation, patients were under optimal drug treatment so as to avoid treatment changes during follow-up.

Following implantation, the biventricular device was programmed to VVI mode at 40 bpm for one month.

After this period, the patients underwent the following:

1) Functional status assessment (NYHA class)

2) Evaluation of Quality of Life status (Minnesota Quality of Life Questionnaire)[23]

3) Echocardiographic examination, including left ventricular dimensions, left ventricular ejection fraction and cardiac output assessment according to the Recommendations of the American Society of Echocardiography[24].

4) Evaluation of the 6-minute walking distance achieved[25]. The test was conducted twice and the mean value was taken into consideration.

5) Cardiopulmonary exercise test (Dargie protocol), including the assessment of the maximal oxygen consumption during the test[26].

After initial evaluation, the device was programmed to biventricular pacing (VDD 40-140 bpm). The optimal atrioventricular delay was programmed, according to echocardiographic findings[27]. This interval was always less than the intrinsic atrioventricular delay in order always to pace the ventricles. Thus, patients remained in VDD biventricular pacing for the subsequent 3-month period. Following this, a repeated evaluation was performed, as previously described.

In case of patients with previously implanted pacemakers and pacemaker-dependency, the devices were not programmed to VVI mode. These patients were initially assessed before implantation of the biventricular device, which was immediately programmed to biventricular pacing. Atrioventricular delay and pacing intervals remained unchanged.

In the patient with chronic atrial fibrillation in whom biventricular pacing was conducted, the device was also immediately programmed to VVI mode and follow-up data were not included in the study.

The assessment of the device during follow-up comprised pacing and sensing threshold evaluation 1, 4 and 7 months post-implantation. After this

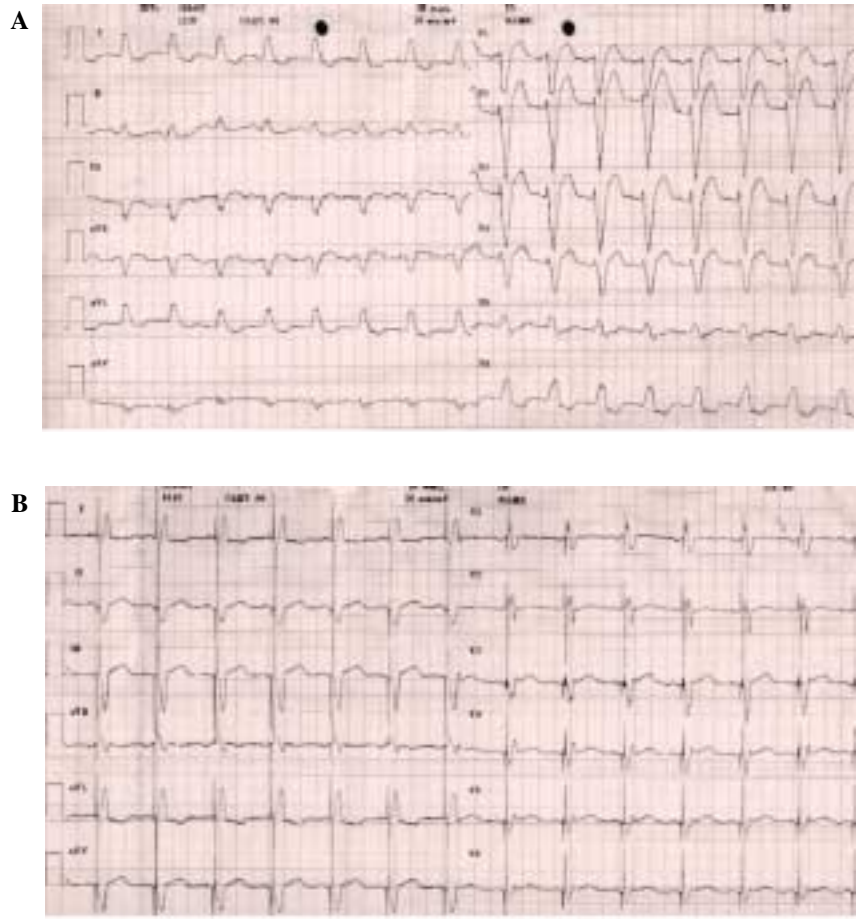

Figure 3. Twelve-lead electrocardiogram prior to (A) and following (B) biventricular pacing.

period, device follow-up was conducted every 6 months.

Results

Follow-up results are expressed as mean value±1 SD. Statistical evaluation was performed by ANOVA. Statistically significant results were considered those when $p<0.05$.

In 32/36 study patients (88%) a biventricular device was successfully implanted, with the methodology previously described. In 3 patients, the insertion of the electrode in the coronary sinus vasculature was not feasible, due to inability to enter the coronary sinus ostium. One of them had a history of aortic valve replacement (twice) and the remaining 2 had previously undergone coronary bypass grafting. In another patient with history of large myocardial infarction, left electrode implantation was not possible due to inability to attain satisfactory pacing threshold. In the remaining 32 patients, successful electrode implantation was performed in the coronary sinus branches (22 defibrillators /10 pacemakers). In more detail, in 21 patients the Easytrak (Guidant, St Paul, MN)[21] system was used for the left ventricular electrode implantation, while in the remaining 11 the IncSync (Medtronic, Inv., MN)[22]. In 30 patients, the electrode was implanted in a posterior or posterolateral branch and in 2 patients, in the great cardiac vein.

During electrode insertion, coronary sinus dissection was observed in 2 patients. Despite this, the electrode was finally successfully positioned. No other complications were observed.

The mean duration of the procedure was 142±83 min and the mean fluoroscopy time 31±17 min. A gradual decrease was observed in the duration of the procedure and fluoroscopy time; specifically the

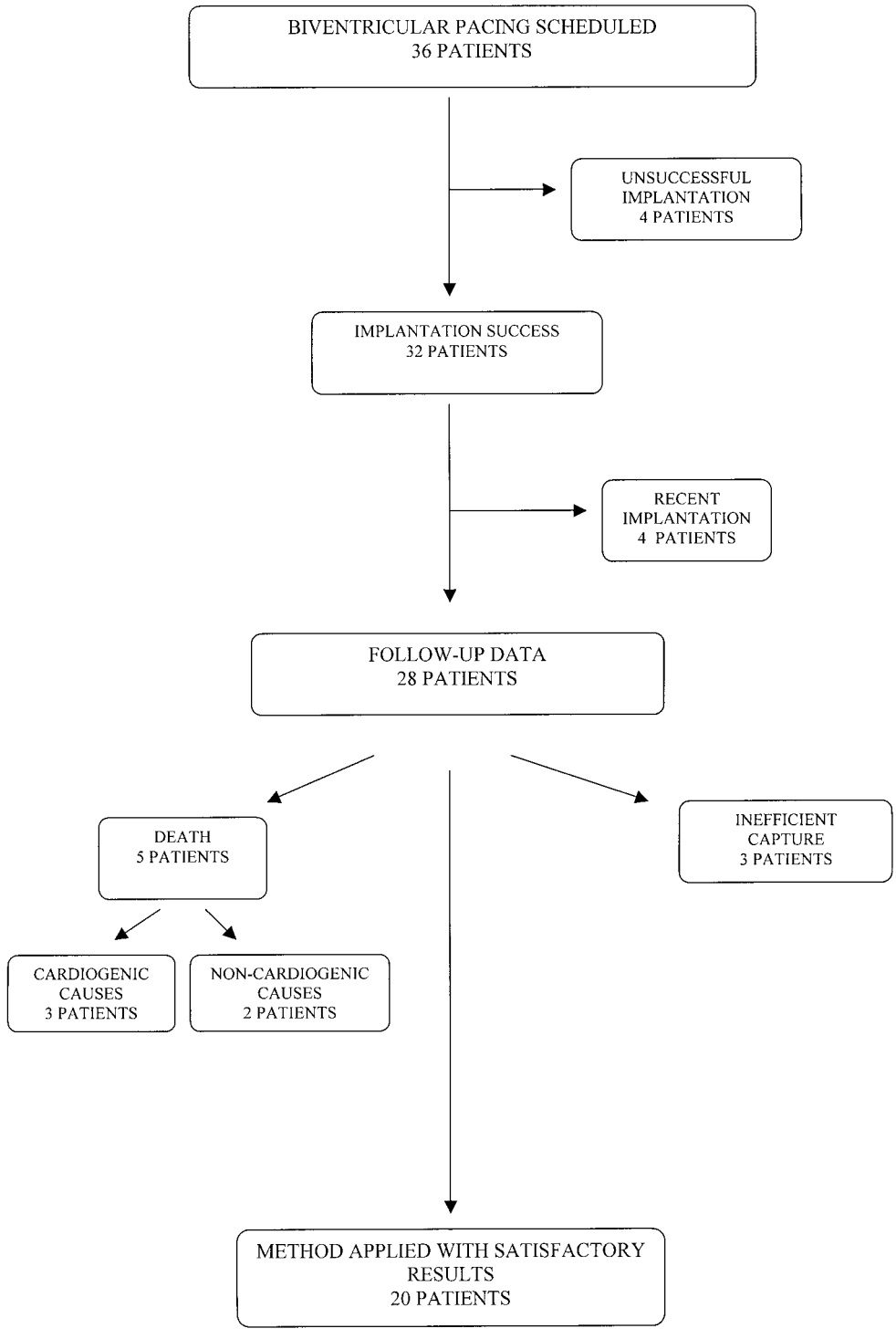

Figure 4. Patients' outcome following 7 months of biventricular pacing.

respective mean values for the last 5 patients were 110±14 min and 18±5 min.

At implantation, the mean pacing threshold regarding left ventricular electrode was 1.85±0.7 V/ 0.5 msec (range 0.6 V/0.5 msec to 3.6 V/0.5 msec) while the sensing threshold was 9.4±4.1 mV. QRS width was reduced by pacing from 185±18 msec to 170±13 msec ($p<0.05$). This reduction in QRS duration is characteristically shown in figure 3.

Following this, study patients were followed-up as previously described (Figure 4). In 4 patients in whom the device was recently implanted, no 3-month

Table 2. Characteristics of the patients in whom the effect of biventricular pacing was assessed.

Number of patients	20
Age (years)	64±8
Ischemic cardiomyopathy	11
Dilated cardiomyopathy	9
Sinus rhythm	20
PR duration (msec)	195±10
QRS duration (msec)	189±18

follow-up data are available; therefore, only implantation data have been included in the report.
Among the remaining 28 patients, 3 died of cardiogenic causes during the first 3 post-implantation months. Two of them had been in cardiogenic shock before implantation; one showed impressive improvement following biventricular pacing, which was immediately applied, but died suddenly one week post-implantation. The second remained in cardiogenic shock, despite pacing and died of pump failure 1 month later. The third patient was in functional class IIIb, showed no improvement after pacing and died 2 months later of pump failure, despite immediate programming to biventricular pacing.

Two more patients died of non-cardiogenic causes: one 8 months later of pulmonary fibrosis due to amiodarone treatment; the second, 3 months later due to gastrointestinal hemorrhage.

In 2 patients inefficient capture of the coronary sinus was observed 4 months post-implantation. In one, a significant increase in left ventricular pacing threshold was observed (6V/0.5 msec) at the 7-month follow-up visit. In 2 of these 3 patients, the left ventricular electrode had been implanted in the middle cardiac vein; it was successfully repositioned to a posterolateral branch of the coronary sinus by reusing the Easytrak system. The third patient initially remained in high-output biventricular pacing (7.0 V/0.5 msec); eventually, the left ventricular electrode was also repositioned due to capture failure (Easytrak system).

In this way, in the 20 patients who had an uneventful post-operational course for a 7-month period, pacing and sensing thresholds were 1.9±2.6 V/0.5 msec and 9.8±4.4 mV respectively 1 month later, 1.8±2.3 V/0.5 msec and 11.5±3.2 mV 4 months later, 1.6±2.4 V/ 0.5 msec and 12±5.3 mV 7 months post-implantation.

As previously described, 21 patients were followed-up after 3 months of biventricular pacing. One was in chronic atrial fibrillation and his follow-up data were not included in the results. An improvement was thus observed in the functional status following 3 months of biventricular pacing (from 3.0±0.4 to 1.7±0.5, $p<0.0001$) in the remaining 20 patients (Tables 2 and 3). An improvement was also observed in quality of life, as assessed by the Minnesota Questionnaire score (from 45±16 to 24±8, $p<0.001$).

An improvement was also observed in the echocardiographically assessed cardiac output (from 4.3±1.2 lt/min to 4.9±1.2 lt/min, $p<0.05$), while LVEF was not significantly elevated (from 25.0±8.1 to 26.5±7.1 %, p: NS).

The 6-minute walking distance increased from 424±62 to 464±81 m ($p<0.005$).

As derived from cardiopulmonary stress test data (18 patients), exercise duration increased from 8.2±3.4 min at baseline to 9.5±3.0 min ($p<0.005$), which was not accompanied by significant increases in maximal oxygen consumption (respective values: 15.3±3.8 ml/kgr/min at baseline and 15.9±3.2 ml/kgr/min following pacing, p: NS).

It should be pointed out that no differences were observed regarding patients' response depending on the type of intraventricular conduction disturbance or QRS duration.

Table 3. Parameters assessed prior to and following biventricular pacing.

	Baseline	**After 3 months of biventricular pacing**
NYHA class	3.0±0.4	1.7±0.5 ($p<0.0001$)
Minnesota Score	45±16	24±8 ($p<0.001$)
6-minute walking distance (min)	424±62	464±81 ($p<0.005$)
Exercise duration (min)	8.2±3.4	9.5±3.0 ($p<0.005$)
Maximal oxygen consumption (ml/kgr/min)	15.3±3.8	15.9±3.2 (p: NS)
Left ventricular ejection fraction (%)	25.0±8.1	26.5±7.1 (p: NS)
Cardiac output (lt/min)	4.3±1.2	4.9±1.2 ($p<0.05$)

Discussion

The present study showed that biventricular pacing exerts a favourable effect on the clinical status of patients with chronic severe heart failure and intraventricular conduction disturbances. Namely, patients were included only if severe heart failure persisted despite maximal drug therapy. Also, all patients had an increased QRS duration of at least 150 msec. These criteria have been set following the favourable results of previous acute hemodynamic studies[12-13] conducted on such patients.

Biventricular pacing system implantation data show a satisfactory proportion of successful implantation results, as previously reported in multicenter studies[21-22-28]. Most of the difficulties during implantation were related to entering the coronary sinus ostium, especially in patients with history of previous cardiac surgery. A second problem was the absence of coronary sinus branches suitable for electrode stabilization (especially lateral or posterolateral branches). In some patients with history of large anterior infarction it has been difficult to achieve acceptable pacing threshold in the coronary sinus branches, possibly due to the existence of postinfarction fibrosis. We must note that we always targeted the lateral or posterolateral branches so as to achieve left ventricular pacing, while avoiding use of the middle cardiac vein, because it resulted in right ventricular pacing. In conclusion, coronary branch selection was conducted by the achievement of satisfactory pacing threshold (in lateral or posterolateral branches if possible); based on the fact that - until recent reports - no satisfactory criteria existed to define the exact pacing sites leading to maximal clinical improvement. Recently, it has been shown[29] that the determination of such sites may be possible. Specifically, it has been found that significant improvement is achieved by pacing the left ventricular site with the most delayed depolarization. This has been specified echocardiographically by using Tissue Doppler Imaging before system implantation. If these results are confirmed biventricular pacing effectiveness is expected to improve.

During the period of study follow-up, the coronary sinus electrode performance was satisfactory. We would also like to point out that electrode repositioning concerned some of the cases initially included in the study. Increasing experience led to an improvement in remote electrode performance.

The study design included device programming to VVI 40 bpm for one month after implantation. In this way, patients were in intrinsic rhythm during this period, following which baseline clinical and laboratory assessment was performed. In this way, we minimized the placebo effect and a possible modification of study results.

Biventricular pacing was accompanied by significant improvement in patients' functional class as well as quality of life, as already shown by previous studies[15-17].

An important finding was the increase in 6-minute walking distance achieved following 3 months of biventricular pacing. This increase expresses patients' functional improvement in everyday life and is accompanied by a better prognosis[30-31].

An improvement was also observed in patients' exercise tolerance, as expressed by increased exercise duration during pacing. Despite this, the increase observed in maximal oxygen consumption was not statistically significant. This may be due to the fact that the number of our study patients was not adequately large to show important differences in this parameter, as larger-scale studies[15] have shown borderline improvement in maximal oxygen consumption following biventricular pacing. Another study[32] has shown no significant improvement in maximal oxygen consumption following pacing. In addition, that biventricular pacing has recently been shown[33] to lead to marked improvement only in patients with low maximal oxygen consumption values; in contrast, no significant benefit was observed with moderate or relatively greater values. Studying patients with moderately affected maximal oxygen consumption values might also have led to the presently observed results.

Following biventricular pacing, a borderline improvement was also observed in the hemodynamic parameters assessed echocardiographically in our study patients. This favourable effect is attributed to an improvement in systolic as well as diastolic left ventricular performance. This is achieved by synchronous left ventricular depolarization[34-35] and, possibly, by an improved left-right ventricular interaction during biventricular pacing[36].

Three recent studies[37-38] also showed that the hemodynamic improvement is defined by the degree of resynchronization of left ventricular segments achieved by biventricular pacing; this can be assessed echocardiographically by the use of Tissue Doppler Imaging. These findings are compatible with the

borderline results of the present study, in which no such echocardiographic criteria were used before device implantation; hence, the hemodynamic response to biventricular pacing possibly involves a wider range of responses.

The importance of selecting the suitable patient for biventricular pacing therapy as well as determining the optimal left ventricular pacing site seems to be significant. Understanding these parameters together with future technical improvements in biventricular devices will considerably improve the effectiveness of the method in the next years.

Conclusion

The present study has shown that biventricular pacing is a safe and effective method for the treatment of patients with severe heart failure. This new pacing technique is associated with a significant improvement in left ventricular performance, functional capacity and quality of life. A better delineation of patients most suitable for this type of therapy is expected to increase its effectiveness.

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