Original articles
Cardiac pacing in heart failure patients with left bundle branch block: impact of pacing site for optimizing left ventricular resynchronization

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Key words:
Heart failure; Pacing; Hemodynamics; Bundle branch block.

Background. **Acute left ventricular pacing has been associated with hemodynamic improvement in patients with congestive heart failure and wide QRS complex. We hypothesized that pacing two left ventricular sites simultaneously would produce faster activation and better systolic function than single-site pacing.**

Methods. **We selected 14 heart failure patients (NYHA functional class III or IV) in normal sinus rhythm with left bundle branch block and QRS > 150 ms. An 8F dual micromanometer catheter was placed in the aorta for measuring +dP/dt (mmHg/s), aortic pulse pressure (mmHg), and end-diastolic pressure (mmHg). Pacing leads were positioned via coronary veins at the posterior base and lateral wall. Patients were acutely paced VDD at the posterior base, lateral wall, and both sites (dual-site) with 5 atrioventricular delays (from 8 ms to PR -30 ms). Pacing sequences were executed in randomized order using a custom external computer (FlexStim, Guidant CRM).**

Results. **Dual-site pacing increased peak +dP/dt significantly more than posterior base and lateral wall pacing. Dual-site and posterior base pacing raised aortic pulse pressure significantly more than lateral wall pacing. Dual-site pacing shortened QRS duration by 22%, whereas posterior base and lateral wall pacing increased it by 2 and 12%, respectively (p = 0.006).**

Conclusions. **In heart failure patients with left bundle branch block, dual-site pacing improves systolic function more than single-site stimulation. Improved ventricular activation synchrony, expressed by paced QRS narrowing, may account for the additional benefit of dual- vs single-site pacing in enhancing contractility. This novel approach deserves consideration for future heart failure pacing studies.**

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Introduction

The increased incidence and prevalence of heart failure place a high priority on novel treatment strategies. Despite improvements in medication regimens, most notably ACE-inhibitors and beta-blockers, a sizable proportion of patients suffer from poor quality of life due to severe limitations during effort and daily activities. Recently, atrial-synchronous biventricular pacing has emerged as a promising therapeutic modality for patients with dilated cardiomyopathy and discoordinated wall motion associated with left bundle branch block[1-4]. In such patients, preexcitation of the left ventricle improves pump efficiency by a more coordinated contraction. Although experimental studies have demonstrated a close relationship between the left ventricular pacing site and the magnitude of ventricular function response[5,6], no human study to date has directly compared the hemodynamic effects of specific left ventricular pacing sites, nor it has been attempted to pace two sites simultaneously.

The present study tested the following hypotheses: 1) pacing the left ventricular base

at a posterior location (the area of latest left ventricular activation in the vast majority of patients with left bundle branch block)[4,7] yields comparable or better hemodynamic effects than the most commonly paced left ventricular lateral free wall; 2) pacing both sites simultaneously (dual-site) provides for faster ventricular activation and possibly, greater left ventricular function improvement than single-site pacing.

Methods

Study patients. This prospective study enrolled 14 patients (9 men, 5 women, aged 25 to 79 years) with heart failure (NYHA functional class III or IV, ejection fraction 26 ± 7%) of ischemic (n = 4) or idiopathic (n = 10) etiology, in normal sinus rhythm and with left bundle branch block (QRS duration > 150 ms). None of the patients had a recent history of atrial or ventricular tachyarrhythmia, severe valve disease, myocardial infarction during the previous 12 weeks, and recent or pending coronary artery revascularization. Chronic medications were maintained up to the initiation of the study. The protocol was approved by the San Raffaele Hospital Ethical Committee. All patients gave written informed consent.

Catheterization and pacing protocol. Patients were studied in a nonsedated, fasting state. An 8F dual micromanometer catheter (SPC-780c, Millar Instruments, Houston, TX, USA) was used to measure aortic and left ventricular pressures, and a quadripolar 6F catheter placed into the right atrium for bipolar sensing. The coronary sinus was engaged via the left subclavian vein with an 8F steerable balloon occlusion guiding catheter (Cardima Vueport, Fremont, CA, USA, Damato- or Multipurpose-type). After assessing coronary vein distribution by occlusive venography, two quadripolar 1.5F electrode catheters (Cardima Pathfinder mini series) were placed, respectively, at the ostium of a posterior or postero-lateral or lateral marginal vein (site for posterior base pacing), and distally in a lateral marginal or postero-lateral vein (site for lateral wall pacing). Pressure catheters and pacing leads were connected to a custom external computer (FlexStim, Guidant CRM, St. Paul, MN, USA), designed to perform a randomized pacing protocol, acquire hemodynamic signals, and provide off-line comparative data analysis[3].

Unipolar pacing in the VDD mode was performed by pacing either the posterior base alone, the lateral wall alone, or both sites simultaneously (dual-site). For each pacing site, a previously reported pacing protocol was executed[3]. Briefly, the protocol consisted of periods of pacing separated by periods of nonpacing in normal sinus rhythm in a 5 paced/15 nonpaced beat duty cycle (Fig. 1). Pacing was performed at five different atrioventricular delays. Each combination of pacing site and atrioventricular delay was repeated 5 times at random for each patient.

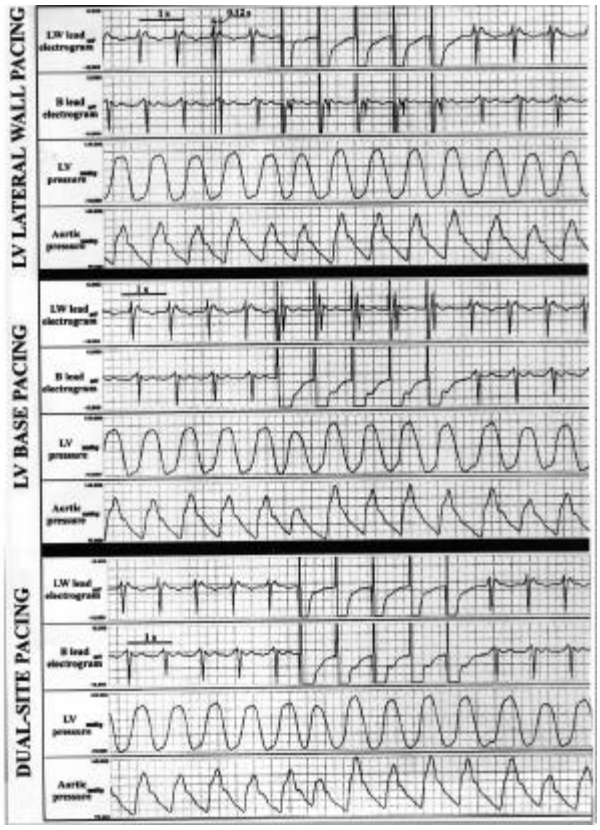

Figure 1. *Tracings of left ventricular (LV) and aortic pressure waveforms and electrograms during VDD pacing sequences at the LV lateral wall (LW) (top panel), posterior base (B) (mid panel) and at both sites simultaneously (bottom panel). During sinus rhythm, simultaneous electrogram recordings from the B and LW leads show that later activation occurs at the B (delay = 0.12 s). During pacing, hemodynamic changes from baseline typically occur at the first paced beat, reach a maximum change during the next 4 paced beats, and then return to baseline levels within a few nonpaced beats. Hemodynamic variables are analyzed by averaging measurements on the second to the fifth paced beat, and percent changes from their mean value during the immediate preceding 6 nonpaced beats (local baseline) are computed.*

Hemodynamic measurements were made automatically with custom software, and included aortic systolic pressure, aortic diastolic pressure, pulse pressure (aortic systolic pressure minus aortic diastolic pressure), left ventricular end-diastolic pressure, and left ventricular pressure derivative maximum (+dP/dt) and minimum (-dP/dt). Hemodynamic parameters were calculated for each beat of a pacing sequence as a percent change from their average value during the immediate preceding 6 nonpaced beats (local baseline) (Fig. 1).

During the procedure, 12-lead ECG tracings were continuously recorded and stored on optical disk (Cardiolab, Prucka Eng., Inc., Houston, TX, USA) for off-line analysis. Reported QRS durations (ms) are a maximum of 12 leads measured manually on the Cardiolab system at a screen speed of 200 mm/s with the use of on-screen calipers.

Statistical analysis. Data are expressed as mean ± SD or percentages, where appropriate. To analyze paced changes in hemodynamic parameters, two-sided paired

Student's t tests were used. Comparisons among pacing sites and atrioventricular delays were performed using repeated ANOVA measures. Statistical significance was set at $p < 0.05$.

Results

Lead placement. No patient developed acute complications during catheterization and pacing. The acute pacing threshold was 1.2 ± 0.9 V, with an impedance of 794 ± 321 ohms. The R wave amplitude was 12.0 ± 6.2 mV. The entire pacing protocol added up to 2500 beats, which, at an average heart rate of 76 b/min, required an average of 32 min per patient.

Simultaneous electrogram recordings at the posterior base and lateral wall during sinus rhythm (Fig. 1) showed that the posterior base was activated later than the lateral wall in 86% of patients, including all those with idiopathic and in 2 out of 4 patients with ischemic cardiomyopathy.

Optimization of atrioventricular delay. Figure 2 shows averaged paced changes from baseline in hemodynamic parameters as a function of the five randomly tested atrioventricular delays for each pacing site. Overall, the hemodynamic effects of dual-site pacing were greater than those of single-site pacing at each atrioventricular delay. However, for each pacing site, the maximum and minimum atrioventricular delays were suboptimal for improving systolic function, whereas the greatest increase in +dP/dt and pulse pressure was achieved at the middle atrioventricular delay settings. In contrast, reduction in chamber filling (decreased end-diastolic pressure) and faster relaxation (increased absolute -dP/dt) were associated with short atrioventricular delays, due to preload decline.

Effects of single- and dual-site pacing. Acute hemodynamic effects of the three pacing strategies averaged over all atrioventricular delays are presented in table I. Systolic function improved significantly with pacing at all left ventricular sites. Single-site pacing at the posterior base and dual-site pacing were significantly better for improving +dP/dt and pulse pressure than single-site pacing at the lateral wall, whereas no significant differences were observed between dual-site and posterior base pacing except for +dP/dt, which was slightly, although significantly ($p = 0.04$) higher with dual-site pacing. Of note, QRS duration was only shortened by dual-site pacing (-22 ± 9%), whereas it did not change during posterior base pacing (+2 ± 4%) and increased with lateral wall pacing (+12 ± 7%).

As for diastolic function parameters, end-diastolic pressure was significantly reduced by pacing at any left ventricular site, whereas a significant increase in -dP/dt was achieved only with dual-site and posterior base stimulation.

Influence of heart failure etiology. Pacing responses of patients grouped by heart failure etiology (ischemic or idiopathic) are reported in figure 3. There were no significant differences (p = NS) between the two groups in changes in dP/dt, pulse pressure, and left ventricular end-

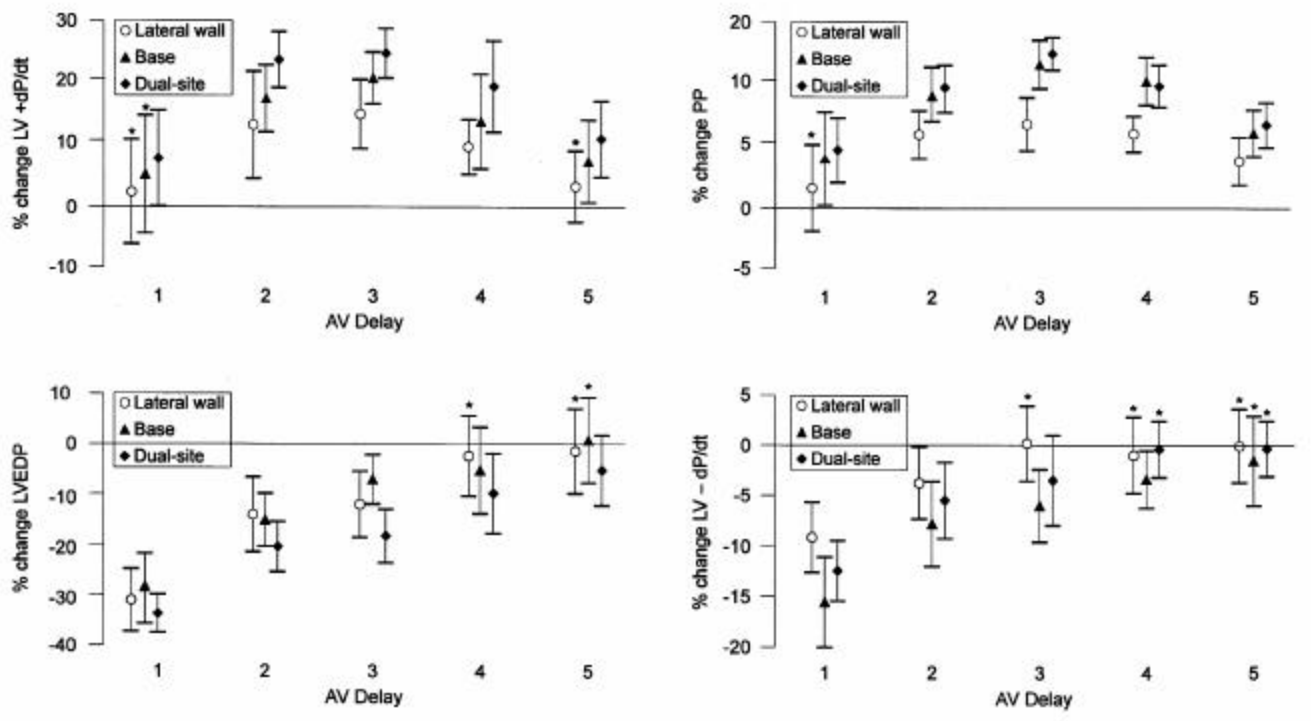

Figure 2. *Average percent change in hemodynamic parameters as a function of five normalized atrioventricular (AV) delays for each left ventricular pacing site. Tested AV delays were as follows: AV 1 = 8 ms; AV 5 = PR - 30 ms; AVs 2, 3 and 4 are equally distributed between AV 1 and AV 5. Data points are shown with SD bars. * values which are not significantly different from baseline (paired Student's t test, p > 0.05). LV +dP/dt = left ventricular pressure derivative maximum; -dP/dt = left ventricular pressure derivative minimum; LVEDP = left ventricular end-diastolic pressure; PP = pulse pressure.*

Table I. Comparison of percent changes in hemodynamic variables during pacing at different left ventricular sites.

Variable	Baseline	Pacing site			p			
		LW (% change)	B (% change)	Dual-site (% change)	ANOVA	LW vs B	LW vs dual-site	B vs dual-site
HR (b/min)	76 ± 14	0.7 ± 3.5	1.1 ± 2.6	0.6 ± 1.9	0.48	0.61	0.39	0.50
LV +dP/dt (mmHg/s)	790 ± 139	18 ± 5*	26 ± 7*	31 ± 6*	0.01	0.04	0.01	0.04
PP (mmHg)	41 ± 7	6 ± 3*	9 ± 5*	14 ± 5*	0.02	0.04	0.01	0.07
ASP (mmHg)	101 ± 13	4 ± 2*	7 ± 2*	8 ± 3*	0.04	0.03	0.02	0.09
LV -dP/dt (mmHg/s)	-653 ± 158	-0.2 ± 6	-5 ± 7*	-6 ± 7*	0.05	0.02	0.03	0.11
LVEDP (mmHg)	22 ± 8	-7 ± 13*	-8 ± 12*	-13 ± 14*	0.33	0.72	0.05	0.03
QRS (ms)	178 ± 18	12 ± 7*	2 ± 4	-22 ± 9*	0.006	0.009	0.001	0.005

Data are expressed as mean ± SD. ASP = aortic systolic pressure; B = left ventricular base; HR = heart rate; LV +dP/dt = left ventricular pressure derivative maximum; -dP/dt = left ventricular pressure derivative minimum; LVEDP = left ventricular end-diastolic pressure; LW = left ventricular lateral wall; PP = pulse pressure. Reported percent changes are averaged over all atrioventricular delays. * $p < 0.05$ vs baseline (two-sided paired Student's t test). ANOVA indicates p value for overall effect of pacing site on hemodynamic change; p values for pairwise comparisons are obtained through the Scheffe's method.

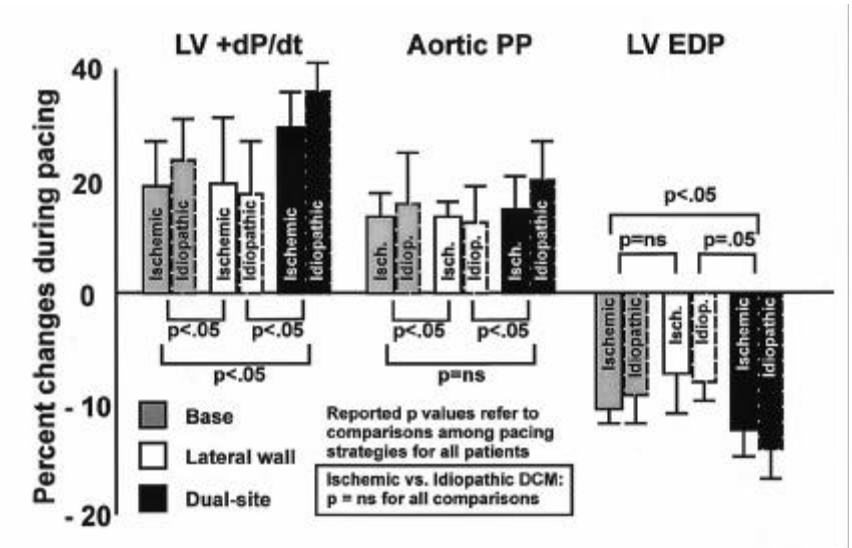

Figure 3. *Bar graph comparing hemodynamic changes produced by single-site pacing from the posterior base or lateral wall and by dual-site pacing. For each of the three pacing strategies, hemodynamic effects were not significantly different in patients grouped by etiology of heart failure (ischemic, n = 4; idiopathic, n =10). DCM = dilated cardiomyopathy. Other abbreviations as in figure 2.*

diastolic pressure for both single pacing sites as well as for dual-site pacing. However, in 2 out of 4 patients who had prior anterior myocardial infarction, the lateral wall site was significantly superior to the posterior base site for both changes in +dP/dt (21 ± 8 vs 16 ± 9%, $p < 0.05$) and pulse pressure (13 ± 5 vs 7 ± 3%, $p < 0.05$).

QRS duration and systolic response. To assess the dependence of the systolic contractile response to pacing on underlying ventricular conduction delay, percent change in +dP/dt was separately regressed onto baseline QRS duration (model 1), paced QRS duration (model 2), and percent changes in QRS (model 3), adjusting for pacing site effects (Fig. 4). Changes in +dP/dt were correlated positively with baseline QRS duration and negatively with paced QRS width. However, the predictive ability of models 1 and 2 was moderate ($r^2 = 0.28$ and 0.27, respectively), and was not independent of the pacing site effect. In model 3, the strong negative correlation between +dP/dt and percent QRS change yielded an r^2 of 0.56, with no independent effect of pacing site. Therefore, percent change in QRS duration itself explained 56% of the variation in contractility.

Discussion

The present study demonstrates that the left ventricular pacing site is a significant determinant of acute hemodynamic response. We are the first to have paced the failing human left ventricle from two sites simultaneously. Our major finding is that dual-site left ventricular pacing enhanced contractility significantly more than posterior base and lateral wall stimulation alone, whereas its effects on pulse pressure (a surrogate for changes in cardiac output)[8], relaxation and filling pressures were similar to those of single-site pacing at the posterior base.

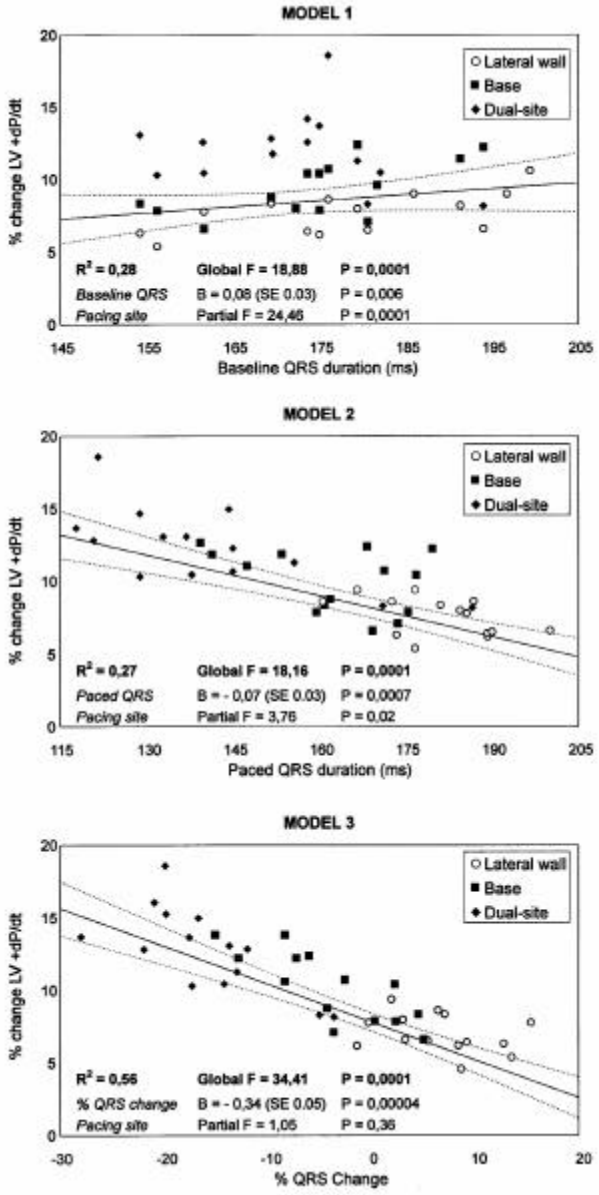

Figure 4. *Multiple regression analysis of percent changes in +dP/dt (dependent variable) modeled as a function of baseline QRS duration (model 1), paced QRS duration (model 2) and percent changes in QRS (model 3), adjusting for pacing site effects. Abbreviations as in figure 2.*

Effect of left ventricular lead position. We performed lateral wall pacing by positioning the lead distally in a lateral or postero-lateral coronary vein. Other acute studies have used different lead positions: Auricchio et al.[3] stimulated the left ventricular apex through epicardial leads implanted via minimal thoracotomy; Kass et al.[2] paced the left ventricular free wall in a position midway between the base and apex using a lateral marginal or anterior cardiac vein, and Blanc et al.[1] paced the lateral wall endocardially. These differences obviate a direct comparison with our results.

Our findings differ from those reported in a retrospective analysis of the PATH-CHF study[9], where the acute hemodynamic effects of single left ventricular pacing sites were compared in a small group of 5 patients. Leads were placed at 3 positions in the anterior vein (apex, mid-anterior, base) and at a mid-lateral site of the lateral vein. The study found that mid-lateral pacing was associated with the largest improvements in left ventricular +dP/dt and pulse pressure, whereas anterior base pacing was consistently the worst site. In our study, we prospectively chose to perform base pacing at a posterior or postero-lateral location. This area has been shown to be the site of latest left ventricular activation in the vast majority of patients with left bundle branch block and nonischemic or ischemic heart disease, except in the subgroup with large anterior scars[4,7]. This was confirmed in our study by simultaneous electrogram recordings at the posterior base and lateral wall during sinus rhythm, showing that posterior base was activated later in 86% of the cases. Thus, in most heart failure patients with left bundle branch block, pacing this site may best correct ventricular activation and contraction asynchrony. This hypothesis, bolstered by our finding of a narrower paced QRS during posterior base than lateral wall pacing, provides a possible explanation for the greater hemodynamic benefit associated with posterior base vs lateral wall stimulation in the present study.

Optimal ventricular resynchronization, however, was achieved through dual-site pacing, which reduced QRS duration by 22%. Indeed, ventricular activation can be expected to be faster when two independent wavefronts are simultaneously propagating, as confirmed by a previous study, in which combined pacing at two right ventricular sites in patients with left ventricular dysfunction produced significantly shorter QRS complexes than either site alone[10].

Paced left ventricular performance: underlying mechanisms. The mechanisms by which pacing-induced ventricular resynchronization translates to improved cardiac performance are poorly understood. It is presumed that the more myocardium activated by muscle conduction before the ectopic activation front enters the specialized conduction system, the wider the QRS complex, and the weaker the beat that occurs[11]. Two previous studies observed a direct relationship between baseline QRS width and systolic response to pacing, supporting the notion that the more dyssynchronous the heart at baseline, the more likely that pacing will ameliorate function[2,3]. In one of these studies[2], however, mechanical improvement was associated with an average QRS widening of approximately 11% during lateral wall stimulation, a result in keeping with our findings.

We observed a strong correlation between an increase in +dP/dt and percent reduction in QRS duration induced by pacing. However, this correlation accounted only for only 56% the variation in contractility (r^2 value of 0.56), suggesting that enhancement in left ventricular contractility depends only in part on more syn-

chronous activation. This is also supported by our finding that single-site pacing at the posterior base appears as effective as dual-site pacing, despite a slight increase in QRS duration.

Indeed, reduction of ventricular conduction delay does not necessarily indicate a normal sequence of left ventricular excitation and mechanics, which was not assessed in this study, but may be altered despite a narrow QRS.

Another major determinant of hemodynamics during atrial synchronous pacing is the programmed atrioventricular delay. Shortening the atrioventricular interval has been shown to diminish mitral regurgitation, lengthen diastolic filling time, and improve the filling pattern. Although we did not assess transmitral flow changes during pacing, our results showed that differences in hemodynamic responses among pacing sites exist at each programmed atrioventricular delay. Thus, optimizing the atrioventricular delay alone does not avert the need for choosing a specific pacing site to maximize hemodynamic effects.

Study limitations. Although our study population was small, it was a relatively selected sample of heart failure patients in spontaneous sinus rhythm with major left ventricular conduction delay. This type of abnormality has been found in as many as 82% of patients with severe heart failure related to dilated cardiomyopathy, either idiopathic or ischemic[12]. Furthermore, we sought to control for other possible sources of bias by testing different pacing strategies in the same patient, thus reducing interpatient variability. The pacing protocol was randomized and performed without knowing the programmed atrioventricular delay and pacing site, and the hemodynamic effects were analyzed over multiple beat sequences using a validated transient stimulation method, which produces immediate changes after the onset of pacing with return to baseline levels within 10 nonpaced beats, thus not affecting hemodynamics during the following pacing sequences[3,8].

We utilized an anatomical approach for lead placement without guidance from electrophysiologic parameters to optimize positioning of the pacing lead at the site where the latest electrogram is sensed. However, simultaneous electrogram recordings from the two pacing catheters allowed us to evaluate the relative activation timing and provide a rationale for the greater benefit achieved with posterior base vs lateral wall pacing in most of our patients.

In conclusion, this study supports the feasibility and safety of acute left ventricular pacing via the coronary veins in patients with dilated hearts. Our hemodynamic findings indicate that pacing from a site with more delayed activation compared with other possible lead positions may enhance contractile response, and that optimal left ventricular function can be obtained by pacing the two sites simultaneously. However, long-term controlled chronic pacing studies are needed to determine whether sustained hemodynamic improvement or a clinically apparent benefit will be obtained through these strategies.

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References

1. Blanc JJ, Etienne Y, Gilard M, et al. Evaluation of different ventricular pacing sites in patients with severe heart failure. Results of an acute hemodynamic study. Circulation 1997; 96: 3273-7.
2. 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: 1567-73.
3. 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.
4. LeClercq CC, Cazeau S, Le Breton H, et al. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. J Am Coll Cardiol 1998; 32: 1825-31.
5. Burkhoff D, Oikawa RY, Sagawa K. Influence of pacing site on canine left ventricular contraction. Am J Physiol 1986; 251: H428-H435.
6. Connelly DT, Kadhiresan V, Ding J, Liu L, Spinelli J. Hemodynamic effects of multisite ventricular pacing in dogs at short atrioventricular delay. (abstr) Pacing Clin Electrophysiol 1999; 22: 781.
7. Vassallo JA, Cassidy DM, Marchlinsky FE, et al. Endocardial activation of left bundle branch block. Circulation 1984; 69: 914-23.
8. Yu Y, Ding J, Liu L, et al. Experimental validation of pulse contour methods for estimating stroke volume at pacing onset. Proc 20th Int Conf IEEE Eng Med Biol Society 1998; 20: 401-4.
9. Auricchio A, Ding J, Kramer A, et al. Comparison of left ventricular pacing sites for heart failure patients. (abstr) Circulation 1998; 98: I-302.
10. Buckingham TA, Candinas R, Attenhofer C, et al. Systolic and diastolic function with alternate and combined site pacing in the right ventricle. Pacing Clin Electrophysiol 1998; 21: 1077-84.
11. Wiggers CJ. The muscular reactions of the mammalian ventricles to artificial surface stimulation. Am J Physiol 1925; 73: 346-78.
12. Wilensky RL, Yudelman P, Cohen AI. Serial electrocardiographic changes in idiopathic dilated cardiomyopathy confirmed at necropsy. Am J Cardiol 1988; 62: 276-83.