

# A Randomized Comparison of Triple-Site Versus Dual-Site Ventricular Stimulation in Patients With Congestive Heart Failure

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- Objectives** We compared the effects of triple-site versus dual-site biventricular stimulation in candidates for cardiac resynchronization therapy.
- Background** Conventional biventricular stimulation with a single right ventricular (RV) and a single left ventricular (LV) lead is associated with persistence of cardiac dyssynchrony in up to 30% of patients.
- Methods** This multicenter, single-blind, crossover study enrolled 40 patients (mean age  $70 \pm 9$  years) with moderate-to-severe heart failure despite optimal drug treatment, a mean LV ejection fraction of  $26 \pm 11\%$ , and permanent atrial fibrillation requiring cardiac pacing for slow ventricular rate. A cardiac resynchronization therapy device connected to 1 RV and 2 LV leads, inserted in 2 separate coronary sinus tributaries, was successfully implanted in 34 patients. After 3 months of biventricular stimulation, the patients were randomly assigned to stimulation for 3 months with either 1 RV and 2 LV leads (3-V) or to conventional stimulation with 1 RV and 1 LV lead (2-V), then crossed over for 3 months to the alternate configuration. The primary study end point was quality of ventricular resynchronization (Z ratio). Secondary end points included reverse LV remodeling, quality of life, distance covered during 6-min hall walk, and procedure-related morbidity and mortality. Data from the 6- and 9-month visits were combined to compare end points associated with 2-V versus 3-V.
- Results** Data eligible for protocol-defined analyses were available in 26 patients. No significant difference in Z ratio, quality of life, and 6-min hall walk was observed between 2-V and 3-V. However, a significantly higher LV ejection fraction ( $27 \pm 11\%$  vs.  $35 \pm 11\%$ ;  $p = 0.001$ ) and smaller LV end-systolic volume ( $157 \pm 69 \text{ cm}^3$  vs.  $134 \pm 75 \text{ cm}^3$ ;  $p = 0.02$ ) and diameter ( $57 \pm 12 \text{ mm}$  vs.  $54 \pm 10 \text{ mm}$ ;  $p = 0.02$ ) were observed with 3-V than with 2-V. There was a single minor procedure-related complication.
- Conclusions** Cardiac resynchronization therapy with 1 RV and 2 LV leads was safe and associated with significantly more LV reverse remodeling than conventional biventricular stimulation. (J Am Coll Cardiol 2008;51:1455–62)  
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Cardiac resynchronization therapy (CRT) by simultaneous or sequential biventricular stimulation alleviates symptoms, improves cardiac function, and prolongs survival in a high percentage of patients who present with drug-refractory

chronic congestive heart failure (CHF), left ventricular (LV) systolic dysfunction, and a wide QRS complex (1–4). Previous studies have shown that CRT causes prominent reverse LV remodeling by decreasing the LV end-systolic and end-diastolic dimensions and by increasing left ventric-

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ular ejection fraction (LVEF) (4,5–10). The prognostic importance of reverse LV remodeling in CRT was prominently highlighted by Yu et al. (5), who found it to be a more reliable predictor of long-term survival than improve-

### Abbreviations and Acronyms

<b>AF</b> = atrial fibrillation
<b>AV</b> = atrioventricular
<b>CHF</b> = congestive heart failure
<b>CRT</b> = cardiac resynchronization therapy
<b>CS</b> = coronary sinus
<b>LV</b> = left ventricle/ventricular
<b>LVEF</b> = left ventricular ejection fraction
<b>LVESV</b> = left ventricular end-systolic volume
<b>NYHA</b> = New York Heart Association
<b>QOL</b> = quality of life
<b>RV</b> = right ventricle/ventricular
<b>2-V</b> = dual-site
<b>3-V</b> = triple-site
<b>6-MHW</b> = 6-min hall walk

ments in clinical status. However, significant LV reverse remodeling, defined as a >10% decrease in left ventricular end-systolic volume (LVESV), is achieved in only 60% of patients with conventional biventricular stimulation (5,6,9). This inconsistent effect of CRT might be due to incomplete resynchronization (6), as intraventricular and interventricular dyssynchrony can persist in 25% to 30% of patients during CRT (11). One might hypothesize that stimulating the LV at a single site is suboptimal and that stimulating multiple LV sites might improve ventricular resynchronization and, consequently, further promote reverse LV remodeling. A short-term hemodynamic study has suggested that stimulating 2 LV sites simultaneously increased dP/dt, pulse pressure, and LV end-

diastolic pressure significantly compared with pacing a single LV site (12).

The TRIP-HF (TRIPle Resynchronization in Paced Heart Failure Patients) trial was designed to examine whether biventricular stimulation with 1 right ventricular (RV) and 2 LV leads increases the response to CRT and produces a greater improvement in cardiac performance and LV remodeling than standard biventricular stimulation in patients with permanent atrial fibrillation (AF).

## Methods

**Study design.** This multicenter, single-blind, randomized crossover study was designed to compare the safety and efficacy of triple-site (3-V) versus dual-site (2-V) biventricular stimulation in patients who remained in New York Heart Association (NYHA) functional class III to IV despite optimal medical therapy and presenting with permanent AF, and who had a slow ventricular rate requiring permanent cardiac pacing. The study protocol was reviewed and approved by the institutional ethics committee of each participating center, and the trial was conducted in compliance with the Declaration of Helsinki.

After successful implantation, the device was programmed to pace in a conventional biventricular configuration for 3 months after implant, to allow for stabilization of the patient's clinical status. After this run-in period, patients were randomly assigned to either 3 months of 3-V followed by 3 months of 2-V stimulation (3-V → 2-V group), or 3 months of 2-V followed by 3 months of 3-V stimulation

(2-V → 3-V group). After a 9-month follow-up, the trial was completed, and the device programming was left to the investigator's choice.

**Study objective.** The primary objective was to compare the global quality of ventricular resynchronization by 2-V versus 3-V stimulation by calculating the Z ratio, an echocardiographic marker of abnormal ventricular activation (13). The main secondary end point was change in LVESV to assess the degree of LV reverse remodeling with 2-V versus 3-V stimulation. Other secondary objectives of the study included: 1) changes in quality of life (QOL), as assessed by the Minnesota Living With Heart Failure questionnaire, and exercise capacity, measured by the 6-min hall walk (6-MHW) test; and 2) procedure-related and overall morbidity and mortality.

**Patient selection and randomization.** All study participants granted their informed consent. They were eligible for enrollment if they fulfilled the following criteria: 1) NYHA CHF functional class III or IV despite optimal medical therapy administered for ≥1 month; 2) permanent AF with a slow ventricular rate requiring permanent cardiac pacing or planned to undergo atrioventricular (AV) node ablation; and 3) LVEF ≤35%. Exclusion criteria were: 1) indication for an implantable cardioverter defibrillator; 2) myocardial infarction, cardiac surgery, or a coronary revascularization procedure within the previous 3 months; 3) chronic pulmonary insufficiency or thyroid disease; 4) need for intravenous inotropic support for CHF; 5) <1-year life expectancy due to a disorder other than CHF; or 6) inability to comply with the follow-up procedures, <18 years of age, or pregnant.

Random assignment of the patients to one versus the other treatment sequence was performed and coordinated centrally.

**Implantation of the biventricular pacemaker system.** A Frontier 5510 CRT pacemaker triple-chamber pulse generator (St. Jude Medical, Sylmar, California) was connected to 1 RV and 2 LV leads. The techniques and instrumentation for implantation, including catheterization of the coronary sinus (CS) and its tributaries, were those routinely applied at each study center. A first LV lead was inserted, if possible, into a postero-lateral or lateral vein. The second LV lead was placed as far as possible from the first lead, in the anterior vein, a high antero-lateral vein, or the middle cardiac vein. The RV lead was implanted according to each center's usual practices. One LV and the RV lead were both connected to the ventricular ports, and the other LV lead was connected to the atrial port of the pulse generator. Thus, in VVI mode, pacing was via the RV and LV1 leads, in a standard biventricular (2-V) configuration, while in DDD mode, with a 25-ms (shortest programmable) AV delay, pacing was via the 3 leads, in a triple-site (3-V) configuration.

**Data collection.** The following information was collected, and measurements were made at the time of patient enrollment and every 3 months, during follow-up visits: 1) 12-lead surface electrocardiogram recorded at 50 mm/s paper

speed; 2) echocardiogram for measurements of: a) LVEF; b) percent fractional shortening; c) aortic velocity time integral; d) severity of mitral and tricuspid insufficiency, expressed as regurgitation flow area in the 2- and 4-chamber views; and e) LV end-diastolic and end-systolic diameters and volumes; 3) Minnesota Living with Heart Failure QOL questionnaire; and 4) 6-MHW test.

All echocardiographic measurements were performed by a core laboratory unaware of the treatment assignments (Appendix).

**Pharmacologic treatment.** Pharmacologic treatment was optimized before enrollment, and all efforts were made to keep it stable for the duration of the study.

**Z ratio calculation.** The overall quality of ventricular resynchronization was assessed by the Z ratio (13), measured from the duration of the ejection and filling times with respect to the overall cardiac cycle (Fig. 1):  $Z\ ratio = (LV\ ejection\ time + LV\ filling\ time)/RR\ interval$ .

When the study was designed, the Z ratio was considered an accurate and reproducible (intraobserver coefficient of variation: 3.9%) (14) measure of abnormal ventricular activation and had been used already to evaluate the benefit of CRT (10).

The main study hypothesis was a significant increase in the Z ratio by 3-V compared with 2-V pacing. During follow-up, the ejection and LV filling times used for the calculation of the Z ratio were measured during pacing at the programmed lower rate of 70 beats/min.

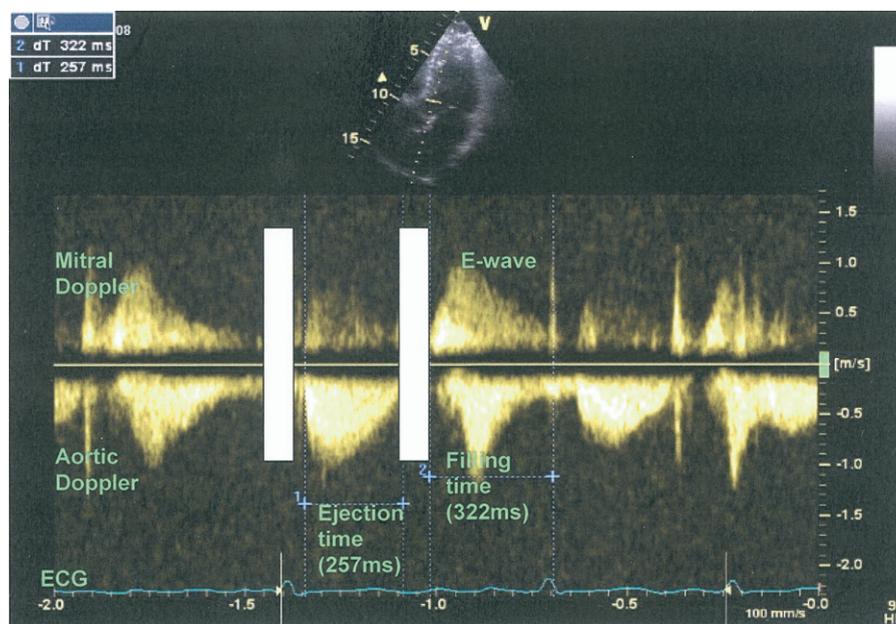
**Sample size calculation.** A total of 27 patients were needed to detect a 10% difference in Z ratio in favor of 3-V

versus 2-V. Assuming a 1-sided, 5% significance level, 90% power, and 20% attrition rate, randomization of 34 patients was calculated.

**Statistical analyses.** Data from the 6- and 9-month visits were combined to compare 2-V with 3-V by Student paired *t* test. The data were also examined for a possible carry-over effect using an unpaired *t* test. Normality of the data was verified using box-and-whisker and normal probability plots. The results were confirmed by nonparametric statistics, including Wilcoxon Mann-Whitney and Wilcoxon signed rank tests. A *p* value <0.05 was considered significant.

## Results

**Flow of the study and dropouts.** Between March 2003 and February 2005, 40 patients (38 men) were enrolled in the trial, by 7 medical centers in 4 European countries (Appendix). The implant of 2 LV leads was unsuccessful in 6 patients, representing an 85% success rate. A standard CRT system was successfully implanted in 4 of these 6 patients, representing a 95% success of at least 1 LV lead implantation. The second LV lead could not be implanted because of no other accessible vein in 2 patients, unstable lead position in 1, and unacceptable pacing threshold in 1 patient. In the 2 remaining patients, no LV lead was implanted, because of CS dissection in 1 and inability to cannulate the CS ostium in the other. One patient, who had undergone successful implantation of the CRT system, died of end-stage CHF before randomization. Therefore, 33



**Figure 1** Calculation of the Z Ratio From Doppler Echocardiography

ECG = electrocardiogram; Z ratio = (left ventricular ejection time + left ventricular filling time)/RR interval.

patients were randomized. During follow-up, 1 patient died of end-stage CHF; 2 patients withdrew their consent to participate; 1 patient developed a pulse generator pocket infection, which required explantation of the CRT system; 1 patient developed loss of capture at the LV1 lead; and, because of cardiac decompensation, the system was reprogrammed from triple- to double-site and from double- to triple-site stimulation in 1 patient each. Ultimately, data from 26 patients were entered in the per-protocol statistical analyses. The flow of patients through the study is illustrated in Figure 2.

**Study population.** The mean age of the 40 patients originally included in the study was  $70 \pm 9$  years and mean LVEF was  $26 \pm 11\%$ ; 27 patients suffered from ischemic heart disease and 35 patients were in NYHA functional class III. Additional baseline clinical characteristics of the study population are listed in Table 1. Atrioventricular node ablation was performed because of uncontrollable ventricular rate in 14 patients (concomitant to the implant procedure in 10 patients, before CRT implant in 4 patients), and 13 patients had a previously implanted single- or dual-chamber pacemaker. The baseline echocardiographic observations made in the overall patient population, in 34 patients who received CRT systems, and in 26 patients eligible for inclusion in the per-protocol analysis are shown in Table 2.

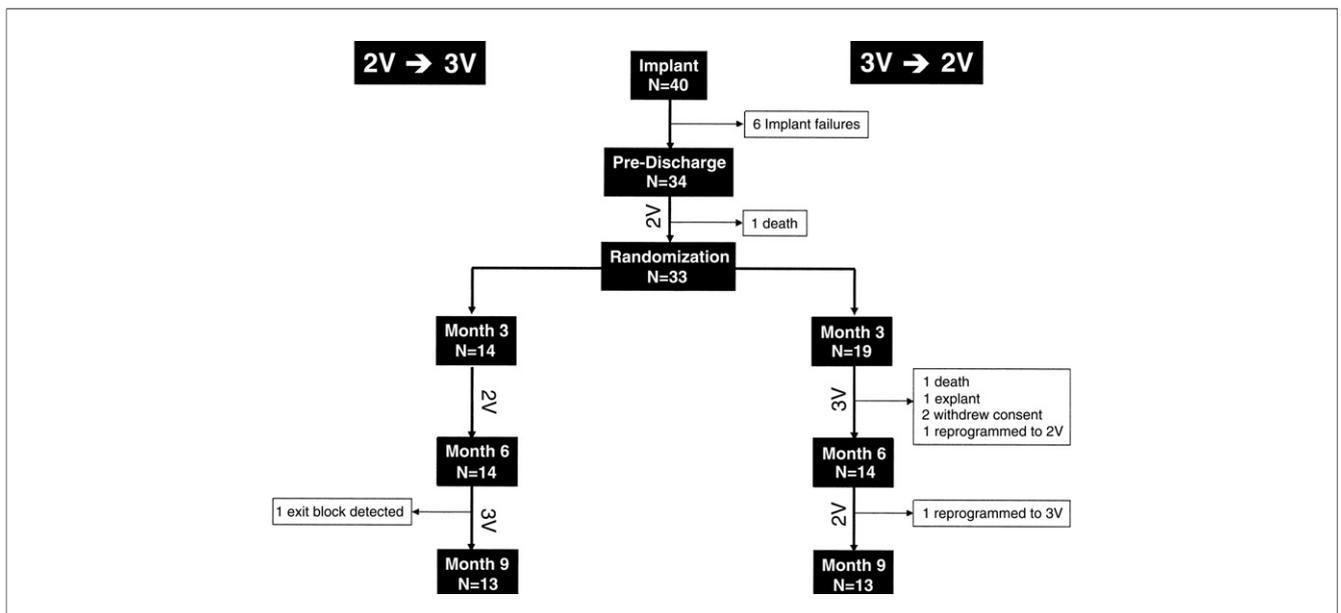
**Procedural observations.** In the 34 patients who underwent successful implantation procedures, the 2 LV leads were placed in a lateral or postero-lateral position in 33 cases, in an antero-lateral position in 14, in an anterior position in 15, in the middle cardiac vein in 4, and in an infero-lateral position in 2 cases. The RV lead was placed in

a septal position in 23 patients (68%), at the apex in 8 patients (24%), and at other locations in 3 patients (8%). A representative example of the position of the 3 leads is shown in Figure 3. The mean duration of the implant procedure and fluoroscopic exposure was  $2.03 \pm 0.97$  h and  $26.3 \pm 24.6$  min, respectively.

**Follow-up observations.** After 3 months of standard biventricular stimulation, the distance covered during the 6-MHW test increased by a mean of 44 m ( $p = 0.0019$ ), QOL score decreased by 15 points ( $p < 0.0001$ ), LVEF increased by 7% ( $p = 0.026$ ), and LVESV decreased by a mean of 20 ml ( $p = 0.048$ ). No significant change was observed in the Z ratio.

**3-V VERSUS 2-V STIMULATION.** No statistically significant difference in Z ratio was observed between 2-V ( $0.78 \pm 0.09$ ) and 3-V stimulation ( $0.76 \pm 0.12$ ) ( $p = 0.9423$ ) (Fig. 4). In contrast, other 2-V versus 3-V comparisons revealed a statistically significant increase in LVEF, from  $27 \pm 11\%$  to  $35 \pm 13\%$  ( $p = 0.0010$ ) (Fig. 5), a decrease in LVESV from  $157.4 \pm 69.0$  cm<sup>3</sup> to  $134.4 \pm 75.2$  cm<sup>3</sup> ( $p = 0.0191$ ) (Fig. 6), and a decrease in LV end-systolic diameter from  $57.0 \pm 11.9$  mm to  $53.9 \pm 10.2$  mm ( $p = 0.0242$ ), all favoring 3-V stimulation (Table 3). The proportion of patients in whom LVESV decreased  $\geq 10\%$  from baseline increased from 67% with 2-V stimulation to 78% with 3-V stimulation ( $p = 0.1573$ ).

In patients in whom LVESV decreased  $\geq 10\%$ , 3-V pacing further decreased nonsignificantly LVESV from  $163 \pm 88$  ml to  $138 \pm 75$  ml. In patients in whom LVESV did not decrease initially, 4 became responders under 3-V pacing and led to a nonsignificant decrease in LVESV from  $147 \pm 57$  ml to  $125 \pm 86$  ml.



**Figure 2** Enrollment, Randomization, and Outcomes of Enrolled Patients, Up to 9 Months of Follow-Up, in Each Study Group

2V = dual-site; 3V = triple-site.

**Table 1** Baseline Characteristics of the Overall Patient Population and of Each Study Group

	Baseline (n = 40)	Implanted (n = 34)	Analyzed (n = 26)
Age, yrs	70 ± 9	71 ± 9	70 ± 8
Men/women (% of patients)	95/5	100/0	100/0
Ischemic/nonischemic heart disease (% of patients)	33/67	29/71	27/73
NYHA functional class III/IV (% of patients)	88/12	88/12	92/8
ACE inhibitor/ARB therapy (% of patients)	90	91	96
Beta-adrenergic blocker therapy (% of patients)	73	73	73
Prior atrioventricular node ablation (number of patients)	14	14	10
Previously implanted system (number of patients)	13	10	6
6-min hall walk test, m	322 ± 125	337 ± 118	352 ± 113
Quality of life score	44 ± 19	42 ± 19	40 ± 20
QRS duration, ms	163 ± 43	162 ± 43	159 ± 47
<b>Left ventricular</b>			
End-diastolic diameter, mm	65 ± 8	66 ± 8	66 ± 7
End-systolic volume, mm <sup>3</sup>	147 ± 75	154 ± 76	154 ± 68
End-diastolic volume, mm <sup>3</sup>	192 ± 85	197 ± 81	197 ± 68
Ejection fraction, %	26 ± 11	24 ± 11	24 ± 11

Unless specified otherwise, values are means ± standard deviation.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NYHA = New York Heart Association.

The distance covered during the 6-MHW test was 430.6 ± 101.5 m in 2-V and 401.6 ± 91.3 m in 3-V (p = 0.0578), and the QOL score was 21.6 ± 18.3 in 2-V compared with 22.1 ± 18.9 in 3-V (p = 0.7541).

The mean QRS width increased from 154.7 ± 24.8 ms in 2-V to 171.4 ± 20.1 ms in 3-V (p = 0.0112).

**Adverse events.** The only procedure-related adverse event was an uncomplicated dissection of the CS. During follow-up, 2 patients (5%) died from end-stage CHF. Other adverse events that occurred during long-term follow-up in the overall patient population are listed in Table 4. These adverse events either prolonged or prompted a hospitalization in 17 instances. One patient hospitalized for cardiac decompensation was prematurely reprogrammed from 2-V to 3-V, and another patient complaining from dyspnea at rest was prematurely reprogrammed from 3-V to 2-V.

## Discussion

This was the first prospective, randomized study to demonstrate that the degree of LV reverse remodeling was significantly greater when long-term CRT was delivered by means of 1 RV and 2 LV leads than when delivered by means of 1 RV and a single LV lead in patients presenting with advanced CHF, permanent AF, and indications for permanent pacing.

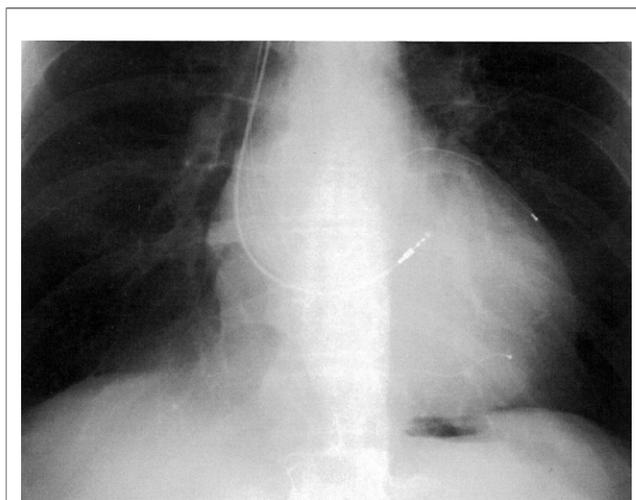
Published studies of the effects of CRT in patients suffering from AF are few (15–19). The MUSTIC (Multi-site Stimulation in Cardiomyopathies) AF study, which compared the effects of single-site RV versus biventricular stimulation in patients with advanced CHF, depressed LV function, and a wide RV-paced QRS complex showed a

**Table 2** Baseline Echocardiographic Observations Made in Baseline, Implant, and Analyzed Patients

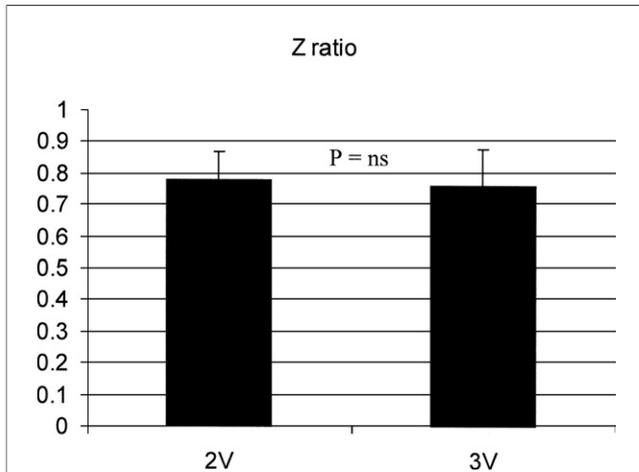
	Baseline (n = 40)	Implant (n = 34)	Analyzed (n = 26)
<b>Left ventricular</b>			
End-systolic volume, ml	147 ± 75	154 ± 76	154 ± 68
End-diastolic volume, ml	192 ± 85	197 ± 80	197 ± 68
Ejection fraction, %	26 ± 11	24 ± 11	24 ± 11
End-diastolic diameter, mm	65 ± 8	66 ± 8	66 ± 7
End-systolic diameter, mm	56 ± 8	57 ± 8	57 ± 8
Ejection time, ms	239 ± 38	237 ± 39	238 ± 36
Filling time, ms	355 ± 116	348 ± 122	344 ± 133
Aortic velocity time integral, cm/s	16.7 ± 9.6	16.7 ± 10.1	16.1 ± 8.3
Z ratio	0.74 ± 0.11	0.74 ± 0.12	0.75 ± 0.12

Values are means ± standard deviation.

Analyzed = patients entered into the per-protocol analysis; Baseline = the overall patient population; Implant = patients who underwent successful cardiac resynchronization therapy system implantations.



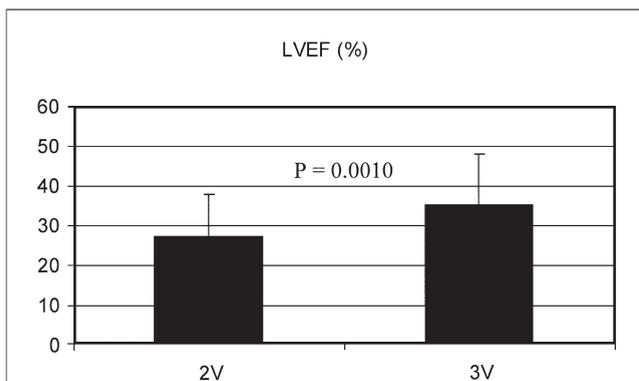
**Figure 3** Representative Frontal Roentgenographic View of the Leads of a Triple-Site, Biventricular Stimulation System



**Figure 4** Evolution of Mean Z Ratio Between Patient Enrollment and End of Follow-Up in Each Study Group

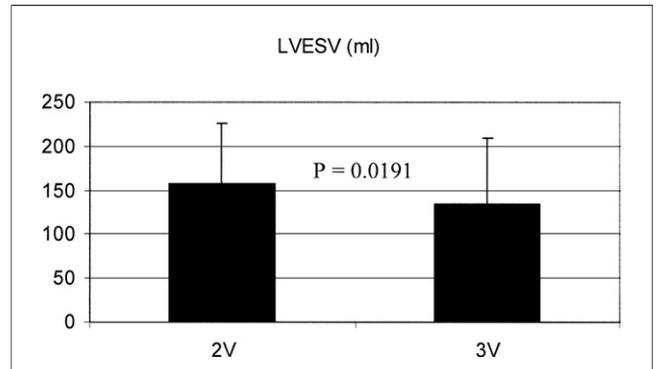
In both groups, after the stabilization phase, the Z ratio increased during the period of triple-site biventricular stimulation, and decreased during dual-site stimulation. Abbreviations as in Figure 2.

significant increase in exercise capacity with biventricular stimulation (15). The PAVE (Biventricular Pacing After Ablate Compared With Right Ventricular Therapy) trial, which included candidates for AV node ablation, regardless of LVEF and QRS duration, and excluded patients in NYHA functional class IV, observed an increase in the distance covered during a 6-MHW and in LVEF by biventricular stimulation, particularly in patients with an LVEF <45% and poorly tolerated AF (16). The OPSITE (Optimal Pacing SITE) trial compared the effects of RV, LV, and biventricular pacing in a heterogeneous population of patients presenting with permanent AF and indication for AV node ablation for severely symptomatic, uncontrolled ventricular rate and depressed LV function or left bundle branch block, or both (17). Compared with RV



**Figure 5** Evolution of Mean LVEF Between Patient Enrollment and End of Follow-Up in Each Study Group

In both groups, after the stabilization phase, left ventricular ejection fraction (LVEF) increased during the period of triple-site biventricular stimulation and decreased during dual-site stimulation. Abbreviations as in Figure 2.



**Figure 6** Evolution of Mean LVESV Between Patient Enrollment and End of Follow-Up in Each Study Group

LVESV = left ventricular end-systolic volume; other abbreviations as in Figure 2.

pacing, biventricular pacing significantly improved QOL, decreased NYHA functional class, and increased LVEF. Gasparini et al. (18) observed that the benefits conferred by CRT in candidates for CRT presenting with AF were limited to patients who had previously undergone ablation of the AV node. In 74 patients with permanent AF and a slow ventricular rate, Kiès et al. (19) found that CRT caused a significant decrease in LV end-systolic, LV end-diastolic, and left atrial diameter, and a significant increase in LVEF. The significant improvement in QOL, increase in distance covered during the 6-MHW test and in LVEF, and decrease in LVESV observed after 3 months of standard biventricular stimulation in our study are consistent with the results of these previous studies.

The effects of long-term CRT delivered by means of 2 LV and 1 RV lead have not been studied systematically. Sassari et al. (20) described a patient presenting with permanent AF and a VVI pacemaker implanted for slow ventricular rate who underwent CRT with 2 leads implanted on the postero-basal and antero-lateral epicardial LV surface, respectively, and an RV lead implanted transvenously. At 3 months of follow-up, a clinical improvement as well as a significant reduction in LV volumes was observed with 3-V pacing. It is noteworthy that the

**Table 3** Combined Echocardiographic Measurements Made at 6 and 9 Months After 3 Months of 2-V Versus 3 Months of 3-V Biventricular Stimulation

Variable	2-V	3-V	p Value
Left ventricular			
End-diastolic volume, cm <sup>3</sup>	213.2 ± 83.6	198.5 ± 95.7	0.2639
End-systolic volume, cm <sup>3</sup>	157.4 ± 69.0	134.4 ± 75.2	0.0191
Ejection fraction, %	27 ± 11	35 ± 13	0.0010
End-diastolic diameter, mm	66.4 ± 8.2	65.1 ± 8.5	0.1773
End-systolic diameter, mm	57.0 ± 11.9	53.9 ± 10.2	0.0242
Aortic velocity time integral, cm	16.0 ± 7.3	15.1 ± 6.0	0.9527
Fractional shortening, %	16 ± 11	18 ± 9	0.0196

2-V = dual-site; 3-V = triple-site.

**Table 4** Adverse Clinical Events in 40 Patients Who Underwent Implantation of CRT Systems

Event	Number (%) of Patients
<b>Procedure-related</b>	
Coronary sinus perforation	1 (2.5)
<b>Long-term</b>	
Severe dyspnea	10 (25)
Diaphragmatic stimulation*	5 (12.5)
Prominent edema	3 (7.5)
Death from end-stage heart failure	2 (5)
Explantation of infected system†	2 (5)
Device hardware reset	1 (2.5)

≥1 adverse event may have occurred in the same patient. \*A dislodged lead was repositioned in 4 of these patients; †the system was reimplemented in 1 patient who completed the study.  
 CRT = cardiac resynchronization therapy.

shortening of the inter- and intraventricular delays was greater with 3-V than with 2-V or “conventional” biven- tricular pacing.

The immediate hemodynamic effects of stimulating a single versus 2 LV sites in 14 patients with low LVEF and wide QRS, in NYHA functional class III or IV and in sinus rhythm, have been reported by Pappone et al. (12). Dual LV stimulation caused significantly greater increases in peak dP/dt and pulse pressure than posterior base or lateral wall pacing.

The TRIP-HF trial showed that, compared with dual-site biven- tricular stimulation, triple-site biven- tricular stimulation further promoted LV reverse remodeling, and further decreased LVESV and increases LVEF. A post hoc analysis of response to CRT, defined by a ≥10% decrease in LVESV, showed that: 1) in responders to 2-V stimulation, 3-V stimulation further improved the magnitude of remodeling; and 2) among the 10 patients who did not respond to 3 months of 2-V, 4 patients became responders to 3-V. The independent prognostic importance of LV remodeling has been confirmed by several studies (21–24). Morbidity and mortality increased, irrespective of CHF etiology, in proportion to LV enlargement and deterioration of contractile performance. In a substudy of the Val-HeFT (Valsartan Heart Failure Trial) study, LV end-diastolic diameter and LVEF measured echocardiographically were powerful predictors of morbidity and mortality, irrespective of treatment (23). Similar observations were made recently by Yu et al. (5) in a nonrandomized study of 141 recipients of CRT systems. A 10% decrease in LVESV after CRT system implantation was strongly predictive of a lower long-term mortality and CHF-related events. This recent report emphasized the increasing relevance of the remodeling process as a biomarker in CHF studies, and slowing or reversing remodeling has become a goal of CHF treatment (25). While therapeutic objectives used to be mostly concentrated on the relief of symptoms, attention is now focused on the slowing or halting of disease progression. Furthermore, the slowing or reversal of cardiac remodeling appears closely

related to the relief of symptoms and improvement in prognosis.

The absence of difference in Z ratio between the 2 pacing modes might have at least 2 explanations. First, since the patients were not selected on the basis of the QRS duration, 30% had a QRS duration <150 ms. Therefore, the baseline Z ratio was  $0.75 \pm 12$ , considerably higher than that observed in the MUSTIC SR trial, where all patients had a QRS duration >150 ms (10). Second, since 3-V stimulation was delivered with 1 LV lead connected to the atrial port and 2 leads to the ventricular ports, with a minimal AV delay of 25 ms in DDDR mode, the QRS during 3-V pacing was longer by a mean value of 25 ms than during “conventional” biven- tricular stimulation.

The absence of further improvement in QOL and increase in distance covered during the 6-MHW test by 3-V stimulation compared with conventional CRT was perhaps due to the prior therapeutic effects conferred by the 3-month run-in period of biven- tricular stimulation.

**Technical considerations.** When this study began, in 2003, all of the new instrumentation designed to facilitate the access to the coronary veins and increase the implanta- tion success rate was not available. Despite this constraint, an acceptable 85% success rate of implantation of 2 LV leads was reached, ≥1 lead was implanted in 95% of patients, and failure to implant any LV lead was limited to 2 patients. These procedural results are similar to those achieved in the main randomized studies of CRT. The overall duration of the implant procedures and fluoroscopic exposure was longer than for standard CRT system implantations and would probably be shorter with the new delivery tools that are currently available. The absence of major procedure- related adverse cardiac events and the relatively low rate of long-term device-related complications, despite the complex- ity of the technique, are noteworthy.

**Study limitations.** This study was conducted in patients presenting with permanent AF in order to examine the sole effect of changing the ventricular activation sequence by chang- ing the ventricular pacing site(s), while avoiding any interfer- ence with atrial function and AV synchrony. Another goal was to obviate the need for Y connectors, which are notorious for increasing the rate of long-term complications. As mentioned previously, a 25-ms delay between 1 LV and the other 2 ventricular leads might have lowered the quality of ventricular resynchronization. The absence of precise assessment of ven- tricular dyssynchrony with techniques that were not widely available when this study was conducted, such as tissue Dopp- ler imaging, is another limitation. Finally, these results, col- lected in a small number of patients during a short follow-up period (3 months), should be confirmed in a larger population over a longer period.

## Conclusions

Triple-site biven- tricular stimulation, with simultaneous stim- ulation of 2 distant LV sites, conferred greater benefits on

LVEF and LVESV than standard 2-V biventricular stimulation. At 3 months of follow-up, 3-V biventricular and conventional biventricular stimulation had similar effects on QOL and 6-MHW. Triple-site biventricular stimulation was achievable with an acceptable rate of complications.

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#### REFERENCES

1. Cazeau S, Leclercq C, Lavergne T, et al. 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.
2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–53.
3. Bristow MR, Saxon LA, Boehmer J, et al. Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140–50.
4. Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization therapy on morbidity and mortality in heart failure (the CARDiac REsynchronization-Heart Failure [CARE-HF] trial). *N Engl J Med* 2005;352:1539–49.
5. Yu CM, Bleeker GB, Fung JW, et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;112:1580–6.
6. Bleeker GB, Bax JJ, Fung JW, et al. Clinical versus echocardiographic parameters to assess response to cardiac resynchronization therapy. *Am J Cardiol* 2006;97:260–3.
7. Donal E, Leclercq C, Linde C, Daubert JC. Effects of cardiac resynchronization therapy on disease progression in chronic heart failure. *Eur Heart J* 2006;27:1018–25.
8. St John Sutton MG, Plappert T, Abraham WT, et al. Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003;107:1985–90.
9. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Circulation* 2006;113:266–72.
10. Duncan A, Wait D, Gibson D, Daubert JC. MUSTIC (Multisite Stimulation in Cardiomyopathies) Trial. Left ventricular remodelling and haemodynamic effects of multisite biventricular pacing in patients with left ventricular systolic dysfunction and activation disturbances in sinus rhythm: sub-study of the MUSTIC (Multisite Stimulation in Cardiomyopathies) trial. *Eur Heart J* 2003;24:384–90.
11. Schuster I, Habib G, Jegu C, et al. Diastolic asynchrony is more frequent than systolic asynchrony in dilated cardiomyopathy and is less improved by cardiac resynchronization therapy. *J Am Coll Cardiol* 2005;46:2250–7.
12. Pappone C, Rosanio S, Oreto G, et al. Cardiac pacing in heart failure patients with left bundle branch block: impact of pacing site for optimizing left ventricular resynchronization. *Ital Heart J* 2000;1:464–9.
13. Zhou Q, Henein M, Coats A, Gibson D. Different effects of abnormal activation and myocardial disease on left ventricular ejection and filling times. *Heart* 2000;84:272–6.
14. Duncan A, O'Sullivan C, Gibson D, Henein M. Electromechanical interrelations during dobutamine stress in normal subjects and patients with coronary artery disease: comparison of changes in activation and inotropic state. *Heart* 2001;85:411–6.
15. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;23:1780–7.
16. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005;16:1160–5.
17. Brignole M, Gammage M, Puggioni E, et al. Optimal Pacing SITE (OPSITE) Study Investigators. Comparative assessment of right, left, and biventricular pacing in patients with permanent atrial fibrillation. *Eur Heart J* 2005;26:712–22.
18. Gasparini M, Auricchio A, Regoli F, et al. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. *J Am Coll Cardiol* 2006;48:734–43.
19. Kiès P, Leclercq C, Bleeker GB, et al. Cardiac resynchronization therapy in chronic atrial fibrillation: impact on left atrial size and reversal to sinus rhythm. *Heart* 2006;92:490–4.
20. Sassara M, Achilli A, Bianchi S, et al. Long-term effectiveness of dual site left ventricular cardiac resynchronization therapy in a patient with congestive heart failure. *Pacing Clin Electrophysiol* 2004;27:805–7.
21. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;76:44–51.
22. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. *N Engl J Med* 1997;336:1350–5.
23. Lee TH, Hamilton MA, Stevenson LW, et al. Impact of left ventricular cavity size on survival in advanced heart failure. *Am J Cardiol* 1993;72:672–6.
24. Wong SP, French JK, Lydon AM, et al. Relation of left ventricular sphericity to 10-year survival after acute myocardial infarction. *Am J Cardiol* 2004;94:1270–5.
25. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol* 2000;35:569–82.

#### APPENDIX

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