Biventricular pacing for patients with severe congestive heart failure: a single center experience

Giosuè Mascioli, Antonio Curnis, Luca Bontempi, Livio Dei Cas

Laboratory of Electrophysiology, Division of Cardiology, University of Brescia, Brescia, Italy

Key words:
Congestive heart failure; Pacing.

Background. **Biventricular pacing is becoming more and more popular as a therapeutic strategy for patients with severe congestive heart failure refractory to medical treatment. The aim of our study was to evaluate the outcome of resynchronization therapy on the clinical and echocardiographic statuses, to determine whether any factors were predictive of a positive or negative result after biventricular pacing and to analyze the survival curves.**

Methods. **From October 1998 to April 2002, 96 patients were selected for biventricular pacing at our center. The implant was successful in 95 (99%) patients. We followed-up the patients at 1, 3 and 6 months and then every 6 months. Follow-up evaluation included a clinical visit, an echocardiogram for the determination of left ventricular diameters, ejection fraction, E and A wave velocities, E/A ratio, E wave deceleration time, entity of mitral regurgitation (calculated as the percentage of the left atrium occupied by the mitral regurgitant jet) and aorto-pulmonary delay (mechanical delay).**

Results. **Sixty-eight of our 96 patients were followed for at least 6 months. We observed a significant reduction in the electrical (QRS from 177 ± 30 to 143 ± 23 ms) and mechanical delay (aorto-pulmonary delay from 55 ± 33 to 25 ± 19 ms). We also observed a significant clinical improvement, as demonstrated by the reduction in the NYHA functional class (from 3.2 ± 0.5 to 2.1 ± 0.8). This clinical improvement was reflected by the increase in ejection fraction (from 23 ± 8 to 36 ± 12%), by the decrease in mitral regurgitation (from 21 ± 18 to 12 ± 12%) and by the increase in E wave deceleration time (from 165 ± 94 to 210 ± 93 ms). Eight patients died during the first year of follow-up, with a mortality rate of 13%. The 2- and 3-year mortality rates were both 25.4%.**

Conclusions. **Even though not randomized, our study enrolled a very homogeneous population of unselected patients; nevertheless, it seems to confirm that biventricular pacing is effective in improving the clinical and instrumental statuses of patients with severe congestive heart failure. Furthermore, it seems to indicate that this treatment could be effective in reducing the mortality rate among such patients.**

(Ital Heart J 2002; 3 (10): 598-602)

Received June 19, 2002; revision received September 3, 2002; accepted September 19, 2002.

Address:

Dr. Giosuè Mascioli

Divisione di Cardiologia
Spedali Civili
Piazzale Spedali Civili, 1
25123 Brescia
E-mail:
gmascioli@inwind.it

Introduction

Over the years, heart failure has become an increasingly serious medical problem[1], especially among older people. Nevertheless, it has been – and it is, somehow – a neglected condition, due to the chronic lack of adequate epidemiological data, of simple diagnostic techniques and of effective treatments[2]. In fact, even though various drugs – such as angiotensin-converting enzyme (ACE)-inhibitors[3], β-blockers[4] and spironolactone[5] – have proven to be effective in these patients, the prognosis of heart failure remains poor. Drugs seem to delay the progression of heart failure, but do not change its natural history. Thus, the disease progression, morbidity and mortality rates have increased dramatically.

Due to the limited economical resources, non pharmacological treatments (such as heart transplantation and implantable assist devices), even though effective, are available for a minority of the patients who need them. These aspects could, at least partially, explain the increasing popularity of a new technique that has proven – even though not in randomized trials – to be effective in patients with severe chronic congestive heart failure.

The rationale of this therapy is based on the high prevalence of an intraventricular conduction delay (left bundle branch block at the surface ECG) among patients with heart failure[6] and on the deleterious effects of this on left ventricular performance[7,8].

Acute studies[9,10] have shown that atrio-biventricular pacing can reduce ventricular asynchrony thus improving left ventricular hemodynamics. Other studies, such as MUSTIC[11] and MIRACLE[12] which includ-

ed a longer follow-up, have confirmed these positive results.

At our center biventricular pacing has been performed since October 1998. We here describe our experience with this technique: from our registry we have analyzed the clinical and echocardiographic follow-up. We also asked a statistician who did not form part of our group which parameters had improved more during follow-up, whether there were any factors that could have predicted a better outcome or factors predictive of death and to analyze the survival curves of these patients.

Methods

Since October 1998, 96 patients have undergone biventricular pacemaker implantation at our center. The implant was successful in 95 (99%) patients. Two patients were implanted with an epicardial lead, in 1 case because the patient, who already had had a permanent single chamber pacemaker, had a bilateral occlusion of the subclavian veins, and in the other because the biventricular pacemaker was implanted during coronary artery bypass graft.

We have decided to analyze the biventricular pacing results after at least 6 months of follow-up: for this reason the study population consists of only 68 patients who meet this requirement. The patients with epicardial leads have been excluded from the analysis: one because lived in another region and the other one because it would have been quite difficult to determine whether the left ventricular improvement was due to revascularization or to biventricular pacing.

The clinical characteristics of the subjects are described in table I.

Pacemaker implant procedure. All leads were implanted via the left subclavian vein in all cases but 2. After having cannulated the subclavian vein, a first lead was positioned at the apex of the right ventricle in order to have a reliable means of stimulating the patient in case of total atrioventricular block during the maneuvers to cannulate the coronary sinus (CS).

Table I. Characteristics of the study population.

Males	53 (78%)
Age (years)	68 ± 8
Follow-up (days)	676 ± 240
Idiopathic dilated cardiomyopathy	33 (49%)
Right bundle branch block	5 (7%)
Atrial fibrillation	6 (9%)
Pacemaker previously implanted	9 (16%)
Biventricular ICD	15 (24.5%)
Basal NYHA class	3.2 ± 0.5
Basal QRS width	177 ± 30

ICD = implantable cardioverter-defibrillator.

Then, the CS was cannulated with a preformed electrophysiological catheter (Supra Biosense Webster, Diamond Bar, CA, USA) which was used as a guide to insert the long sheath into the CS[13]. Once the sheath was inside the CS, the same was occluded with a Swan-Ganz catheter and the venogram in the three standard radiological projections (antero-posterior, right anterior oblique and left anterior oblique) was obtained.

We always attempted to insert the left ventricular lead into a lateral CS branch, but, especially during the initial phase of our experience, the great cardiac vein had to be used in some cases in order to stimulate the left ventricle: as far as the study population is concerned, the left ventricular lead was positioned in 15 patients in a posterior vein, in 19 in a postero-lateral vein, in 24 in a lateral vein, in 6 in an antero-lateral vein, and in 4 in the great cardiac vein.

The atrial lead, always positioned within the right atrial appendage, was the last one to be inserted.

A biventricular pacing threshold < 3 V at 0.50 ms was considered acceptable for chronic stimulation.

Follow-up. All patients underwent clinical and echocardiographic evaluation at 1, 3 and 6 months and then every 6 months. The following echo-Doppler parameters were evaluated at each visit: left ventricular diameters, ejection fraction, entity of mitral regurgitation (taken as the percentage of the left atrium occupied by the mitral regurgitant jet), aorto-pulmonary delay, E and A wave velocities, E/A ratio, and E wave deceleration time. Before any measurement, the atrioventricular delay was optimized using Ritter's formula[14]. The mean optimal atrioventricular delay at the end of follow-up was 112 ± 29 ms.

Statistical analysis. The Student's t test for paired data was used to compare data derived from the basal and post-pacing evaluations. Univariate and multivariate analysis were performed in order to determine whether any factors could have been predictive of a positive or negative outcome following biventricular pacing. The survival curves have been calculated using the actuarial Kaplan-Meier method. A p value of < 0.05 was considered statistically significant.

Results

Clinical follow-up. We have defined as responders to biventricular pacing those patients in whom the NYHA class improved by at least 1 and the ejection fraction increased by at least 10% with respect to the basal value. According to these definitions, there were 56 (85%) "clinical" responders and 52 (82%) "instrumental" responders; in 47 (69%) patients both parameters were found to have improved.

Analyzing the whole population, we observed a significant improvement in the NYHA class which decreased from 3.2 ± 0.5 to 2.1 ± 0.8 (Fig. 1, Table II).

During the first year of follow-up, 8 patients died: 3 suddenly, 3 of worsening heart failure, and 2 of non-cardiac causes (1 of pulmonary embolism following heart transplant and 1 of prostate cancer); the first-year mortality rate was thus 13% (61 patients have at least 1 year of follow-up).

With regard to the whole population, 15 patients have died to date: 7 died suddenly (also including the 2 patients who received an appropriate intervention from the implanted cardioverter-defibrillator), 5 of worsening heart failure, and 3 of non-cardiac causes (the third one died of lung cancer) (Fig. 2).

Table II. Results.

Parameter	Pre-implant	Post-implant
QRS (ms)	177 ± 30	143 ± 23*
NYHA class	3.2 ± 0.5	2.1 ± 0.8*
Hospitalizations (n=)	179	39*
Hospitalizations (days)	2072	336*
End-diastolic diameter (mm)	72 ± 11	69 ± 11
End-systolic diameter (mm)	58 ± 10	57 ± 12
Ejection fraction (%)	23 ± 8	36 ± 12*
E wave velocity (mm/s)	639 ± 284	628 ± 178
A wave velocity (mm/s)	700 ± 218	658 ± 196
E/A ratio	1.03 ± 0.6	1.10 ± 0.6
E wave deceleration time (ms)	165 ± 94	210 ± 93*
Mitral regurgitant jet (%)	21 ± 18	12 ± 12**
Aorto-pulmonary delay (ms)	55 ± 33	25 ± 19*

* = $p < 0.0001$; ** = $p < 0.05$.

In a group of 56 patients with 1-year of follow-up, we observed – in comparison with the year before pacemaker implantation – a reduction in the morbidity rate: hospitalizations dropped by 78% and the hospital stay decreased by 84%.

Effects on drug therapy. We did not observe significant variations for any drugs but β-blockers, the mean dose of which increased from 6.6 ± 12.1 to 17.1 ± 17.3 mg/die; in addition, more patients (24 vs 48) were on β-blockers at follow-up than before pacemaker implantation.

Echo-Doppler follow-up. A reduction in the width of the QRS complex (177 ± 30 vs 143 ± 23 ms) went together with the aorto-pulmonary delay (55 ± 33 vs 25 ± 19 ms).

Although we observed no significant decrease in the left ventricular diameters (end-systolic diameter 58 ± 10 vs 57 ± 12 mm; end-diastolic diameter 72 ± 11 vs 69 ± 11 mm), the ejection fraction improved significantly, increasing from 23 ± 8 to 36 ± 12%. This result was also confirmed in 26 patients in whom radionuclide ventriculography was used in order to determine the ejection fraction (24 ± 8 vs 31 ± 14%, p = 0.06).

Even though the E wave and A wave velocities and the E/A ratio were not significantly modified, the E deceleration time significantly improved (from 165 ± 94 to 210 ± 93 ms). Besides, even the mitral regurgitant jet was significantly reduced (from 21 ± 18 to 12 ± 12%). No other parameter was significantly modified.

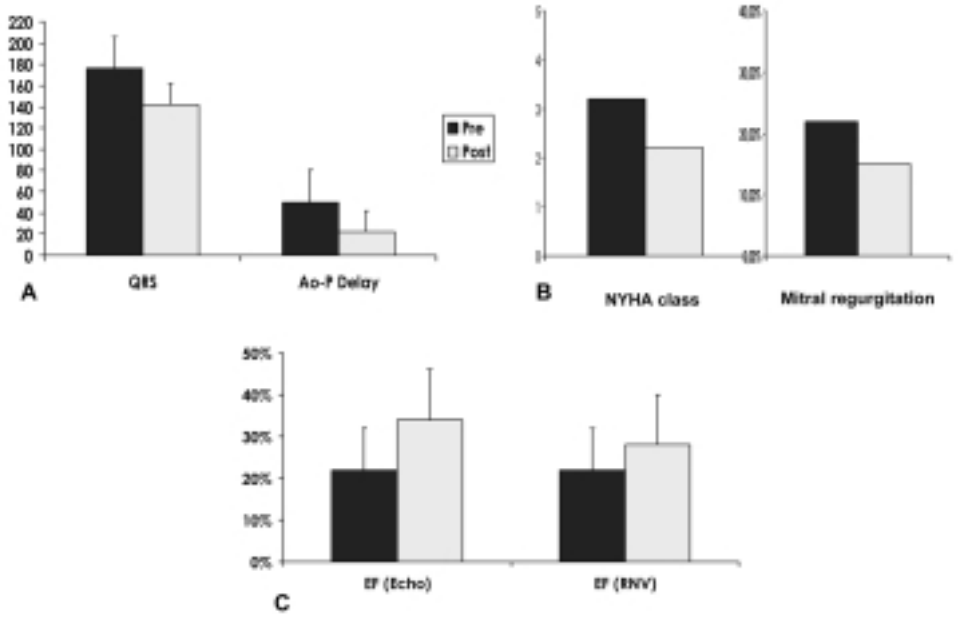

Figure 1. A: *efficacy of resynchronization; reduction in the width of the QRS complex and in the aorto-pulmonary (Ao-P) delay;* B: *reduction in the NYHA class and in mitral regurgitation;* C: *improvement in ejection fraction (EF); measurements obtained by means of echo and of radionuclide ventriculography (RNV).*

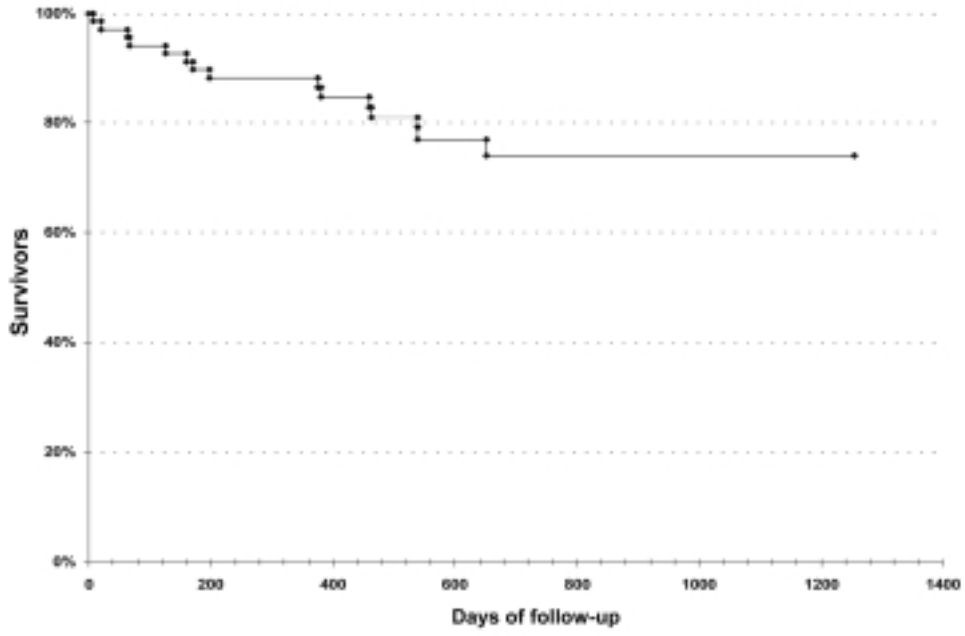

Figure 2. *Kaplan-Meier actuarial survival curve.*

Discussion

This is an observational study that constitutes a single center experience: for this reason the population is very homogeneous, especially as far as patient selection and the implant procedure are concerned. Even though the criteria for patient selection were different, our results are consistent with those of randomized studies, such as MUSTIC[11] and MIRACLE[12], and demonstrate a clinical and instrumental improvement.

Even though our study enrolled only a small number of patients, this clinical and instrumental improvement seems to translate into a significant reduction in the mortality rate (13% at 1 year; 25.4% at 2 and 3 years in our population), compared to the expected mortality for such a severe pathology. In the Framingham study[15] the mortality rate for NYHA classes III and IV was 40% and in the CONSENSUS[16] trial it was 34%. Furthermore, heart failure is a disease with a significant morbidity rate, and even from this point of view biventricular pacing could be effective.

The Karolinska study[17] demonstrated a significant reduction in the number of rehospitalizations and a consequent reduction in the management costs of these patients. We observed similar results[18], with a 78% reduction in rehospitalizations and with an 84% reduction in hospital stay.

Even though further randomized multicenter trials and longer follow-ups are needed in order to confirm these observational studies, it is quite clear that biventricular pacing can be highly effective in a subset of patients with severe congestive heart failure.

The identification of those patients who will benefit from this treatment and the understanding of the mechanisms that lead to such an improvement still constitute a challenge for clinicians.

In our population, the ejection fraction significantly improved even though the left ventricular diameters did not change. This could be explained by a more synergic action of all segments (we did not evaluate this particular aspect) and by an improvement in left ventricular filling, as demonstrated by the improvement in the E wave deceleration time in our study and by the improvements in the isovolumetric relaxation time and in the pre-ejection period reported by other authors[19].

It is even more problematic to identify responders (as we defined them): even though we divided our patients into different groups according to the etiology of the cardiomyopathy (ischemic vs non-ischemic), to the rhythm (sinus rhythm or atrial fibrillation), to the type of interventricular defect (right vs left bundle branch block) and to the basal ejection fraction or basal QRS width, we were not able to find any significant differences in terms of "responsiveness" to biventricular stimulation and in terms of the prediction of mortality.

In our experience, neither did the left lead position permit us to determine any significant difference in terms of results. This could be due to the small numbers, even though in a recent study Garrigue et al.[19] found a significant hemodynamic improvement with biventricular pacing even if the left lead was positioned within the great cardiac vein.

This aspect could, again, reflect our lack of knowledge on the different mechanisms of impairment of the left ventricular function in patients with an inter and intraventricular delay, that is to say that it could be that the lateral wall is not always the latest to be activated and, as a consequence, it may be that the lateral branch

of the CS is not always the best position for the left lead.

In conclusion, biventricular pacing has provided clinicians who deal with congestive heart failure with a new promising technique for the treatment of these patients. Even though specifically designed trials are needed to understand the effect of this treatment on the hard endpoints (mortality), results derived from observational studies similar to ours seem to demonstrate its efficacy.

A study designed to improve the understanding of the mechanisms by which resynchronization therapy acts is needed.

References

1. Braunwald E. Shattuck Lecture - Cardiovascular medicine at the turn of the millennium: triumphs, concerns and opportunities. N Engl J Med 1997; 337: 1360-9.
2. Cleland JF, Erdmann E, Ferrari R, et al. Guidelines for the diagnosis of heart failure. Eur Heart J 1995; 16: 741-51.
3. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000; 355: 1575-81.
4. Bristow NR. Beta-adrenergic receptor blockade in chronic heart failure. Circulation 2000; 101: 558-69.
5. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341: 709-17.
6. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian Network on Congestive Heart Failure. Am Heart J 2002; 143: 398-405.
7. Grines LC, Bashore TM, Boudoulas H, et al. Functional abnormalities in isolated left bundle branch block: the effect of interventricular asynchrony. Circulation 1989; 79: 845-53.
8. Ziao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. Br Heart J 1991; 66: 443-7.
9. Breithard OA, Stellbrink C, Franke A, et al. Acute effects of cardiac resynchronization therapy on left ventricular Doppler indices in patients with congestive heart failure. Am Heart J 2002; 143: 34-44.
10. Mansourati J, Etienne Y, Gilard M, et al. Left ventricular-based pacing in patients with chronic heart failure: comparison of acute hemodynamic benefits according to underlying disease. Eur J Heart Fail 2000; 2: 195-9.
11. Cazeau S, Leclercq C, Lavergne T, et al, for the Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001; 344: 873-80.
12. Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). J Card Fail 2000; 6: 369-80.
13. Curnis A, Mascioli G, Bianchetti F, et al. Implantation of a single chamber pacemaker in patients with triple mechanical valve prosthesis: utilization of coronary sinus distal branches to stimulate the left ventricle. Pacing Clin Electrophysiol 2002; 25: 239-40.
14. Ritter P, Dib JC, Lelievre T, et al. Quick determination of the optimal atrioventricular delay at rest in patients paced in DDD mode for complete atrioventricular block. (abstr) Eur J Clin Pharmacol 1994; 4: 39.
15. Ho KK, Andersen M, Kannel WB, et al. Survival after onset of congestive heart failure in Framingham Heart Study subjects. Circulation 1993; 88: 107-15.
16. The CONSENSUS Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316: 1429-35.
17. Braunschweig F, Linde C, Gadler F, Ryden L. Reduction of hospital days by biventricular pacing. Eur J Heart Fail 2000; 2: 399-406.
18. Curnis A, Bontempi L, Bordonali T, et al. Cost-efficacy analysis of biventricular stimulation: results of the Brescia study. (abstr) J Am Coll Cardiol 2002; 39 (Suppl B): 183B.
19. Garrigue S, Bordachar P, Reuter S, et al. Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: prospective hemodynamic study. Heart 2002; 87: 529-34.