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Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation

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Background One third of chronic heart failure patients have major intraventricular conduction and uncoordinated ventricular contraction. Non-controlled studies suggest that biventricular pacing may improve haemodynamics and well-being by reducing ventricular asynchrony. The aim of this trial was to assess the clinical efficacy and safety of this new therapy in patients with chronic atrial fibrillation.

Methods Fifty nine NYHA class III patients with left ventricular systolic dysfunction, chronic atrial fibrillation, slow ventricular rate necessitating permanent ventricular pacing, and a wide QRS complex (paced width $\geq$200 ms), were implanted with transvenous biventricular-VVIR pacemakers. This single-blind, randomized, controlled, crossover study compared the patients' parameters, as monitored during two 3-month treatment periods of conventional right-univentricular vs biventricular pacing. The primary end-point was the 6-min walked distance, secondary end-points were peak oxygen uptake, quality-of-life, hospitalizations, patients' preferred study period and mortality.

Results Because of a higher than expected drop-out rate (42%), only 37 patients completed both crossover phases. In the intention-to-treat analysis, we did not observe a significant difference. However, in the patients with effective therapy the mean walked distance increased by 9·3% with biventricular pacing (374 ± 108 vs 342 ± 103 m in univentricular; $P=0{\cdot}05$). Peak oxygen uptake increased by 13% ($P=0{\cdot}04$). Hospitalizations decreased by 70% and 85% of the patients preferred the biventricular pacing period ($P<0{\cdot}001$).

Conclusion As compared with conventional VVIR pacing, effective biventricular pacing seems to improve exercise tolerance in NYHA class III heart failure patients with chronic atrial fibrillation and wide paced-QRS complexes. Further randomized controlled studies are required to definitively validate this therapy in such patients.
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Introduction

Despite the combination of various proven drug therapies[1–5], some patients with chronic heart failure remain refractory to full medical treatment with limited therapeutic possibilities. Of the various non-pharmacological approaches, ventricular resynchronization by biventricular pacing has gained increasing interest since its introduction in 1994[6,7]. Results from acute haemodynamic studies with temporary pacing[8–14] and those from early pilot studies with permanent pacing[7,15–17] are encouraging in selected heart failure patients with chronic left ventricular systolic dysfunction and major intraventricular conduction delay. Controlled

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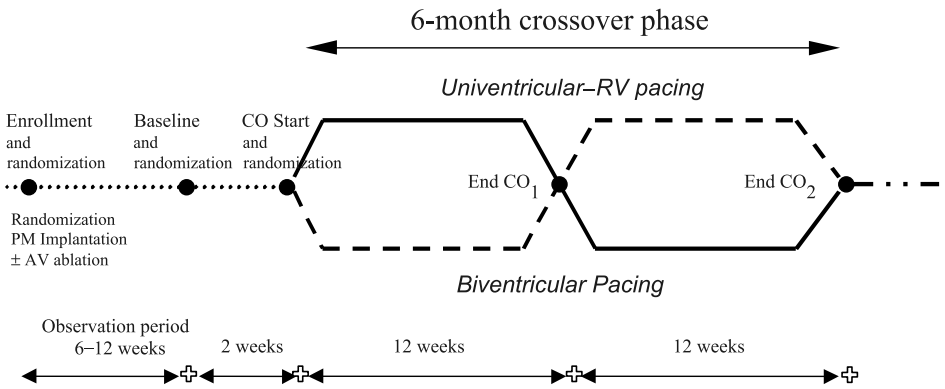

Figure 1 **The study design. Patients were randomized to 3 months each of either conventional right-univentricular VVIR pacing or biventricular VVIR pacing. PM = pacemaker; ablation = AV node radiofrequency ablation; end CO_1 = end of crossover phase 1; end CO_2 = end of crossover phase 2; + = follow-up visit.**

studies are now under way to assess the clinical value of this novel therapy. MUSTIC (MUltisite STimulation In Cardiomyopathies) was the first controlled randomized study conducted in this field. This single-blind crossover trial aimed at assessing the clinical efficacy of ventricular resynchronization in two different groups of heart failure patients: patients with stable sinus rhythm and no classical pacemaker indication[18], and patients with chronic atrial fibrillation who required permanent ventricular pacing because of a slow ventricular rate. This paper reports the results in the atrial fibrillation population.

Material and methods

Patient selection

All patients gave their informed consent before inclusion. All had had severe chronic heart failure (NYHA Class III for at least 1 month before inclusion under optimized treatment including at least diuretics and ACE inhibitors at the maximum tolerated dose). Left ventricular systolic dysfunction was defined by an LV radionuclide ejection fraction <35% and an end-diastolic diameter >60 mm at echocardiography. All patients had persistent (>3 months) atrial fibrillation requiring permanent ventricular pacing due to a slow ventricular rate, either spontaneously or induced by AV node radiofrequency ablation. A right ventricular (RV) paced QRS duration >200 ms with a 10% deviation tolerance was required as an index for electrical ventricular dyssynchrony. The 6-min walked distance had to be <450 m. Exclusion criteria have been previously described[18].

Study design

This European multicentre single-blind trial involved 15 centres in six countries (see Appendix). The study protocol was approved by local ethics committees. The study included a 6-month randomized crossover phase comparing biventricular with right-univentricular VVIR pacing during two 3-month periods (Fig. 1). Treatment order was allocated at inclusion according to a fully randomized block design. Biventricular pacemaker implantation and, when required, radiofrequency AV node ablation were performed at inclusion. A 6-week (non-ablated patients) to 12-week (ablated patients) observation period was then undertaken with the pacemaker programmed right-univentricular to verify chronic heart failure stability and appropriate function of the pacing system, whilst reversing any tachycardia-induced cardiomyopathy in the subgroup of patients who required AV node ablation. Pacemaker programming remained unchanged throughout the study with a basic rate of 70 bpm and a sensor-driven rate at 85% of individual 'maximal predicted heart rate'. The crossover phase began after completion of the observation period and was followed by a longitudinal period during which the pacemaker was programmed to the mode applied during the period preferred by the patient. Only results from the crossover phase are reported here.

Pacemaker implantation

All leads were implanted transvenously according to a method already described[19]. The LV target site was preferably mid-lateral. The right ventricular lead was positioned as far from the left as possible. The pacemakers used were standard dual-chamber, rate-responsive units (ELA Medical, France and Medtronic Inc., U.S.A.). The LV and RV leads were connected to the atrial and ventricular ports, respectively. The interventricular delay was set to the shortest programmable value (30 ms) to synchronize pacing of the two ventricles. Implantation results were assessed from the lead positions on chest X-rays and from modifications in QRS duration on a 12-lead surface ECG.

Medication

No modification other than diuretic dosage adjustment was accepted between inclusion and the end of the crossover phase. Medication was monitored by follow-up interviews and prescription checks.

Patient evaluation

At baseline, at randomization and at the end of each crossover phase, the patients were evaluated with the 6-min walked distance[18–20], quality-of-life as assessed by the Minnesota Living-With-Heart-Failure questionnaire[21], NYHA classification, medication, need for hospitalization, 12-lead surface ECG, 24-h Holter monitoring, pacemaker interrogation and cardiopulmonary exercise testing as previously described[18].

A core analysis of all ECG data was performed to assess the validity of inclusion criteria after pacemaker implantation (paced QRS duration), and the percentage of paced ventricular cycles at the end of each study period. A pacing percentage <75% was considered as evidence of persistent intrinsic conduction, and failure of therapy delivery.

End-points

The primary end-point was the 6-min walked distance. Secondary end-points were peak oxygen uptake, quality-of-life, hospital admissions for decompensated heart failure, mortality and the patient's preferred period at the end of crossover.

Statistical analysis

Based on previous mortality reports in class III patients we estimated the mortality rate at 6 months at 10%. Moreover, a 10% LV lead implantation failure rate and a 20% premature termination for loss of LV capture or unstable heart failure was expected. We estimated a 10% increase in 6-min walked distance with biventricular pacing. With a 95% confidence level and 95% power, the sample size was 22 patients. On the Minnesota rating scale, an expected 10% reduction resulted in a 30-patient sample. However, considering the above mortality and drop-out rates, we targeted a 40-patient sample.

All analyses were based on the intention-to-treat principle. Thus all patients who were assessed at baseline before starting the crossover phase were included in the analysis, but each clinical efficacy end-point could only be assessed in patients with no data missing after completion of both crossover phases. Baseline characteristics were assessed using the Chi-square test for dichotomous variables and Student's t-test or Wilcoxon's non-parametric test for quantitative or categorical variables. The scores obtained for all efficacy criteria were compared using Wilcoxon's test and according to a 2-period/2-treatment crossover design. Period and carry-over effects were checked before treatment efficacy was evaluated. Morbidity and mortality data were compared during the first crossover period and were described for all other phases. The threshold of significance was set at 0·05.

Results

Study progress and drop-outs (Fig. 2)

Sixty-four patients gave their informed consent to participate in the study between March 1998 and June 1999 and were equally distributed in the two treatment arms. Five exited before implantation. Thus LV lead implantation was attempted in 59 patients with a 92% success rate. A lateral position was reached in 70% of cases and the mean acute pacing threshold was $1{\cdot}4 \pm 0{\cdot}8$ V. Early dislodgment occurred in five patients and could be successfully corrected in three. Overall, 87% of the patients in whom LV lead implantation was attempted had a fully functional biventricular pacing system at the end of the crossover phase.

Of the 54 patients who were successfully implanted, eight additional patients left the study for various reasons (Fig. 2) either immediately after implantation or during the 6- to 12-week observation period. Forty-five patients were thus evaluated at baseline and 43 entered the crossover phase and formed the 'intention-to-treat' analysis population. During the two crossover phases, four patients were withdrawn. Finally, 39 (61%) patients completed the two crossover phases.

Analysing 24-h Holter ECG recordings and pacemaker files showed that two non-ablated patients had a very low percentage of paced ventricular cycles, ranging from 17 to 40% and 35 to 50%, respectively. The therapy was considered as undelivered in these two cases, in contrast to the other 37 patients where the pacing percentage ranged from 97 to 100%. This group of 37 patients constituted the efficacy analysis set.

Study population (Table 1)

Forty-three patients, mean age 63 years, entered the crossover phase. At baseline, 41 patients were still in NYHA class III when two improved to class II after 3 months of rate-control with right-univentricular pacing. Exercise tolerance was severely impaired as reflected by a mean 6-min walked distance of 329 m and a mean peak VO_2 of $12{\cdot}9$ ml . min^{-1} . kg^{-1}. Left ventricular systolic dysfunction was of idiopathic origin in 30 cases (70%) and ischaemic in 13. The mean LV ejection fraction was 26 ± 10%. The mean RV-paced QRS duration was 209 ± 18 ms. The ratio of ablated vs non-ablated patients was 27/16 (63% vs 37%).

All patients received diuretics and ACE-inhibitor or equivalent at the maximal tolerated doses. Digoxin,

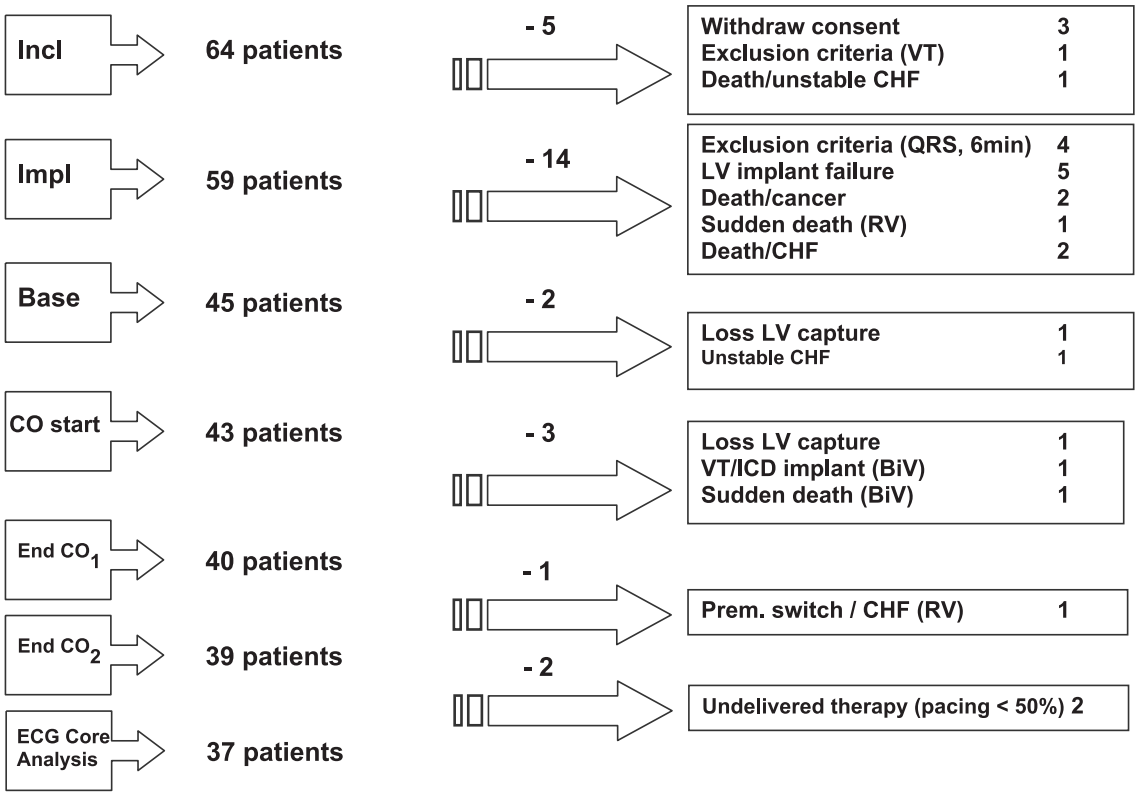

Figure 2 **Study progress and drop-outs. This figure indicates the time of occurrence and the causes of the 27 study exits. Incl=inclusion time; impl=implantation time; base=baseline; CO start=entry in the crossover phase; end CO_1=end of crossover phase 1; end CO_2=end of crossover phase 2; VT=ventricular tachycardia; CHF=congestive heart failure; LV=left ventricular; RV=right ventricular (pacing); ICD=implantable cardioverter defibrillator ; BIV=biventricular (pacing).**

Table 1 Study population

	Baseline	All patients	Distribution in the two treatment-arms		*P* value
			1st treatment arm (BIV-UniRV)	2nd treatment arm (UniRV-Biv)	
Number of patients	45	43	25	18	
Sex ratio men/women	37/8	35/8	21/4	14/4	0·70
Age (years)	66 ± 9	65 ± 8	65 ± 9	66 ± 9	0·76
Weight (kg)	79 ± 17	76 ± 14	77 ± 13	74 ± 14	0·70
6-min walked distance (m)	324 ± 76	329 ± 85	338 ± 95	317 ± 71	0·64
Peak VO_2 (ml . min^{-1} kg^{-1})	12·7 ± 3·8	12·9 ± 4·8	12·8 ± 4·9	13 ± 4·8	0·9
Quality-of-life score	46 ± 22	44 ± 22	40 ± 23	50 ± 20	0·11
Heart rate (beats . min^{-1})	73 ± 6	74 ± 5	75 ± 6	74 ± 5	0·53
Paced QRS duration (ms)	207 ± 17	209 ± 18	209 ± 21	208 ± 12	0·71
His bundle ablation (Yes/No)	29/16	27/16	18/6	9/9	0·14
Previous PM (Yes/No)	23/22	22/21	13/12	9/9	0·90
Left ventricular EF (%)	25 ± 10	26 ± 10	23 ± 7	30 ± 12	0·07
Left ventricular EDD (mm)	68 ± 7	68 ± 8	70 ± 9	66 ± 7	0·07

In the first treatment arm, the pacemaker was programmed biventricular (Biv) during the first 3 months then right univentricular (Uni-RV) during the second cross over period. In the second arm, the reverse order was applied; VO_2=oxygen uptake; PM=pacemaker; EF=ejection fraction (radionuclides) EDD=end-diastolic diameter.

beta-blockers and spironolactone were given in 25 (58%), 10 (23%) and 7 (16%) patients, respectively.

There were no statistically significant differences in clinical baseline characteristics between the two treatment arms (Table 1). The difference in patient number was related to a higher drop-out rate in the second treatment-arm (uni right ventricular followed by biventricular pacing) (n=14) as compared to the first

Table 2 Results of intention-to-treat analysis

		Right uni ventricular		Biventricular		Δ	*P*
		n	mean ± SD	n	mean ± SD		
Treatment arm 1	6 min walked test distance (m)	18	360 ± 101	18	389 ± 109	+29	
	Peak VO_2 (ml . kg^{-1} min^{-1})	17	13·9 ± 4·4	17	15·7 ± 4·1	+1·8	
	QOL score	21	35·9 ± 20·1	21	32·4 ± 21·8	− 3·5	
Treatment arm 2	6 min walked test distance (m)	20	324·2 ± 98	20	332·5 ± 128·1	+8	
	Peak VO_2 (ml . kg^{-1} min^{-1})	15	12·8 ± 3·6	15	13·7 ± 3·9	+0·9	
	QOL score	18	41·5 ± 23·1	18	36·0 ± 19·5	− 5·5	
Treatment arms 1+2	6 min walked test distance (m)	38	341 ± 100	38	359 ± 121	+18	ns
	Peak VO_2 (ml . kg^{-1} min^{-1})	32	13·4 ± 4·0	32	14·8 ± 4·1	+1·4	0·08
	QOL score	39	38·5 ± 21·4	39	34·1 ± 20·6	− 4·4	ns
	Patient preference	39*	4	39	33		0·001

VO_2=oxygen uptake; QOL=quality of life; n=number of patients without missing data; *=2 patients did not indicate any preference.

Table 3 Efficacy analysis set

		Right-univentricular		Biventricular		Δ	*P*
		n	mean ± SD	n	mean ± SD		
Treatment arm 1	6 min walked test distance (m)	18	360 ± 101	18	389 ± 109	+29	
	Peak VO_2 (ml . kg^{-1} min^{-1})	17	13·9 ± 4·4	17	15·7 ± 4·1	+1·8	
	QOL score	21	35·9 ± 20·1	21	32·4 ± 21·8	− 3·5	
Treatment arm 2	6 min walked test distance (m)	16	323 ± 105	16	358 ± 109	+35	
	Peak VO_2 (ml . kg^{-1} min^{-1})	13	12·2 ± 3·1	13	13·8 ± 4·2	+1·6	
	QOL score	16	40·6 ± 24·3	16	35·1 ± 20·4	− 5·5	
Treatment arms 1+2	6 min walked test distance (m)	34	342 ± 103	34	374 ± 108	+32	0·05
	Peak VO_2 (ml . kg^{-1} min^{-1})	30	13·2 ± 3·9	30	14·9 ± 4·2	+1·7	0·04
	QOL score	37	37·9 ± 21·8	37	33·6 ± 21	− 4·3	0·11
	Patient preference	37	33	37	4		0·001

VO_2=oxygen uptake; QOL=quality of life; n=patients without missing data.

(biventricular followed by uni right ventricular pacing) (n=57). This could be explained by the fact that most of the drop-out occurred during the observation period and the treatment order was allocated at the inclusion time and not at baseline just before starting the crossover period.

Therapy delivery

QRS duration decreased by a mean of 18% (P=0·0001) with biventricular pacing as compared with right-univentricular pacing (171 ± 19 vs 209 ± 18 ms).

Clinical end-points

The intention-to-treat analysis showed no statistically significant difference in either primary or secondary end-points between the two pacing modes (Table 2).

In contrast, analysing the 37 patients where therapy was effectively delivered (Table 3) revealed significant improvement with biventricular pacing of both the 6-min walked distance (mean global difference=+9·3%; P=0·05) and peak VO_2 uptake (mean global difference=+13%; P=0·04) when compared with right-univentricular pacing. There was a trend towards better quality of life under biventricular pacing (mean global difference=−11%) but the difference was not statistically significant (P=0·09). This can be partially explained by the heterogeneity between the two treatment arms at baseline with a mean score of 40 ± 23 in one arm and of 50 ± 20 in the other arm (Table 1).

Hospitalizations

To avoid the carry-over effect of a crossover study, statistical comparisons were made during the first 3-month period only. The hospitalization rate was very low (n=3). At admission, the pacemaker was programmed in the univentricular mode in two patients and biventricular in one. When considering the whole 6-month crossover phase, 10/44 patients (23%) were hospitalized for heart failure decompensation during the univentricular pacing period (total of 11 hospitalizations), as compared to only three (7%) during the biventricular period.

Mortality

Before entering the crossover phase, four patients (6·3%) died from cardiovascular cause and two additional patients from non-cardiovascular causes (cancer). During the whole 6-month crossover phase, only one patient (2·3%) died, in his sleep after 100 days in biventricular pacing. The total mortality rate during this mean 9-month interval was 10·9% (7/64 patients).

Patient preference

At the end of the crossover phase patients were blindly asked by the study nurse which 3-month study period they preferred. Thirty-three (84·6%) indicated the period corresponding to the biventricular pacing phase and only four the period corresponding to the univentricular pacing phase ($P<0·001$). Two patients showed no preference.

Discussion

This is the first controlled study which shows that ventricular resynchronization by biventricular pacing is preferred by most chronic heart failure patients with chronic atrial fibrillation who require permanent cardiac pacing for slow ventricular rate.

In all chronic heart failure patients, the prevalence of permanent atrial fibrillation is relatively high at approximately 20%[22,23], but may even reach 40% of patients with advanced heart failure[1,24]. The prognostic value of atrial fibrillation in chronic heart failure remains controversial[24–27]. Our study focused on a specific population of chronic heart failure patients with atrial fibrillation and intraventricular conduction delay attested by a RV-paced QRS duration >200 ms. The prognosis is probably very bleak in that sub-population, as suggested by the data from the Italian Network on Heart Failure (Baldasseroni L, MD, Maggioni A, MD, *et al*., unpublished data, 2000), who found that chronic atrial fibrillation was associated with a significantly higher 1-year mortality rate in heart failure patients with intraventricular conduction delay than in those in sinus rhythm (26·5% vs 14·5%; $P<0·001$). That can be related to Farwell *et al*.'s[28] recent findings that 40% of potential candidates to biventricular pacing were in chronic atrial fibrillation.

The interrelations that exist between atrial fibrillation and heart failure are complex. There are three main contributing factors: (i) the loss of atrial contribution, (ii) heart rate irregularity and (iii) frequently fast ventricular rate[29–31]. It has now been accepted that rate control by AV node ablation and permanent VVIR pacing may improve more often within 3 months, albeit partially, left ventricular systolic dysfunction and its clinical consequences in chronic heart failure patients with persistent atrial fibrillation and fast ventricular rate[29–31]. This explains why a 3-month time interval was chosen as the monitoring period from pacemaker implantation to the beginning of crossover in our study. Unfortunately tolerance of right ventricular pacing was sometimes poor and resulted in study withdrawals which partially accounted for the higher-than-expected drop-out rate (33%) before the beginning of the crossover phase.

The effects of biventricular or LV pacing in chronic heart failure patients with atrial fibrillation have so far been little studied. In an acute haemodynamic study, Etienne *et al*.[32] showed an equal degree of improvement in pulmonary capillary wedge pressure and systolic arterial pressure in patients with sinus rhythm and in patients with atrial fibrillation. In a non-controlled pilot study, a French group[33] assessed the long-term clinical effects of permanent biventricular pacing in patients with sinus rhythm and in patients with persistent atrial fibrillation. Biventricular pacing was associated with a more pronounced improvement in atrial fibrillation patients, probably reflecting the combined effects of rate control and biventricular pacing. Another small, non-controlled and non-randomized study evaluated the effect of LV pacing in patients with advanced heart failure, permanent atrial fibrillation left bundle branch block associated with LV systolic dysfunction. The results observed in patients has shown that LV pacing might also improve symptoms and exercise tolerance in such patients[34].

In contrast to these studies, the present trial made crossover comparisons between two active pacing modes whose only difference was the ventricular pacing site, rate control being a prerequisite. These differences probably account for the modest though statistically significant difference observed between biventricular pacing and classic right univentricular pacing in patients with effective therapy.

Study limitations

The results from this study are to be interpreted against the methodological limitations imposed by the investigational plan. The higher-than-expected drop-out rate (27 patients or 42% withdrew before completing the 6-month crossover phase) and patient heterogeneity at baseline greatly limited the statistical power of the trial. The fact that randomization order was determined at inclusion rather than at baseline (Fig. 1) explains the non-uniformity of the two treatment-arms. Moreover, the potential deleterious effects of uni right ventricular pacing during the observation period were probably underestimated when designing the study protocol.

Seven of the study withdrawals were linked to technical difficulties with left ventricular pacing. In fact, the 92% implantation success rate and 87% long-term effectiveness of this recently introduced technique[19] is very encouraging. The advances in implantation technique and device technology[35] may further improve the success rate.

Another cause for withdrawal was the secondary identification of exclusion criteria. Three patients dropped out after implantation because of an RV-paced QRS duration <180 ms. This could not have been foreseen before implantation because this parameter depended on the right ventricular lead implantation site, which itself was determined at implant by the left ventricular lead positioning. Finally, according the ECG inclusion criteria (QRS duration >200 ms with RV pacing) this study would be theoretically applied only in this patients without baseline spontaneous QRS criteria.

In addition, ECG-Holter core analysis identified two non-ablated patients in whom >50% intrinsic conduction occurred regardless of programming mode. Those observations illustrate the necessity, except in rare cases of chronic and perfectly stable AV block, for systematic AV node ablation in this type of chronic heart failure patients with atrial fibrillation, so as to ensure permanent and full biventricular capture. That prerequisite is absolutely necessary to assess the clinical effectiveness of the treatment.

Lastly, failing full and comprehensive assessment at inclusion, the combined benefits of rate control and VVIR pacing, either in classic right-univentricular or in biventricular mode could not be assessed. The study design chosen may have underrated biventricular pacing by reducing the magnitude of the clinical benefits noted.

Conclusion

Within the limits of that study, ventricular resynchronization through biventricular pacing tends to improve exercise tolerance and was the pacing mode preferred by most chronic heart failure patients with chronic atrial fibrillation and intraventricular conduction delay, the majority of whom had been subject to AV-node ablation. However, further studies are needed to confirm this favourable trend and to assess the real clinical impact of ventricular resynchronization therapy in chronic heart failure patients with chronic atrial fibrillation, especially in terms of morbidity and mortality. At the time being, this novel treatment should not yet be recommended for this group of patients.

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References

[1] The CONSENSUS Trial Study Group. Effects 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.

[2] Flather MD, Yusuf S, Kober L *et al.* for the ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. The Lancet 2000; 355: 1575–81.

[3] Pitt B, Poole-Wilson PA, Segal R, on behalf of the Elite II investigators. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial — the Losartan Heart Failure Survival Study Elite II. The Lancet 2000; 355: 1582–7.

[4] Bristow MB. Adrenergic receptor blockade in chronic heart failure. Circulation 2000; 101: 558–69.

[5] Pitt B, Zannad F, Remme WJ *et al.*, for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341: 709–17.

[6] Cazeau S, Ritter P, Bakdach S *et al.* Four chamber pacing in dilated cardiomyopathy. PACE 1994; 17: 1974–9.

[7] Bakker FP, Meijburg HW, de Vries JW *et al.* Biventricular pacing in end-stage heart failure improves functional capacity and left ventricular function. J Interv Cardiac Electrophysiol 2000; 4: 395–404.

[8] Cazeau S, Ritter P, Lazarus A *et al.* Multisite pacing for end-stage heart failure. PACE 1996; 19: 1748–57.

[9] Blanc JJ, Etienne Y, Gilard M *et al.* Evaluation of different ventricular pacing sites in patients with severe heart failure. Circulation 1997; 96: 3273–7.

[10] Leclercq C, Cazeau S, Le Breton H *et al.* Acute haemodynamic effects of biventricular DDD pacing in patients with end-stage heat failure. J Am Coll Cardiol 1998; 32: 1825–31.

[11] Kass D, Chen C, Curry C *et al.* Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation 1999; 99: 1567–73.

[12] Auricchio A, Stellbrink C, Block M *et al.* for the Pacing Therapies for Congestive Heart Failure Study Group. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. Circulation 1999; 99: 2993–3001.

[13] Nelson GS, Curry CW, Wyman BT *et al.* Predictors of systolic augmentation from left-ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000; 101: 2703–9.

[14] Nelson GS, Berger RD, Fetics BJ *et al.* Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. Circulation 2000; 102: 3053–9.

[15] Leclercq C, Cazeau S, Ritter P *et al.* A pilot experience with permanent biventricular pacing to treat advanced heart failure. Am Heart J 2000; 140: 862–70.

[16] Gras D, Mabo P, Tang T *et al.* Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync study. PACE 1998; 21: 2249–55.

[17] Alonso C, Leclercq C, Victor F *et al.* Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in heart failure. Am J Cardiol 1999; 84: 1417–21.

[18] Cazeau S, Leclercq C, Lavergne T *et al.* Clinical effects of multisite biventricular pacing in heart failure patients without a classical pacemaker indication. N Engl J Med 2001; 344: 873–80.

[19] Daubert C, Ritter P, le Breton H *et al.* Permanent left ventricular pacing with transvenous leads inserted into the coronary veins. PACE 1998; 21: 239–45.

[20] Guyatt GH, Sullivan MJ, Thompson PJ *et al.* The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985; 132: 919–23.

[21] Rector TS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure: II. Content, reliability and validity of a new measure — the Minnesota living with heart failure questionnaire. Heart Failure 1987; 3: 198–207.

[22] CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomized trial. The Lancet 1999; 353: 9–13.

[23] MERIT-HF Study Group. Effect of Metoprolol CR/XL in chronic heart failure: Metroprolol CR/XL Randomized Intervention in Congestive Heart Failure (MERIT-HF). The Lancet 1999; 353: 2001–7.
[24] Middelkauf HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. Circulation 1991; 84: 40–48.
[25] Crijns HJ, Tjeerdsma G, De Kam PJ *et al*. Prognostic value of the presence and development of atrial fibrillation in patients with advanced heart failure. Eur Heart J 2000; 21: 1238–45.
[26] Stevenson WG, Stevenson LW, Middelkauf HR *et al*. Improving survival for patients with atrial fibrillation and advanced heart failure. J Am Coll Cardiol 1996; 28: 1458–63.
[27] Mahoney P, Kimmel S, De Nofrio *et al*. Prognostic significance of atrial fibrillation in patients at a tertiary medical center referred for heart transplantation because of severe heart failure. Am J Cardiol 1999; 83: 1544–7.
[28] Farwell D, Patel NR, Hall A *et al*. How many people with heart failure are appropriate for biventricular resynchronization? Eur Heart J 2000; 21: 1246–50.
[29] Edner M, Caidahl K, Bergfelt L *et al*. Prospective study of left ventricular function after radiofrequency ablation of atrioventricular junction in patients with atrial fibrillation. Br Heart J 1995; 74: 261–7.
[30] Rodriguez LM, Smeets RM, Baiyan X *et al*. Improvement in left ventricular function by ablation of atrioventricular nodal conduction in selected patients with lone atrial fibrillation. Am J Cardiol 1993; 72: 1137–41.
[31] Brignole M, Menozzi C, Gianfranchi L *et al*. Assessment of atrioventricular junction ablation and VVIR pacemaker vs pharmacological treatment in patients with heart failure and chronic atrial fibrillation. Circulation 1998; 98: 953–60.
[32] Etienne Y, Mansourati J, Gilard M *et al*. Evaluation of left ventricular based pacing in patients with congestive heart failure and atrial fibrillation. Am J Cardiol 1999; 83: 1138–40.
[33] Leclercq C, Victor F, Pavin D *et al*. Comparative effects of permanent biventricular pacing for refractory heart failure in patients with stable sinus rhythm or chronic atrial fibrillation. Am J Cardiol 2000; 85: 1154–6.
[34] Lupi G, Brignole M, Oddone D *et al*. Effects of left ventricular pacing on cardiac performance and on quality of life in patients with drug-refractory heart failure. Am J Cardiol 2000; 86: 1267–70.
[35] Alonso C, Leclercq C, Pavin D *et al*. Six-year experience of transvenous left ventricular lead implantation for permanent biventricular pacing in patients with advanced heart failure. Heart 2001; 86: 405–10.

Appendix

In addition to the authors, the following persons participated in the Study: *Study board:* Jean-Claude Daubert (Chair), Cecilia Linde (Co-Chair), Christophe Bailleul, Serge Cazeau, Lukas Kappenberger, Richard Sutton; *Safety and Adverse Events Committee:* Christine Alonso, Henry J. Dargie, Philippe Lechat; *Independent Statistics Center:* Jean-Sebastien Hulot, Philippe Lechat; *Technical Advisers:* Daniel Gras, Philippe Ritter, Stuart Walker; *Core Analysis Center:* Christine Alonso, Rennes (ECG-Holter), Derek Gibson, London (Echocardiography), Cecilia Linde, Stockholm (QOL), William McKenna, London (CPX); *Study Team:* Christophe Bailleul (study manager), Klaudia Coombs, Catherine Fournier, Marcel Limousin (Ela Recherche), Luca Mollo, Stan Myrum (Medtronic), Jean-Mathieu Torralba, Marie-Christine Vandrell; *Investigators — France:* Etienne Aliot, Serge Cazeau, Jacques Clémenty, J. Claude Daubert, Christian De Chillou, Jean-Claude Deharo, Pierre Djiane, Stéphane Garrigue, Daniel Gras, Louis Guize, Mustapha Jarwe, Salem Kacet, Didier Klug, Thomas Lavergne, Arnaud Lazarus, Christophe Leclercq, Alain Lemouroux, Philippe Mabo, Jacques Mugica, Akli Otmani, Jean-Luc Rey, Philippe Ritter, Nicolas Sadoul, Nicolas Savon; *Germany:* Thomas Lawo, Berndt Lemke, Stephan von Dryander; *Italy:* Gerardo Ansalone, Renato Ricci, Massimo Santini; *Sweden:* Frieder Braunschweig, Fredrik Gadler, Cecilia Linde; *Switzerland:* Xavier Jeanrenaud, Lukas Kappenberger, Xavier Lyon; *United Kingdom:* Melissa Fitzgerald, Michael D. Gammage, Guy A. Haywood, William J. McKenna, Terry Levy, Andrew J. Marshall, Howard Marshall, Faizel Osman, Vince Paul, Edward Rowland, Richard Sutton, Chetan Varma, Stuart Walker.