EFFECTS OF MULTISITE BIVENTRICULAR PACING IN PATIENTS WITH HEART FAILURE AND INTRAVENTRICULAR CONDUCTION DELAY

SERGE CAZEAU, M.D., CHRISTOPHE LECLERCQ, M.D., THOMAS LAVERGNE, M.D., STUART WALKER, M.D., CHETAN VARMA, M.D., CECILIA LINDE, M.D., STÉPHANE GARRIGUE, M.D., LUKAS KAPPENBERGER, M.D., GUY A. HAYWOOD, M.D., MASSIMO SANTINI, M.D., CHRISTOPHE BAILLEUL, PH.D., AND JEAN-CLAUDE DAUBERT, M.D., FOR THE MULTISITE STIMULATION IN CARDIOMYOPATHIES (MUSTIC) STUDY INVESTIGATORS*

ABSTRACT

Background One third of patients with chronic heart failure have electrocardiographic evidence of a major intraventricular conduction delay, which may worsen left ventricular systolic dysfunction through asynchronous ventricular contraction. Uncontrolled studies suggest that multisite biventricular pacing improves hemodynamics and well-being by reducing ventricular asynchrony. We assessed the clinical efficacy and safety of this new therapy.

Methods Sixty-seven patients with severe heart failure (New York Heart Association class III) due to chronic left ventricular systolic dysfunction, with normal sinus rhythm and a duration of the QRS interval of more than 150 msec, received transvenous atriobiventricular pacemakers (with leads in one atrium and each ventricle). This single-blind, randomized, controlled crossover study compared the responses of the patients during two periods: a three-month period of inactive pacing (ventricular inhibited pacing at a basic rate of 40 bpm) and a three-month period of active (atriobiventricular) pacing. The primary end point was the distance walked in six minutes; the secondary end points were the quality of life as measured by questionnaire, peak oxygen consumption, hospitalizations related to heart failure, the patients' treatment preference (active vs. inactive pacing), and the mortality rate.

Results Nine patients were withdrawn from the study before randomization, and 10 failed to complete both study periods. Thus, 48 patients completed both phases of the study. The mean (±SD) distance walked in six minutes was 23 percent greater with active pacing (399±100 m vs. 326±134 m, $P<0.001$), the quality-of-life score improved by 32 percent ($P<0.001$), peak oxygen uptake increased by 8 percent ($P<0.03$), hospitalizations were decreased by two thirds ($P<0.05$), and active pacing was preferred by 85 percent of the patients ($P<0.001$).

Conclusions Although it is technically complex, atriobiventricular pacing significantly improves exercise tolerance and quality of life in patients with chronic heart failure and intraventricular conduction delay. (N Engl J Med 2001;344:873-80.)

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THE aging of the population has made chronic heart failure an increasingly important health problem.[1] It is the leading medical cause of hospitalization, and its economic cost continues to increase. Despite important therapeutic advances with angiotensin-converting–enzyme (ACE) inhibitors[2,3] or angiotensin II–receptor blockers,[4] beta-blockers,[5] and spironolactone,[6] the prognosis of patients with chronic heart failure remains poor. The benefit of medical treatment is probably short-lived,[7,8] merely delaying the inevitable progression to heart failure that is refractory to drug treatment. As the disorder progresses, the well-being and exercise tolerance of patients deteriorate dramatically, and the rates of hospitalization increase. Nonpharmacologic therapies (such as heart transplantation and the use of implantable assist devices) are considered only in the later stages of the disease,[8,9] but access to such therapies is restricted.

It was against this backdrop of limited resources and the need for less expensive and simpler alternatives that resynchronization therapy by means of multisite biventricular pacing was proposed.[10] The rationale for this therapy is based on the high (30 to 50 percent) prevalence of intraventricular conduction delay among patients with heart failure[11-13] and on the resultant poor coordination of ventricular contraction and relaxation,[14-16] which in turn enhances the hemodynamic consequences of chronic left ventricular systolic dysfunction. Short-term studies have shown that atriobiventricular pacing (with leads in one atrium and each ventricle) significantly improves hemodynamics by reducing ventricular asynchrony.[17-23] Results from uncontrolled studies of permanent biventricular pac-

From InParys, Saint-Cloud, France (S.C.); the Centre Cardio-Pneumologique, Centre Hospitalier Universitaire, Rennes, France (C. Leclercq, J.-C.D.), Hôpital Broussais, Paris (T.L.); Harefield Hospital, Harefield, United Kingdom (S.W.); St. George's Hospital, London (C.V.); Karolinska Hospital, Stockholm, Sweden (C. Linde); Hôpital Cardiologique du Haut Levêque, Bordeaux, France (S.G.); Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (L.K.); Derriford Hospital, Plymouth, United Kingdom (G.A.H.); Ospedale San Filippo Neri, Rome (M.S.); and ELA Recherche, Le Plessis Robinson, France (C.B.). Address reprint requests to Dr. Daubert at the Département de Cardiologie et Maladies Vasculaires, Centre Cardio-Pneumologique, Hôpital Pontchaillou–Centre Hospitalier Universitaire, 35033 Rennes CEDEX, France, or at jean-claude.daubert@CHU-rennes.fr.

Other authors were Philippe Mabo, M.D. (Centre Cardio-Pneumologique); Arnaud Lazarus, M.D. (InParys); Philippe Ritter, M.D. (Hôpital Broussais); Terry Levy, M.D. (Harefield Hospital); and William McKenna, M.D. (St. George's Hospital).

*The members of the study group are listed in the Appendix.

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ing[24-26] show a sustained improvement in terms of symptoms, exercise tolerance, and well-being. In contrast, univentricular, right-sided pacing in patients with sinus rhythm has been found to benefit only a small subgroup of patients.[27-29] The aim of this single-blind, randomized, controlled crossover study was to assess the clinical efficacy and safety of transvenous atriobiventricular pacing in patients with severe heart failure and major intraventricular conduction delay but without standard indications for a pacemaker.[30]

METHODS

Selection of Patients

All patients gave their written informed consent before enrollment. All had severe heart failure due to idiopathic or ischemic left ventricular systolic dysfunction, an ejection fraction of less than 35 percent, and an end-diastolic diameter of more than 60 mm. All patients were in sinus rhythm with a QRS interval of more than 150 msec and without a standard indication for insertion of a pacemaker.[30] Before study entry, patients had been in New York Heart Association (NYHA) class III for at least one month while receiving the optimal treatment, including at least diuretics and ACE inhibitors at the maximal tolerated dose.

The criteria for exclusion were hypertrophic or restrictive cardiomyopathy, suspected acute myocarditis, correctable valvulopathy, an acute coronary syndrome lasting less than three months, recent coronary revascularization (during the previous three months) or scheduled revascularization, treatment-resistant hypertension, severe obstructive lung disease, an inability to walk, reduced life expectancy not associated with cardiovascular disease (less than one year), or an indication for the implantation of a cardioverter–defibrillator.[30]

Study Design

The trial involved 15 centers in Europe; the study protocol was approved by local ethics committees in the six participating countries. Enrollment began in March 1998 and was completed one year later. The study included a six-month randomized crossover phase, during which atriobiventricular (active) pacing was compared with ventricular inhibited (inactive) pacing at a basic rate of 40 bpm, each for a period of three months in random order (Fig. 1). Implantation was performed after a one-month observation period to verify the stability of heart failure (defined as no need to change treatment and no change in functional class). After implantation, the pacemaker was programmed to be inactive. Patients were randomly assigned to study groups within the following two weeks, after the proper performance of the pacing system had been ascertained. Randomization of the order of treatment followed a block design with stratification according to study center. The single-blind, crossover phase (active vs. inactive) then began, followed by a period during which the pacing system was programmed according to the preference of the patient (on the basis of the two periods during the crossover phase). Only the results from the crossover phase are reported here.

Implantation of Pacemakers

All leads were implanted transvenously. The atrial lead was placed high in the right atrium. The left ventricular lead was placed in a tributary of the coronary sinus, according to a previously described method.[31] Specially designed electrodes were used. A venogram helped to optimize the position of the lead. The target site was preferably the lateral wall, midway between base and apex, but other lateral or posterior sites were also acceptable. The great cardiac vein or the middle cardiac vein was used only when other sites were not accessible. The right ventricular lead was positioned as far as possible from the left ventricular lead. The pacemakers were triple-output devices that made use of standard dual-chamber technology, with built-in adapters to synchronize the pacing of the two ventricles (Chorum 7336 MSP, ELA Medical, Montrouge, France, and InSync 8040, Medtronic, Minneapolis). Results of the implantations were assessed from the positions of the leads on chest x-ray films and from changes in the width of the QRS interval on 12-lead surface electrocardiograms.

Programming of Pacemakers

At randomization, the pacemaker was programmed to be either inactive or active. The basic pacing rate was set at 40 bpm and the upper rate limit at 85 percent of the maximal predicted heart rate according to the age and sex of the patient. Each patient underwent Doppler echocardiography to determine the optimal atrioventricular delay (electrical delay between atrial and ventricular excitation) during atriobiventricular pacing.[32]

Medication

No modification in medication other than adjustment of the dose of diuretic was permitted between the time of enrollment and the end of the crossover phase of the study. Compliance was monitored by means of follow-up interviews and prescription checks.

Evaluation of Patients

At base line, the time of randomization, and the end of each of the two periods during the crossover phase, the patients were evaluated according to the distance walked in six minutes, the quality of life as assessed with use of the Minnesota Living with Heart Failure questionnaire,[33] the NYHA classification, the need for medication, the need for hospitalization, 12-lead surface electrocardiography, and cardiopulmonary exercise testing.

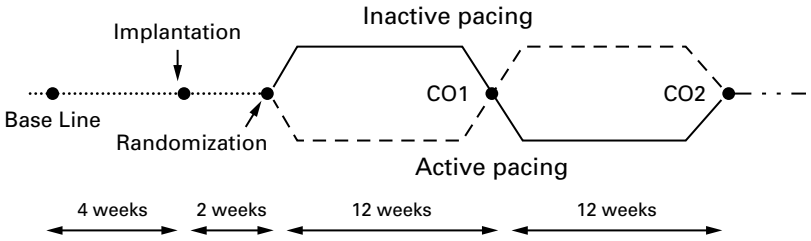

Figure 1. Design of the Study.

Patients were randomly assigned to three months each of inactive pacing (ventricular, inhibited at a basic rate of 40 bpm) and active pacing (atriobiventricular). CO1 denotes the end of crossover period 1, and CO2 the end of crossover period 2.

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The six-minute-walk test was carried out according to the recommendations of Guyatt and colleagues and Lipkin et al.[34,35] Base-line evaluation included a training test to confirm that the patient could complete the six-minute-walk test. Each visit included two tests with an interval of at least three hours between them. The maximal difference between the two tests was 15 percent, and the value recorded was the mean of the results of the two tests.

The Minnesota questionnaire[33,36] contains 21 questions regarding patients' perception of the effects of heart failure on their daily lives. Each question is rated on a scale of 0 to 5, producing a total score between 0 and 105. The higher the score, the worse the quality of life.

End Points

The primary end point was the distance walked in six minutes. The main secondary end point was the quality of life. Other secondary end points were peak oxygen uptake, hospital admissions because of decompensated heart failure, the patient's preference with regard to pacing (active vs. inactive) at the end of the crossover phase, and death.

Statistical Analysis

On the basis of previous reports of mortality rates in patients in NYHA class III, we estimated a 10 percent mortality rate at six months. Moreover, we expected a 10 percent rate of failure of the implantation of the left ventricular lead and a 20 percent rate of premature termination because of loss of left ventricular pacing efficacy or unstable heart failure. We estimated that there would be a 10 percent increase in the distance walked in six minutes with active pacing. For a study with a 95 percent confidence level and 95 percent power, the total target sample needed was estimated to be 22 patients. For the Minnesota quality-of-life score, a predicted 10 percent reduction with active pacing necessitated a 30-patient sample. However, considering the estimated mortality and dropout rates, we determined that a 40-patient sample was needed.

All analyses were based on the intention-to-treat principle. Thus, all enrolled patients were included in the analysis, but each efficacy end point could be assessed only in patients with no data missing after the completion of both crossover phases. Base-line characteristics were assessed with the use of the chi-square test for dichotomous variables and Student's t-test or Wilcoxon's nonparametric test for quantitative or categorical variables. The responses obtained for all criteria assessing clinical efficacy were compared with the use of the Wilcoxon test and according to a two-period and two-treatment (two-by-two) crossover design. Period and carryover effects were checked before the efficacy of treatment was evaluated. Morbidity and mortality were compared during the first crossover period and were described for all other phases of the study. The stability of the results was assessed by a per-protocol analysis, which included only patients without any deviations from the protocol. The threshold of significance was set at 0.05.

RESULTS

Study Population

Sixty-seven patients (50 men and 17 women) with a mean age of 63 years were included in the study. Heart failure was of ischemic origin in 25 patients. All patients were in NYHA class III at the time of enrollment, despite the use of optimal treatment, including ACE inhibitors or the equivalent in 96 percent of patients, diuretics in 94 percent, digoxin in 48 percent, amiodarone in 31 percent, beta-blockers in 28 percent, and spironolactone in 22 percent. The main base-line characteristics of the patients are listed in Table 1.

Implantation

Three patients withdrew from the study before implantation, two because of unstable heart failure (one

TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDY POPULATION AT BASE LINE AND AT THE TIME OF RANDOMIZATION.*

CHARACTERISTIC	AT BASE LINE	AT RANDOMIZATION			
	ALL PATIENTS (N=67)	ALL PATIENTS (N=58)	FIRST STUDY GROUP (N=29)	SECOND STUDY GROUP (N=29)	P VALUE†
Sex (M/F)	50/17	43/15	19/10	24/5	0.13
Age (yr)	63±10	64±9	64±11	64±8	0.91
Weight (kg)	78±17	78±18	79±19	78±16	0.97
Distance walked in six minutes (m)	320±97	350±109	354±110	346±111	0.82
Peak oxygen uptake (ml/kg of body weight/min)	13.7±3.9	13.8±4.4	13.5±8.4	14.1±4.6	0.41
Quality-of-life score‡	51±20	47±22	48±19	46±25	0.66
Heart rate (bpm)	75±13	75±13	75±12	75±14	0.89
QRS interval (msec)	176±19	174±20	172±22	175±19	0.48
PR interval (msec)	215±43				
Left bundle-branch block (% of patients)	87				
Left ventricular ejection fraction (%)	23±7				
Left ventricular end-diastolic diameter (mm)	73±10				

*Plus–minus values are means ±SD. In the first study group, the pacemaker was programmed to be active first and then inactive. In the second study group, the pacemaker was programmed to be inactive first and then active.

†P values are for the comparison between the two study groups at randomization.

‡A higher score indicates a poorer quality of life (range, 0 to 105).

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of whom subsequently died) and one because of a preexisting indication for pacing. Implantation of a left ventricular lead was attempted in 64 patients, with a 92 percent success rate. A lateral position was reached in 80 percent of the patients, and the mean (±SD) pacing threshold was 1.4±1.1 V. Early dislodgment occurred in eight patients and was successfully corrected in five. Overall, 88 percent of the patients had a functional left ventricular lead at the end of the crossover phase.

Study Dropouts and Randomization

Six additional patients were removed from the study before randomization, five because of failed implantation of the left ventricular lead and one because of sudden death while the device was inactive. Therefore, 58 patients were randomly assigned to and equally distributed between two study groups. There were no significant differences in the main clinical characteristics between the groups (Table 1).

At randomization, the width of the QRS complex had acutely decreased by a mean of 10 percent with active pacing (157±30 msec, as compared with 174±20 msec during spontaneous rhythm; $P<0.002$). The optimal atrioventricular delay was 108±43 msec.

Clinical Results

Results are shown in Table 2. During the active phase, the mean distance walked in six minutes was 23 percent longer ($P<0.001$) than during the inactive phase (Fig. 2). In the per-protocol analysis, which included 23 patients, the mean distance walked was 375±83 m during the inactive period, as compared with 424±83 m during the active period ($P<0.004$).

The Minnesota score decreased by a mean of 32 percent ($P<0.001$) with active pacing (Fig. 3). Peak oxygen uptake increased by a mean of 8 percent ($P<0.03$). No significant carryover and period effects were noted.

Because of the crossover design, hospitalizations were analyzed in the first period only. Three hospitalizations for heart failure occurred during active pacing, as compared with nine during inactive pacing ($P<0.05$).

Patients' Preferences

At the end of the crossover phase, the patients — who had no knowledge of the order of treatment — were asked which three-month period they had preferred. Forty-one (85 percent) preferred the period corresponding to the active-pacing mode ($P<0.001$), two (4 percent) preferred the period corresponding to the inactive-pacing mode, and five (10 percent) had no preference.

Safety

Ten patients did not complete the two crossover periods, including five who did not complete the first period. One withdrew his consent at the time of randomization. Two had uncorrectable loss of left ventricular pacing efficacy. During inactive pacing, one patient had severe decompensation leading to a premature switch to active pacing. One patient died suddenly after 26 days of active pacing.

During the second crossover period, five additional patients dropped out, including three for worsening heart failure. The only instance of decompensation with active pacing was attributed to rapidly progres-

TABLE 2. THE DISTANCE WALKED IN SIX MINUTES, THE PEAK OXYGEN UPTAKE, AND THE QUALITY-OF-LIFE SCORE (ASSESSED WITH THE MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE) AFTER THREE MONTHS OF INACTIVE OR ACTIVE PACING.*

STUDY GROUP	TOTAL NO. OF PATIENTS	ACTIVE PACING	INACTIVE PACING
First study group			
Distance walked in six minutes (m)	22	384.1±78.9	336.1±128.3
Peak oxygen uptake (ml/kg/min)	18	15.9±5.8	15.3±5.9
Quality-of-life score†	23	33.3±22	42.6±20.9
Second study group			
Distance walked in six minutes (m)	24	412.9±116.9	316.2±141.8
Peak oxygen uptake (ml/kg/min)	20	16.4±3.6	14.8±3.9
Quality-of-life score†	22	25.7±20.4	44±25
Both study groups			
Distance walked in six minutes (m)	46	399.2±100.5	325.7±134.4‡
Peak oxygen uptake (ml/kg/min)	38	16.2±4.7	15±4.9§
Quality-of-life score†	45	29.6±21.3	43.2±22.8‡

*Plus–minus values are means ±SD. In the first study group, the pacemaker was programmed to be active first and then inactive. In the second study group, the pacemaker was programmed to be inactive first and then active.

†A higher score indicates a poorer quality of life (range, 0 to 105).

‡$P<0.001$ for the comparison with active pacing.

§$P=0.029$ for the comparison with active pacing.

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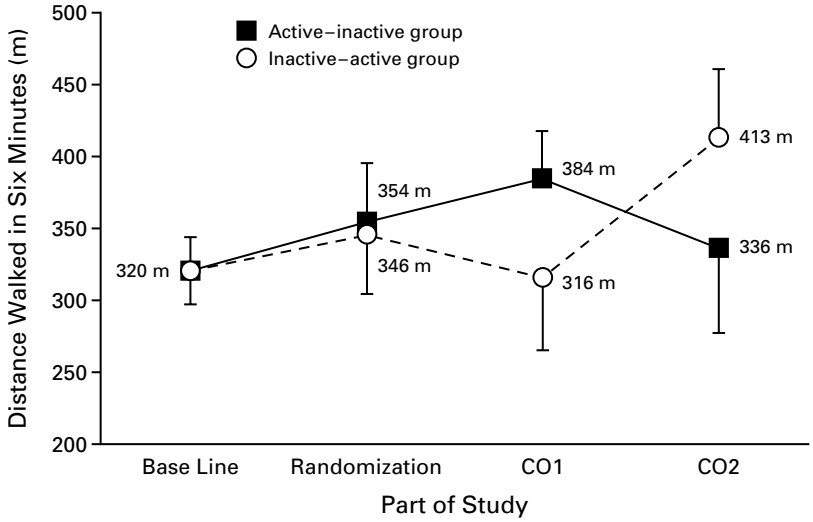

Figure 2. Distance Walked in Six Minutes at Specified Times during the Study.
The mean (±SD) values are given for each part of the study. CO1 denotes the end of crossover period 1, and CO2 the end of crossover period 2.

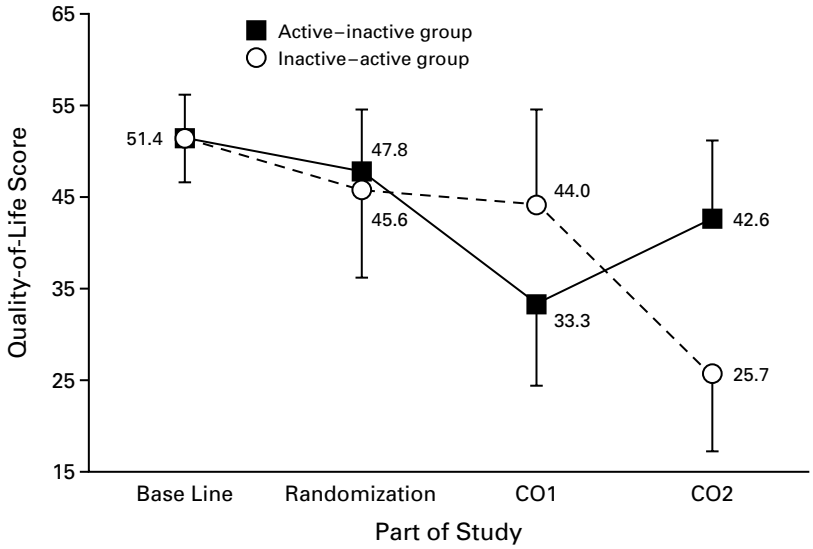

Figure 3. Quality-of-Life Score (Assessed with the Minnesota Living with Heart Failure Questionnaire) at Specified Times during the Study.
The mean (±SD) values are given for each phase of the study. CO1 denotes the end of crossover period 1, and CO2 the end of crossover period 2. A higher score indicates a poorer quality of life (range, 0 to 105).

sive aortic stenosis. One patient died from acute myocardial infarction a few hours after a premature switch to active pacing because of severe decompensation. Another patient had decompensation as persistent atrial fibrillation occurred during inactive pacing. One patient died suddenly two hours after switching from inactive to active pacing. Finally, one patient withdrew from the study because of lung cancer. The total number of deaths was three during the six-month crossover phase of the study.

DISCUSSION

This study shows that ventricular resynchronization significantly improves exercise tolerance and the quality of life in patients with severe heart failure who have sinus rhythm and major intraventricular conduction

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delay but who do not have a standard indication for the implantation of a pacemaker.

To be included, patients had to have been in NYHA class III for at least one month. The purpose of this criterion was to select patients whose condition was stable enough for them to withstand a 7.5-month study, including a 6-month crossover phase. Earlier, uncontrolled studies[24] showed that despite clinical improvement, mortality remained high in patients in class IV whose condition was unstable, as compared with the much lower mortality in patients who were in class III at the time of implantation.

Optimal medical therapy principally involved two classes of drugs: ACE inhibitors (or angiotensin II–receptor blockers) and diuretics, prescribed at the maximal tolerated doses in 98 percent of patients. Conversely, beta-blockers and spironolactone were prescribed to many fewer patients, since these two drugs were not recognized as effective treatments for severe heart failure when the study protocol was approved.[5,6] No changes in treatment were permitted between the time of inclusion and the end of the crossover phase. We were therefore able to conclude that any clinical changes noted during the crossover periods were induced by the pacing modes, by the natural history of the disease, or by both.

Ventricular asynchrony was assessed by electrocardiography and defined as a QRS interval of more than 150 msec during the intrinsic conduction. This empirical choice was later supported by studies of acute hemodynamic changes,[21-23] which showed that atriobiventricular or atrial–left ventricular pacing had beneficial effects, mostly in patients with an intrinsic QRS interval of more than 150 msec.

Cardiac-resynchronization therapy requires simultaneous stimulation of both ventricles, in synchrony with atrial activity. The main technical difficulty is to ensure reliable left ventricular pacing. Early attempts at permanent biventricular pacing[10,18,22] used an epicardial lead implanted in the left ventricle by thoracotomy or thoracoscopy, but the transvenous route quickly became the standard procedure.[31] After catheterization of the coronary sinus, the transvenous approach permits insertion of the lead into an epicardial vein over the left ventricular free wall; experience with the procedure and improvements in lead technology have dramatically increased the success rate of implantation. The optimal site of implantation, however, remains to be determined. Results from short-term studies[37] suggest that the lateral wall, midway between base and apex, is optimal. In our study, this target location was reached in 80 percent of the patients. Finally, the reliability of the transvenous route was confirmed, because 88 percent of the patients had a functional lead in the left ventricle at the end of the second crossover period.

This trial was designed primarily to assess the clinical efficacy of multisite biventricular pacing. To that end, a crossover design was chosen. This design, which makes every patient his or her own control, is probably ideal for the initial evaluation of such a therapeutic intervention, whereas parallel trials that require a large study population are better suited to the assessment of treatments that have shown promise in earlier crossover trials and to the evaluation of long-term morbidity and mortality. A potential downside of the crossover design is that the treatments administered during the first period may have a carryover effect in the second period. In this study, analysis revealed the absence of any significant carryover effect for the main selected end points. Another methodologic issue is the possible influence of study dropouts on results, but a per-protocol analysis found a significant difference in the primary end point in favor of active pacing.

Exercise tolerance (as indicated by the six-minute-walk test) was chosen as the primary end point. Peak oxygen uptake, measured during cardiopulmonary exercise testing, has been considered as a reference measurement in patients with heart failure,[38,39] which can be used to assess the maximal exercise tolerance. However, this variable only remotely reflects the functional impairment endured during activities of daily life. Furthermore, peak oxygen uptake can be interpreted only by a sophisticated technique whose reproducibility must be ascertained — a fact that may restrict its practical use in multicenter trials. Therefore, the distance walked in six minutes, which correlates with the peak oxygen uptake,[40,41] was chosen as the primary end point. The use of this test to assess the effect of therapy in previous studies[42] showed that the minimal variation required to confirm with 99 percent confidence that a real change has occurred is 10 percent. This threshold of 10 percent was used in our study to determine the sample size. In fact, we observed a mean global difference of 23 percent in favor of active pacing.

The Minnesota questionnaire introduced by Rector et al.[33] is commonly used for the assessment of patients with heart failure, and its clinical value has been established.[36] The quality-of-life score from this questionnaire was defined as the main secondary end point in this study. The mean global difference in this score observed between the two pacing modes was 32 percent. The magnitude of improvement for both the distance walked in six minutes and the quality-of-life score was greater than that previously seen in drug trials of the same duration and with similar patients.[36,43]

In contrast, the results with respect to mortality and morbidity should be interpreted with caution in this relatively small study, which had limited follow-up. The significantly lower number of hospitalizations with atriobiventricular pacing during the first crossover period is encouraging, but it involves only a short time. Mortality was 7.5 percent (5 of 67 patients) during the 7.5 months of the protocol, but randomized studies involving a large number of patients and

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extended follow-up will be necessary to reach conclusions regarding the morbidity and mortality associated with atriobiventricular pacing.

In conclusion, our results support the therapeutic value of ventricular resynchronization in patients who have severe heart failure and major intraventricular conduction delay. Atriobiventricular pacing significantly improved symptoms, exercise tolerance, and the quality of life and was associated with a reduced number of hospitalizations for decompensated heart failure. However, further studies are needed to assess the long-term clinical effect of this therapeutic approach.

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APPENDIX

The following persons participated in the study: Study Board: J.-C. Daubert (chair), C. Linde (cochair), C. Bailleul, S. Cazeau, L. Kappenberger, R. Sutton; Safety and Adverse Events Committee: C. Alonso, H.J. Dargie, P. Lechat; Independent Statistics Center: J.-S. Hulot, P. Lechat; Technical Advisers: D. Gras, P. Ritter, S. Walker; Core Analysis Center: C. Alonso, Rennes, France (electrocardiography and Holter monitoring), D. Gibson, London (echocardiography), C. Linde, Stockholm, Sweden (quality of life), and W. McKenna, London (cardiopulmonary exercise test); Monitoring and Data Management Team: C. Bailleul (study manager), K. Coombs, C. Fournier, M. Limousin (ELA Recherche), L. Mollo, S. Myrum (Medtronic), J.-M. Torralba, M.-C. Vandrell; Investigators — France: E. Aliot, S. Cazeau, J. Clémenty, J.-C. Daubert, C. De Chillou, J.-C. Deharo, P. Djiane, S. Garrigue, D. Gras, L. Guize, M. Jarwe, S. Kacet, D. Klug, T. Lavergne, A. Lazarus, C. Leclercq, A. Lemouroux, P. Mabo, J. Mugica, A. Otmani, J.-L. Rey, P. Ritter, N. Sadoul, and N. Savon; Germany: T. Lawo, B. Lemke, and S. von Dryander; Italy: G. Ansalone, R. Ricci, and M. Santini; Sweden: F. Braunschweig, F. Gadler, and C. Linde; Switzerland: X. Jeanrenaud, L. Kappenberger, and X. Lyon; United Kingdom: M. Fitzgerald, M.D. Gammage, G.A. Haywood, W.J. McKenna, T. Levi, A.J. Marshall, H. Marshall, F. Osman, V. Paul, E. Rowland, R. Sutton, C. Varma, and S. Walker.

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