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FOCUS ISSUE: CARDIAC RESYNCHRONIZATION THERAPY

Cardiac Resynchronization With Sequential Biventricular Pacing for the Treatment of Moderate-to-Severe Heart Failure

Angel R. León, MD,* William T. Abraham, MD,†‡ Susan Brozena, MD,¶ James P. Daubert, MD,§ Westby G. Fisher, MD,†‖ John C. Gurley, MD,† Chang Seng Liang, MD,§ George Wong, MD,# for the InSync III Clinical Study Investigators

Atlanta, Georgia; Lexington, Kentucky; Columbus, Ohio; Rochester, New York; Evanston, Illinois; Philadelphia, Pennsylvania; and Peoria, Arizona

OBJECTIVES The InSync III study evaluated sequential cardiac resynchronization therapy (CRT) in patients with moderate-to-severe heart failure and prolonged QRS.

BACKGROUND Simultaneous CRT improves hemodynamic and clinical performance in patients with moderate-to-severe heart failure (HF) and a wide QRS. Recent evidence suggests that sequentially stimulating the ventricles might provide additional benefit.

METHODS This multicenter, prospective, nonrandomized, six-month trial enrolled a total of 422 patients to determine the effectiveness of sequential CRT in patients with New York Heart Association (NYHA) functional class III or IV HF and a prolonged QRS. The study evaluated: whether patients receiving sequential CRT for six months experienced improvement in 6-min hall walk (6MHW) distance, NYHA functional class, and quality of life (QoL) over control group patients from the reported Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial; whether sequential CRT increased stroke volume compared to simultaneous CRT; and whether an increase in stroke volume translated into greater clinical improvements compared to patients receiving simultaneous CRT.

RESULTS InSync III patients experienced greater improvement in 6MHW, NYHA functional class, and QoL at six months compared to control (all $p < 0.0001$). Optimization of the sequential pacing increased (median 7.3%) stroke volume in 77% of patients. No additional improvement in NYHA functional class or QoL was seen compared to the simultaneous CRT group; however, InSync III patients demonstrated greater exercise capacity.

CONCLUSIONS Sequential CRT provided most patients with a modest increase in stroke volume above that achieved during simultaneous CRT. Patients receiving sequential CRT had improved exercise capacity, but no change in functional status or QoL. (J Am Coll Cardiol 2005;46: 2298–304) © 2005 by the American College of Cardiology Foundation

Interventricular (V-V) conduction delay commonly occurs in patients with chronic systolic heart failure (HF) and produces dyssynchronous ventricular contraction that further impairs cardiac function (1–4). Recent studies demonstrated that cardiac resynchronization therapy (CRT) utilizing simultaneous biventricular (Bi-V) pacing improves the hemodynamic and clinical performance of patients with moderate-to-severe HF and a V-V conduction delay by correcting dyssynchronous ventricular contraction (5–13).

The degree and mechanical manifestations of ventricular dyssynchrony vary widely among patients with HF and a V-V conduction delay (14). Sequential Bi-V stimulation uses a programmable V-V pacing interval, which can be individually tailored to potentially maximize electromechanical resynchronization. Small, short-term studies demonstrated further improvement in systolic and diastolic function during sequential Bi-V CRT (12,14–16). The present study more thoroughly evaluates the clinical and hemodynamic effects of sequential Bi-V pacing using the InSync III CRT device (17).

METHODS

The InSync III clinical study used a multicenter, prospective, nonrandomized design to evaluate the clinical effectiveness of sequential Bi-V CRT. The study compared its effectiveness to the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) control group that received optimal pharmacological therapy alone. Additional post-hoc analysis compared the effectiveness of sequential CRT to simultaneous CRT provided to the MIRACLE treatment group (5). The MIRACLE study utilized many of the same investigational centers and had the same inclusion and exclusion criteria, implant procedure, therapy delivery scheme,

From the *Carlyle Fraser Heart Center/Division of Cardiology, Emory University, Atlanta, Georgia; †University of Kentucky, Lexington, Kentucky; ‡The Ohio State University Heart Center, Columbus, Ohio; §University of Rochester Medical Center, Rochester, New York; ‖Northwestern University, Evanston, Illinois; ¶University of Pennsylvania, Philadelphia, Pennsylvania; and #Cardiac Solutions, Peoria, Arizona. This study was supported by Medtronic Inc., Minneapolis, Minnesota. Drs. Leon, Abraham, Brozena, Daubert, Fisher, and Gurley have been speakers for Medtronic Inc. Drs. Leon, Abraham, Daubert, and Fisher are consultants to Medtronic Inc.

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Abbreviations and Acronyms

Bi-V	= biventricular
CRT	= cardiac resynchronization therapy
HF	= heart failure
LV	= left ventricle/ventricular
MIRACLE	= Multicenter InSync Randomized Clinical Evaluation trial
NYHA	= New York Heart Association
PHD	= prehospital discharge
QoL	= quality of life
RV	= right ventricle/ventricular
V-V	= interventricular
6MHW	= 6-min hall walk

and primary end point analysis as the present trial (5). Both studies enrolled patients with New York Heart Association (NYHA) functional class III or IV HF, a left ventricular (LV) ejection fraction ≤35%, a QRS duration ≥130 ms, and an LV end-diastolic diameter of ≥55 mm. Before either study entry, all candidates must have received optimal and stable pharmacological therapy, including an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker and a beta-blocker in most patients. The protocol discouraged initiation of beta-blockade during the six-month evaluation period. Patients were excluded from the study if they had any of the following: an indication for implantable cardioverter-defibrillator or pacemaker, the presence of a previously implanted pacing system or an indication/contraindication to a standard pacing system, persistent atrial arrhythmias, a baseline 6-min hall walk (6MHW) distance ≥450 m, unstable angina, acute myocardial infarction, coronary artery revascularization within three months before enrollment, changes in beta-blocker doses within three months before enrollment, intermittent inotropic drug therapy (more than two outpatient dose infusions per week), severe primary pulmonary disease, or primary valvular disease.

The investigational review board at each participating institution reviewed and approved the study protocol and patient consent form; all enrolled patients provided written, informed consent.

Device description. The InSync III Model 8042 pulse generator (Medtronic Inc. Minneapolis, Minnesota) provides atrial-synchronous, sequential Bi-V stimulation for CRT. The device can stimulate either ventricle first, with a programmable interval between the first and second ventricular pacing output ranging between 4 and 80 ms. The nominal, or simultaneous, V-V setting uses a 4-ms LV-right ventricle (RV) sequence. The device senses intrinsic ventricular activity through the RV lead, LV lead, or a combination of both (RV cathode to LV cathode). Incorporation of a V-V refractory period prevents double-counting of a single ventricular depolarization sensed in both ventricles.

Study protocol. Patients who met the entry criteria and provided signed consent underwent the following baseline assessment: determination of NYHA functional class, 12-lead electrocardiogram, 6MHW test, and quality of life (QoL) survey using the Minnesota Living with Heart Failure Questionnaire. Echocardiographic determination of the LV ejection fraction and LV end-diastolic diameter had to be performed within 12 months before the baseline evaluation.

All patients underwent an implant attempt utilizing standard right atrial and RV pacing leads and one of three LV transvenous leads (Models 2187, 2188, or 4193, Medtronic, Inc.) positioned within a cardiac vein. Patients with a successful implant received active CRT for the six-month duration of the trial. The designated pacing mode, VDD, provided atrial-synchronous Bi-V pacing at either nominal or sequential Bi-V settings without the confounding effect of sensor-driven atrial pacing on cardiac performance.

All patients with a successful implant underwent full interrogation of the device, reassessment of QoL, follow-up 6MHW test, estimation of NYHA functional class, and monitoring of the background drug regimen before hospital discharge (PHD) and at one, three, and six months after implant. At PHD, three and six-month echocardiographic evaluation included optimization of the atrioventricular and V-V stimulation intervals. Echocardiography-Doppler interrogation first determined the optimal atrioventricular interval that maximizes transmitral filling using the Ritter method (18). We kept the right-atrium-to-LV interval constant at the optimal setting while varying the LV-RV interval in random sequence −80 (RV first) to +80 ms (LV first) to identify the V-V offset producing the greatest LV stroke volume. Echocardiography-Doppler examination of LV outflow determined stroke volume at each V-V setting as the product of the measured aortic velocity time integral and the LV outflow tract cross-sectional area determined by two-dimensional echocardiography. We defined the improvement in stroke volume as the difference between the stroke volume at the optimal V-V setting and stroke volume at the nominal, or simultaneous, V-V setting.

Statistical analysis. Evaluating the clinical effectiveness of the InSync III CRT device and its V-V timing feature served as the primary objective of this study. The primary clinical efficacy end points for CRT included NYHA functional class, QoL, and 6MHW distance; the improvement in stroke volume served as the primary end point in analyzing the effectiveness of the V-V timing feature.

For CRT therapy efficacy, changes from baseline to the six-month visit were calculated. The mean changes were then compared between the InSync III patients and the MIRACLE control group using two-sided, two-sample *t* tests. We evaluated all patients with valid end point scores in the analysis. Based on Hochberg's multiple comparison procedure (19), the study achieved its prespecified objective if the differences in all three end points had a p value ≤0.05, if two had a p value ≤0.025, or if one had a p value ≤0.0167. We estimated the median percent improvement of stroke volume from the nominal to the optimal V-V setting. The V-V timing feature was considered effective if the median

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Table 1. InSync III and MIRACLE Control and Treatment Groups Demographic Comparison

Characteristic	InSync III Treatment (6-Month Visits) (n = 359)	MIRACLE Control (6-Month Visits) (n = 207)	MIRACLE Treatment (6-Month Visits) (n = 217)
Gender			
Male	211 (58.8%)	142 (68.6%)*	145 (66.8%)
Female	148 (41.2%)	65 (31.4%)	72 (33.2%)
Age (yrs)	65.8 (10.8)	64.8 (11.4)	63.7 (10.5)
Ejection fraction (%)	21.5 (6.9)	22.0 (6.2)	21.8 (6.2)
NYHA functional classification			
III	329 (91.6%)	192 (92.8%)	198 (91.2%)
IV	30 (8.4%)	15 (7.2%)	19 (8.8%)
QRS duration (ms)	163.9 (21.6)	164.7 (20.4)	167.8 (20.7)†
LVEDD (mm)	68.4 (9.4)	68.3 (9.6)	69.8 (9.7)
Underlying heart disease			
Ischemic	166 (46.2%)	119 (57.5%)*	110 (50.7%)
Nonischemic	193 (53.8%)	88 (42.5%)	107 (49.3%)
Myocardial infarction	124 (34.5%)	92 (44.4%)*	89 (41.0%)
Beta-blocker usage	255 (71.0%)	118 (57.0%)*	137 (63.1%)†
Atrial rhythm history			
History of atrial arrhythmia	322 (89.7%)	182 (87.9%)	188 (86.6%)
Normal sinus rhythm	37 (10.3%)	25 (12.1%)	29 (13.4%)
Ventricular rhythm history			
History of ventricular arrhythmia	283 (78.8%)	163 (75.1%)	0.3014
Normal sinus rhythm	76 (21.2%)	54 (24.9%)	
Prior surgery	215 (59.9%)	130 (59.9%)	0.9964
Coronary artery bypass	103 (28.7%)	58 (26.7%)	0.6110
Angioplasty	46 (12.8%)	34 (15.7%)	0.3370
Left bundle branch block	305 (85.0%)	180 (82.9%)	0.5218

Values are either mean (SD) or n (%). *p values <0.05 between InSync III treatment and MIRACLE control at baseline; †p values <0.05 between InSync III treatment (sequential cardiac resynchronization therapy [CRT]) and MIRACLE treatment (simultaneous CRT). The p values were calculated from two-sample *t* tests for continuous variables and from the Pearson chi-square test for categorical variables.

LVEDD = left ventricular end-diastolic diameter; MIRACLE = Multisite InSync RAndomized CLinical Evaluation; NYHA = New York Heart Association.

improvement exceeded 10% at all three time points (PHD, three months, and six months) using the sign test. We considered a p value ≤0.05 as statistically significant.

RESULTS

Patient disposition and implant data. Investigators and coordinators enrolled 422 patients at 28 centers in the U.S. between November 30, 2000, and June 4, 2002. Table 1 displays the baseline clinical characteristics of the patients enrolled in the respective studies in the MIRACLE program.

System implantation succeeded in 397 of 422 (94%) of the enrolled patients. The majority of implants (387 of 422) required only one attempt. Nine patients received the CRT device on the second attempt, and one implant succeeded after a third attempt. The distribution of successfully implanted LV leads consisted of 67% at the lateral region, 14% at the anterior region, 14% at the posterior region, and 5% at the apical region. The total implant procedure time averaged 152.1 min (range: 54 to 450 min), and the time to LV lead placement averaged 20.3 min (range: 0 to 270 min). Patient follow-up experience ranged between 0.7 and 25.5 months and averaged 13.9 ± 6.0 months.

We documented 41 perioperative (occurring either during implant or within seven days) system- or procedure-related complications in 37 patients, and 38 complications in 36 patients during the postoperative six-month follow-up period (Table 2). Complications classified as "other" consisted of any event requiring intervention, as well as device reprogramming, including, but not exclusively, acidosis, nausea, acute respiratory distress, peripheral intravenous infiltration, lead connection problem, etc.

Overall clinical efficacy. Figures 1A to 1C compare the clinical effectiveness of CRT in the InSync III group to the MIRACLE control group and the MIRACLE CRT treatment group at six months after implant; CRT significantly improved 6MHW distance, QoL, and NYHA functional classification in the InSync III population from baseline to six months (all $p < 0.0001$). The Wilcoxon rank-sum test produced all p values <0.0001. Even after a regression model adjusted for differences in baseline patient characteristics between the InSync III and MIRACLE control groups (Table 1), CRT significantly improved each primary end point for the InSync III patients ($p = 0.0009$ for 6MHW; $p = 0.0049$ for QoL; and $p < 0.0001$ for NYHA functional class). At six months InSync III patients walked

Table 2. Patients With Complications During InSync III Implant Attempts and Follow-Up

Description	Implant Attempts	Percentage	6 Months	Percentage
LV–lead-related*	5	1.2%	17	4.3%
RA–lead-related*	4	0.9%	4	1.0%
RV–lead-related*	1	0.2%	2	0.5%
Implant–tool-related*	8	1.9%	N/A	—
Pocket-related (including infection)	2	0.5%	7	1.8%
Heart block	3	0.7%	N/A	—
Junctional/VT/VF	3	0.7%	N/A	—
CHF decompensation	1	0.2%	N/A	—
Hemo/pneumothorax	3	0.7%	N/A	—
Thrombosis	N/A	—	4	1.0%
Other†	11	2.6%	4	1.0%
Total patients‡	37	8.8%	36	9.1%

*Includes atrial fibrillation, coronary sinus or cardiac vein dissection or perforation, diaphragmatic/muscle stimulation, dislodgement, elevated threshold, failure to capture/exit block, and palpitations; †Includes acidosis (1), acute renal failure (1), acute respiratory distress (1), anemia (1), connector error (1), dehydration (1), hypovolemia (1), nausea (1), paroxysymal nocturnal dyspnea (1), peripheral intravenous infiltration (1), pericardial effusion (1), pulmonary embolism (1), respiratory acidosis (1), respiratory decompensation (1), and stroke/cerebrovascular accident (1); ‡patients could have experienced more than one complication.

CHF = congestive heart failure; LV = left ventricular; RA = right atrial; RV = right ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

an average of 61 m farther than they did at baseline and reported a 22-point improvement in QoL score. In addition, 253 of 359 patients (70%) improved at least one class on the NYHA scale.

Incremental benefit of sequential Bi-V pacing. The ability to vary the V-V interval increased stroke volume in 81% of the InSync III patients at six months (Table 3). Stroke volume improved (optimal vs. nominal V-V setting) by 8.6% (median percentage) at PHD, 8.4% at three months, and 7.3% at six months. Sixty-four patients (17%) at PHD, 49 patients (14%) at three months, and 49 patients (14%) at six months experienced a ≥20% improvement in stroke volume during sequential Bi-V pacing.

In the subset of patients who achieved maximum stroke volume at a V-V setting other than nominal (LV stimulation precedes RV by 4 ms) (Table 4), the median improvements in stroke volume were 11.3%, 10.4%, and 9.8% at PHD, three, and six months, respectively.

Figure 2 illustrates the distribution of the optimal LV-RV settings at PHD, three, and six months. More than 75% of patients at each assessment had an optimal LV-RV setting between −40 ms to +40 ms. The majority of patients had an optimal V-V setting delivering LV stimulation first (55%, 54%, and 58% at the PHD, three, and six months visits, respectively). The proportion of patients with a nominal, or simultaneous, optimal V-V setting remained fairly stable over time (23%, 20%, and 19% at PHD, three, and six months, respectively). The proportion of patients with an optimal V-V setting delivering RV stimulation first also remained consistent at the three follow-up visits (23%, 26%, and 23%, respectively).

A post-hoc comparison of clinical efficacy end points between the InSync III and MIRACLE treatment groups revealed no significant difference in the effect of optimized sequential and simultaneous CRT on NYHA functional class or QoL improvement. However, the InSync III group experienced a greater improvement in 6MHW from baseline to six months compared to the MIRACLE simultaneous CRT treatment group (Table 5, p values from two-sample *t* tests). The Wilcoxon rank-sum test produced similar results with p values of 0.0015, 0.1958, and 0.3364 for the 6MHW, QoL, and NYHA functional class, respectively. The improvement in 6MHW distance seen in InSync III patients continued even after adjusting for differences in baseline 6MHW, age, beta-blocker use, QRS duration, gender, and LV end-diastolic diameter between the two groups ($p = 0.0016$).

An analysis of changes in stroke volume during sequential CRT and several baseline characteristics (Table 6) identified patients with a history of myocardial infarction as the only subgroup experiencing statistically significant improvement in stroke volume ($p = 0.03$) during optimal versus nominal V-V setting. The improvement in stroke volume at the optimal V-V interval continued throughout all follow-up intervals (PHD, three, and six months). Increase in stroke volume in NYHA functional class IV patients with an optimized V-V setting was not statistically significant ($p = 0.1344$), yet it was consistent across all follow-up intervals (PHD, three, and six months).

At the time of database closure on March 7, 2003, 65 patients had died. The classification scheme labeled 47 as cardiac related and 18 as noncardiac. Arrhythmia accounted for 26, and HF for 18 of the cardiac-related deaths. One patient died from an acute myocardial infarction, one due to an electrolyte imbalance from diuretic misuse, and one due to drug-induced hypotension. The events committee classified one arrhythmic death as possibly procedure- or device-related.

DISCUSSION

Until recently, commercially available CRT devices delivered only simultaneous Bi-V stimulation. Although simultaneous Bi-V CRT reduces patient symptoms and improves ventric-

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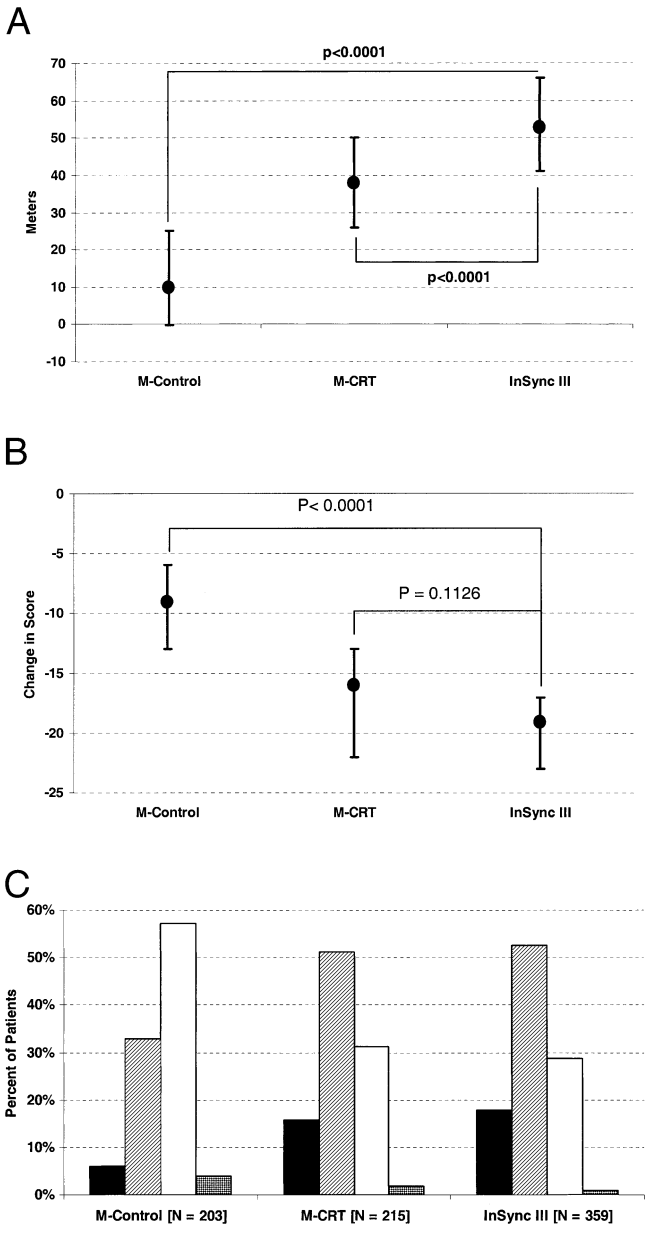

Figure 1. Median changes in 6-min hall walk **(A)**, quality of life score **(B)**, and changes in New York Heart Association functional class **(C)** after six months. **Black bars** = improved two or more; **diagonally lined bars** = improved; **white bars** = no change; **dotted bars** = worsened. M = Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial; M-CRT = MIRACLE Cardiac Resynchronization Therapy trial.

ular function, exercise capacity, and QoL in patients with moderate-to-severe HF and V-V conduction delays (5–13), about 30% of patients still do not respond to this therapy (20).

The ability to change the ventricular activation sequence might better overcome intrinsic conduction delay, improve cardiac performance, and increase the likelihood of a clinical response (20). Several small, short-term studies of sequential Bi-V pacing using various V-V intervals have shown improved hemodynamic performance (14–17). Whether sequential Bi-V CRT produces demonstrable clinical benefits remains undetermined.

Table 3. Percentage Improvement in Stroke Volume*

Visit	n	% Patients Improved	Median	Range	95% LCB
Prehospital discharge	376	77.1%	8.6%	0%–93.5%	7.7%
Three-month	344	79.9%	8.4%	0%–69.6%	7.6%
Six-month	338	80.8%	7.3%	0%–58.7%	6.3%

*Results shown are based on all patients with interventricular timing assessments performed according to protocol.
LCB = lower confidence bound.

We evaluated the overall clinical effectiveness of sequential Bi-V pacing in a large cohort of NYHA functional class III and IV HF patients in whom CRT was indicated. This approach significantly improves NYHA functional class, QoL, and 6MHW distance compared to control patients from MIRACLE who received conventional medical therapy alone. Varying the V-V interval with echocardiographic guidance incrementally increased stroke volume in the majority of InSync III patients. One-half of the sequentially paced patients experienced at least a 10% increase in stroke volume at six months, while 14% of patients demonstrated a ≥20% improvement in stroke volume at six months. In 75% of the InSync III patients, the optimal V-V interval was within a relatively narrow range of −40 ms (stimulating the RV 40 ms before the LV) to +40 ms (stimulating the LV 40 ms before the RV). Stimulating the LV before the RV most often yielded optimal stroke volume. The proportions of patients with LV first, nominal, and RV first remained stable over time.

Sequential Bi-V CRT might improve ventricular stroke volume by compensating for less than optimal LV lead position, by tailoring ventricular timing to correct for individual heterogeneous ventricular activation patterns commonly found in patients with LV dysfunction and HF (14), or by overcoming regional conduction abnormalities across infarcted myocardium. Indeed, sequential Bi-V CRT improved stroke volume preferentially in InSync III patients with previous myocardial infarction, suggesting that the ability to vary V-V timing may have compensated for infarct-related conduction block. However, the InSync III study protocol did not systematically assign lead positions at different segments along the LV; thus, we cannot offer a comprehensive analysis of whether sequential V-V activation compensates for seemingly suboptimal lead position.

Clinically, sequential Bi-V pacing provided mixed results. InSync III patients did not demonstrate significantly greater

Table 4. Percent Improvement in Stroke Volume for the Subset of Patients With Maximum Stroke Volume at a V-V Delay Other Than Nominal

Follow-Up Visit	n	Median	p Value*	Range	95% LCB
Prehospital discharge	290	11.3%	0.009	0.5%–93.5%	10.2%
Three months	275	10.4%	0.114	0.3%–69.6%	9.7%
Six months	273	9.8%	0.548	0.4%–58.7%	8.3%

*Test for percentage improvement in stroke volume ≥10% (sign test).
LCB = lower confidence bound; V-V = interventricular.

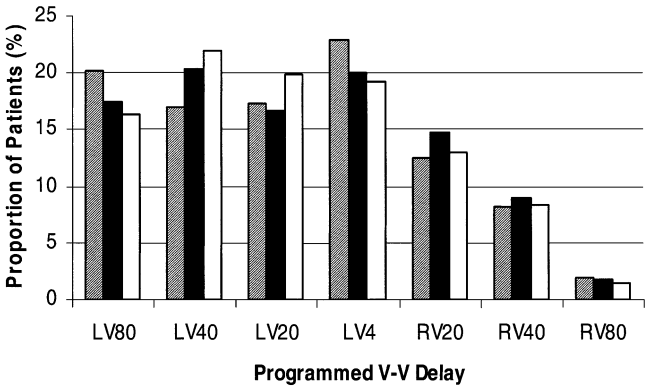

Figure 2. Optimal interventricular timing settings at prehospital discharge, three, and six months. **Diagonally lined bars** = prehospital discharge; **black bars** = three months; **white bars** = six months.

improvement in NYHA functional class or QoL when compared to patients who received simultaneous Bi-V pacing in the MIRACLE study. InSync III patients did experience a significant improvement in exercise capacity, demonstrating a median change in the 6MHW distance 40% greater (53 vs. 37.9 m) than that of the MIRACLE patients receiving simultaneous Bi-V CRT. However, post-hoc analysis failed to show a correlation between improvement in stroke volume and improved exercise capacity in the InSync III patients (Spearman correlation analysis between the changes in stroke volume and changes in 6MHW showed that the correlation coefficient was −0.0868 at three months and −0.0473 at six months. The p values were 0.1132 and 0.3977, respectively). Using the improvement in NYHA functional class as an indicator of a positive response to CRT, the response to sequential CRT in InSync III did not differ from the response to simultaneous CRT in MIRACLE. Furthermore, the differences in study design prohibit drawing any meaningful clinical explanations in the differences in these outcomes.

Study limitations. Comparing the effects of sequential Bi-V CRT to the control arm from the MIRACLE study and using the simultaneous Bi-V CRT arm of MIRACLE against which to test the clinical effects of incremental improvements in stroke volume limit the comparison of efficacy in this open-label evaluation of sequential CRT. However, the patient baseline characteristics, the investigative centers, and the overall study inclusions and end points in the InSync III clinical study closely resemble those of MIRACLE. Furthermore, any baseline differences in 6MHW, age, beta-blocker use, QRS duration, gender, and LV end-diastolic diameter did not confound the results of the InSync III study.

The InSync III protocol measured LV stroke volume using Doppler sampling at the aortic outflow. Small changes

Table 5. Comparison of Change From Baseline to Six Months of InSync III and MIRACLE Treatment Groups on Patient Outcomes

	InSync III	MIRACLE CRT	p Value*
6-min hall walk	(n = 340)	(n = 216)	
Median	53.0	37.9	<0.0001
Range	−314.0 to 613.0	−437.0 to 248.8	
Quality-of-life score	(n = 355)	(n = 216)	
Median	−19.0	−16.0	0.1126
Range	−91.0 to 29.0	−88.0 to 47.0	
NYHA functional class	(n = 359)	(n = 215)	
Median	−1.0	−1.0	0.3827
Range	−3.0 to 1.0	−3.0 to 1.0	

*p values were calculated from two-sample *t* tests.
CRT = cardiac resynchronization therapy; other abbreviations as in Table 1.

Table 6. Comparison of Stroke Volume Improvement Among InSync III Subgroups

Characteristics	InSync III 394 Patients	Median % SV Improvement	p Value*
Gender			
Male	232 (58.9%)	8.1%	0.5099
Female	162 (41.1%)	7.9%	
Age (yrs)			
≤65	165 (41.9%)	7.9%	0.5980
≥65	229 (58.1%)	8.2%	
Ejection fraction (%)			
≤20	222 (56.4%)	7.8%	0.4471
>20	172 (43.7%)	8.5%	
NYHA functional class			
III	358 (90.9%)	7.9%	0.1344
IV	36 (9.1%)	10.1%	
QRS duration (ms)			
<160	140 (35.5%)	8.3%	0.5926
≥160	254 (64.5%)	7.9%	
LVEDD (mm)			
<70	228 (57.9%)	8.5%	0.1728
≥70	166 (42.1%)	7.6%	
HF etiology			
Ischemic	186 (47.2%)	8.3%	0.3786
Nonischemic	208 (52.8%)	7.9%	
Myocardial infarction			
Yes	139 (35.3%)	8.9%	0.0322
No	255 (64.7%)	7.7%	
Beta-blocker use			
Yes	275 (69.8%)	7.9%	0.2868
No	119 (30.2%)	8.6%	
Atrial rhythm history			
History of atrial arrhythmia	40 (10.1%)	8.1%	0.7240
Normal sinus rhythm	354 (89.9%)	8.1%	
Ventricular rhythm history			
History of ventricular arrhythmia	85 (21.6%)	7.2%	0.4983
Normal sinus rhythm	309 (78.4%)	8.2%	
Prior surgery			
Yes	160 (40.6%)	8.0%	0.5381
No	234 (59.4%)	8.1%	
Left bundle branch block			
Yes	333 (84.5%)	8.0%	0.0978
No	61 (15.5%)	8.3%	

Values are n (%). *The p values were calculated from the Wilcoxon rank-sum test.
HF = heart failure; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association; SV = stroke volume.

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in the angle of incidence between the outflow jet and the ultrasound transducer or a small miscalculation of the outflow tract dimension can introduce significant error into the calculation of LV stroke volume. In an effort to maintain consistency in the echocardiography-Doppler methodology, sonographers underwent training, obtained measurements at the same phase of the respiratory cycle, and selected the V-V stimulation sequence during testing in a random order to reduce potential bias. The relative stability of the optimal V-V sequence during the six-month follow-up supports the consistency of the method used. No noninvasive assessment of cardiac function has emerged as an ideal tool to analyze the incremental changes in cardiac output produced by atrioventricular and V-V timing changes in ambulatory patients. Clinical reports on digital plethysmography or chest impedance determination of aortic volume failed to identify a method superior to the echocardiography-Doppler examination. Ongoing clinical trials of sequential Bi-V stimulation will measure oxygen consumption at peak exercise to compare its efficacy against simultaneous pacing. The adoption of other end points for analysis will help to further determine the incremental benefit of varying the V-V interval during CRT.

Conclusions. Sequential Bi-V CRT with a V-V interval tailored to each patient led to a modest increase in stroke volume compared to simultaneous Bi-V CRT. Clinically, over the short-term, sequential Bi-V CRT led to greater patient exercise capacity, but not fewer symptoms or improved QoL when compared to patients receiving simultaneous Bi-V CRT. The likelihood of response appears similar; however, in certain individuals, optimization of the V-V delay may be useful in maximizing the response to CRT and enhances the magnitude of response. Longer-term, randomized, controlled trials with objective end points will help further define the role of programmable V-V timing in CRT patient management.

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Reprint requests and correspondence: Dr. Angel R. León, Cardiology, MOT 6th Floor, Emory Crawford Long Hospital, 550 Peachtree Street, Atlanta, Georgia 30308. E-mail: angel_leon@emoryhealthcare.org.

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