

Effect of Resynchronization Therapy Stimulation Site on the Systolic Function of Heart Failure Patients

Christian Butter, MD; Angelo Auricchio, MD, PhD; Christoph Stellbrink, MD; Eckart Fleck, MD; Jiang Ding, PhD; Yinghong Yu, MS; Etienne Huvelle, MD, MSEE; Julio Spinelli, PhD; on behalf of the Pacing Therapy for Chronic Heart Failure II (PATH-CHF-II) Study Group

Background—Cardiac resynchronization therapy (CRT) improves systolic function in heart failure patients with ventricular conduction delay by stimulating the left ventricle (LV) or both ventricles (biventricular, BV). Optimal LV site selection is of major clinical interest for CRT device implantation; however, the dependence of hemodynamics on LV stimulation site has not been established. Thus, the objective of this study was to compare the hemodynamic response to CRT for 2 LV coronary vein sites: the free wall and anterior wall.

Methods and Results—A total of 30 patients (mean NYHA class, 2.7; mean QRS interval, 152 ms; mean PR interval, 194 ms) enrolled in the PATH-CHF-II trial were studied. CRT was administered with LV and BV stimulation in VDD mode at 4 AV delays. LV stimulation was at the lateral free wall or anterior wall, whereas right ventricular stimulation was fixed near the apex. LV+dP/dt_{max} and aortic pulse pressure changes from baseline during CRT were compared for LV sites. Free wall sites with LV and BV stimulation yielded significantly larger LV+dP/dt_{max} (14% versus 6%, $P<0.001$ for LV; 12% versus 5%, $P<0.001$ for BV) and pulse pressure (8% versus 4%, $P<0.001$ for LV; 9% versus 5%, $P<0.001$ for BV) compared with anterior sites. In one third of patients, CRT at free wall sites increased LV+dP/dt_{max}, whereas it decreased at anterior sites over most AV delays.

Conclusion—CRT with LV free wall stimulation produced significantly better LV systolic performance compared with anterior stimulation. Further studies are warranted to prove the clinical superiority of the LV free wall as a site for long-term CRT. (*Circulation*. 2001;104:3026-3029.)

Key Words: heart failure ■ bundle-branch block ■ pacing ■ contractility ■ electrical stimulation

Cardiac resynchronization therapy (CRT) has been demonstrated to improve systolic function in heart failure patients with conduction system disorders. Stimulation chamber seems to be a dominant factor in determining the short-term hemodynamic response to CRT.^{1,2,3} The impact of stimulation chamber on hemodynamic improvement is known to depend on the type of the conduction system defect.⁴ For example, in patients with left bundle-branch block, stimulating the left ventricle (LV) has been shown to improve systolic performance more than stimulating the right ventricle (RV).¹

In addition to stimulation chamber, initial reports have suggested that the stimulation site within a chamber might play an important role in the outcome of CRT.^{5,6} To date, however, no study has systematically evaluated the impact of LV stimulation site on short-term hemodynamics. Because choosing an optimal stimulation site is of major clinical interest for long-term CRT, it is important to investigate whether individual transvenous stimulation sites can affect

systolic performance. Therefore, the objective of this study was to compare the short-term hemodynamic impact of CRT at the 2 most accessible areas of the LV using coronary vein-based lead systems⁵—namely, the free wall and the anterior wall.

Methods

Study Group

The PATH-CHF II study was prospectively designed to test short-term hemodynamic changes during CRT delivered via multiple stimulation configurations. The major inclusion criteria were dilated cardiomyopathy of any origin, with NYHA class \geq II, ejection fraction \leq 30%, and QRS duration \geq 120 ms. The major exclusion criteria were acute cardiac failure crisis, coronary artery bypass graft or myocardial infarction within the last 3 months, valvular stenosis, previous valve replacement or reconstruction, unstable angina, any type of pacemaker indication, or history of chronic atrial fibrillation.

The 43 patients enrolled in this study were assigned randomly to a protocol that was designed for short-term LV site comparison. Complete paired data sets of free wall versus anterior wall stimulation were obtained in only 30 patients because of unsuccessful lead

Received September 26, 2001; revision received November 6, 2001; accepted November 6, 2001.

From the German Heart Institute and Charité, Campus Virchow Klinikum, Berlin (C.B., E.F.), the Division of Cardiology, University Hospital, Magdeburg (A.A.), and the Department of Cardiology, Rhein-Westfälische Technische Hochschule University Hospital, Aachen (C.S.), Germany; and Guidant-Cardiac Rhythm Management (J.D., Y.Y., E.H., J.S.).

Correspondence to Christian Butter, MD, Department of Internal Medicine/Cardiology, Charité, Campus Virchow Clinic, Humboldt University and German Heart Center, D-13353 Berlin, Germany. E-mail butter@dhzb.de

© 2001 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

placement (in 9 patients) and intermittent capture, excessive premature ventricular contractions, or instrumentation issues (in 4 patients). The demographic data (mean±SD) include sex (17 men and 13 women), age (59±9 years), etiology (18 dilated cardiomyopathy [DCM] and 12 coronary artery disease [CAD]), NYHA class (2.7±0.5), QRS width (152±17 ms), PR interval (194±26 ms), ejection fraction (23±8%), LV end-diastolic diameter (74±12 mm), LV+dP/dt_{max} (789±222 mm Hg/s), aortic pulse pressure (45±17 mm Hg), and LV end-diastolic pressure (22±10 mm Hg).

The institutional review boards of the participating institutions approved the study protocol. Each patient signed a written consent before the test.

Catheterization

Temporary pacing leads were used for the short-term study and were placed in the right atrium and RV apex. A venogram imaged in 2 different angulations (left anterior oblique 30° and anteroposterior) was obtained to determine the anatomy of the coronary sinus venous system. An LV pacing electrode (Easytrak, Guidant Corp) was placed either in the free wall region via the lateral or posterior vein or in the anterior region via the great cardiac vein. After femoral artery and venous puncture using the Seldinger technique, two 8-French dual transducer micromanometer catheters (SPC-780c, Millar Instruments) were inserted into the heart to provide RV, aortic, and LV pressures. Pressure catheters and pacing leads were connected to an external pacing computer (FlexStim, Guidant Corp) to execute the pacing protocol and to acquire hemodynamic signals.

Protocol and Data Analysis

For each patient, CRT was applied univentricularly (LV) and biventricularly (BV) at both the free wall and anterior regions. For each site and configuration (LV or BV), VDD stimulation mode (atrial sensing followed by ventricular stimulation) was used with 4 preset AV delays (evenly spaced between 0 and 50 ms less than the intrinsic AV interval). Each combination of site and AV delay was repeated randomly 4 times in a sequence of 6 stimulated beats and 14 nonstimulated beats.⁶ Intrinsic conduction delays were measured during sinus rhythm from the atrial electrode-sensed event to the peak depolarization at each LV site. Conduction delay differences between LV sites were calculated from these values.

Data were checked for abnormal events (eg, ectopic beats or noncapture). Abnormal beats and their immediate neighboring beats were excluded from further analysis. For each stimulation episode, values of LV+dP/dt_{max} and aortic pulse pressure (PP) were calculated on the basis of a previously reported technique.¹⁻⁶ Briefly, hemodynamic indices were averaged over the last 4 stimulated beats and compared with an average (baseline) of the immediately preceding 6 nonstimulated beats. All episodes with the same site/AV delay combination were averaged, and from this average the CRT response was determined.

Statistical Analysis

All statistical comparisons were performed using the CRT responses obtained at the best AV delay for each site. For comparisons within an individual, hemodynamic responses were compared by a 2-tailed, unpaired Student's *t* test. There was a maximum of 16 cardiac cycle responses in each stimulation data set. For comparisons between individuals, the averaged individual hemodynamic responses to each stimulation site were compared with a 2-tailed, paired Student's *t* test. *P*<0.05 was considered statistically significant. Data are presented as mean±SEM.

Results

In the majority of patients, free wall stimulation (FWS) and anterior wall stimulation (AWS) increased LV+dP/dt_{max} over a wide range of AV delays during both LV and BV CRT. However, opposite responses were observed in 9 of the 30 patients (30%) during LV CRT and 11 of the 30 patients (37%) during BV CRT (Figure 1A and 1B). In every case in which an opposite response was observed, LV+dP/dt_{max} increased for FWS and decreased with AWS.

LV+dP/dt_{max} increased by an average of 14% during FWS compared with 6% during AWS for LV CRT (*P*<0.001). Increases were significantly different between FWS and AWS in 25 of 30 patients (10 of 12 CAD patients, 15 of 18 DCM patients) and larger with FWS in 23. For BV CRT, LV+dP/dt_{max} increased an average of 12% during FWS

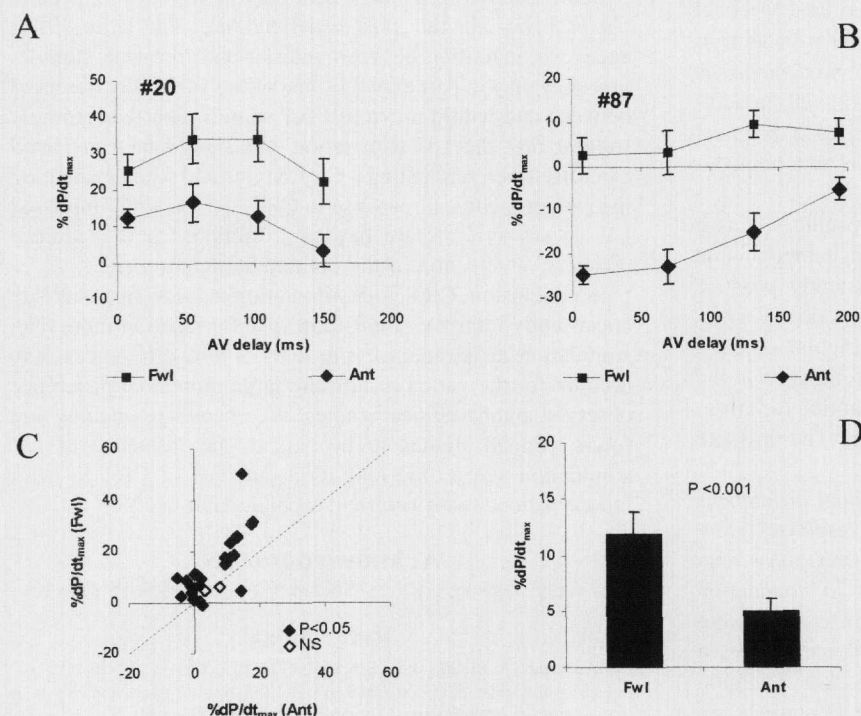


Figure 1. BV CRT: Graphs demonstrate individual and group LV+dP/dt_{max} response during stimulation at free wall (Fwl) and anterior (Ant) sites. A, Percentage changes in LV+dP/dt_{max} (%dP/dt_{max}) in 1 patient who responded positively with both Fwl and Ant stimulation at all AV delays. B, Similar to A for another patient who responded positively with Fwl stimulation but negatively with Ant stimulation at all AV delays. C, Scatter plot comparing %dP/dt_{max} with Fwl and Ant stimulation. Each point (n=30) is the response for 1 patient at the optimum AV delay. Symbols represent individual patients who experienced a significant (◆) or nonsignificant (◇) difference between Fwl and Ant stimulation response. Points above the identity line (dashed) have a larger Fwl stimulation response. D, Summary data demonstrating significant LV+dP/dt_{max} benefit of Fwl versus Ant stimulation for all patients (n=30, *P*<0.001).

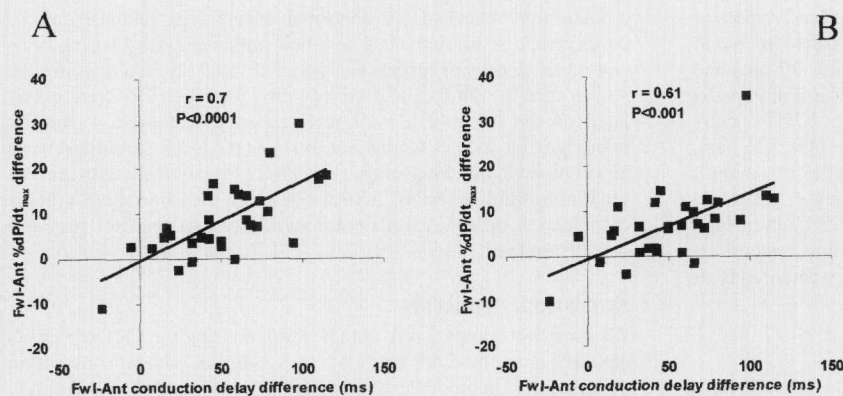


Figure 2. Correlation between free wall (Fwl) and anterior wall (Ant) intrinsic conduction delay differences and the LV+dP/dt_{max} response differences during Fwl and Ant stimulation for LV CRT (A) and BV CRT (B). Positive conduction delay differences correspond to more delayed Fwl activation. Positive LV+dP/dt_{max} differences correspond to a larger Fwl stimulation response (percentage change from baseline). Least squares linear regression lines shown.

compared with 5% during AWS ($P < 0.001$), and increases were significantly different in 24 of 30 patients (8 of 12 CAD patients, 16 of 18 DCM patients) and larger during FWS in 22 (Figure 1C and 1D).

Similarly, PP increased 8% during FWS compared with 4% during AWS for LV CRT ($P < 0.001$) and 8.6% during FWS compared with 4.4% during AWS for BV CRT ($P < 0.001$). For LV CRT, the PP response was significantly different between FWS and AWS in 16 of 30 patients and was larger during FWS in 15 patients. For BV CRT, the PP response was significantly different in 13 of 30 patients and larger during FWS in all 13 patients.

In almost all patients (28 of 30), intrinsic conduction delays were longer to the free wall than to the anterior wall site. The magnitude of the free wall and anterior wall conduction delay differences was positively correlated with the difference in LV+dP/dt_{max} observed between FWS and AWS (Figure 2).

Discussion

CRT is emerging as a long-term therapy for symptomatic heart failure in patients with conduction disturbances.^{7,8,9} Although most studies have determined that stimulation in the LV would yield better results than stimulation in the RV for patients with left bundle-branch block, the effects of different stimulation sites within the LV have not been systematically explored. In addition, no information is available with regard to a potential relationship between the LV lead location, short-term hemodynamic response, and long-term outcome.

Our results clearly suggest that the LV pacing site is a critical factor in determining the short-term hemodynamic response to CRT. LV free wall sites consistently produce better short-term hemodynamic responses than do LV anterior sites, regardless of CRT mode (univentricular or BV). Importantly, in one third of tested patients, stimulation at the LV anterior region worsened hemodynamic function, whereas LV free wall stimulation improved it. The opposite pattern was never observed.

These results cannot be explained by regional differences in ischemic lesions because hemodynamic responses were equal in CAD and non-CAD patients. However, these data may be explained by regional differences in conduction delays because the hemodynamic response differences were proportional to the conduction delay differences between sites. We propose that stimulating a later-activated LV region produces a larger response because it more effectively re-

stores regional activation synchrony. An analogous argument has been made to explain why LV stimulation is much more effective than RV stimulation at improving hemodynamics in patients with delayed LV activation.¹ Just as it is necessary to preexcite the delayed ventricle to improve interventricular synchrony, it may be necessary to preexcite the delayed LV region to improve intraventricular synchrony. Concordant with this hypothesis, we found that LV free wall sites consistently are more delayed and more effective for CRT than are the LV anterior wall sites. Correspondingly, the negative effect of anterior wall stimulation in some patients may be the consequence of preexciting an already early-activated region and thus increasing the regional activation asynchrony.

The current practice of CRT has relied on a rapidly evolving mélange of LV access techniques, ranging from epicardial leads to transvenous systems, most of which have not permitted prospective selection of the LV stimulation site. Unfortunately, with transvenous systems, the anterior vein is the largest and easiest coronary vein to access. As a result, CRT in many cases up to now may have been implemented with an anterior vein site, which may be the most expedient but probably not the most beneficial site. The large differences we quantified between anterior and free-wall stimulation sites may in part explain some of the variability observed between and within previous CRT studies. Our data strongly suggest that the LV stimulation site should be considered carefully when implanting a CRT device and when evaluating the patient's clinical response to CRT. To that end, improved LV access systems are needed to simplify and guarantee prospective selection of the optimal stimulation site.

In conclusion, CRT with stimulation at a LV free wall site consistently improves short-term systolic function more than stimulation at an anterior site does. These differences may account for the varied results and large individual difference observed among clinical studies. We encourage ongoing and future clinical studies to investigate the influence of LV stimulation site on the long-term outcome of CRT in heart failure patients with ventricular conduction delays.

Acknowledgments

This study was supported by Guidant Corporation, St Paul, Minn.

References

1. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation*. 1999;99:2993-3001.

2. Cazeau S, Gras D, Lazarus A, et al. Multisite stimulation for correction of cardiac asynchrony. *Heart*. 2000;84:579–581.
3. Nelson GS, Berger RD, Fetters BJ, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation*. 2000;102:3053–3059.
4. Kass DA, Chen CH, Curry C, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation*. 1999;99:1567–1573.
5. Auricchio A, Klein H, Tockman B, et al. Transvenous biventricular pacing for heart failure: can the obstacles be overcome? *Am J Cardiol*. 1999;83(suppl):136D–142D.
6. 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;1:464–469.
7. Bakker PF, Meijburg HW, de Vries JW, et al. Biventricular pacing in end-stage heart failure improves functional capacity and left ventricular function. *J Interv Card Electrophysiol*. 2000;4:395–404.
8. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001;344:873–880.
9. Reuter S, Garrigue S, Bordachar P, et al. Intermediate-term results of biventricular pacing in heart failure: correlation between clinical and hemodynamic data. *Pacing Clin Electrophysiol*. 2000;23(Pt II): 1713–1717.