# Patient Selection for Cardiac Resynchronization Therapy

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## Abstract

Left or biventricular (BiV) pacing, or cardiac resynchronization therapy (CRT) is a new treatment for patients with advanced congestive heart failure (CHF) and left bundle branch block (LBBB). This therapy is based on the theory that synchronous BiV pacing is able to reduce atrioventricular (AV), inter- and intraventricular dyssynchrony (DYS). Although there is convincing evidence that CRT increases the left ventricular ejection fraction (LVEF), decreases mitral regurgitation (MR), and improves symptoms caused by heart failure, and reduces combined end points of all-cause mortality and hospitalization, the proportion of non-responders (NR) to this therapy has been described and high as about one third to one half of patients with heart failure and LBBB. Here we review factors that may be responsible for this relatively high prevalence, and the ways for more accurate patient selection ***(Iranian Heart Journal 2003; 4 (4):49-56).***

**Key words**: Cardiac resynchronization ■Non-responder ■ Dyssynchrony ■ Patient Selection

An essential subject in CRT is the identification of patients most likely to respond, that is those patients with significant AV and/or inter- and/or intraventricular mechanical DYS who would most likely benefit from CRT.[1-4] Almost all prospective, controlled studies on CRT have been conducted in patients with severe CHF and a wide QRS complex.[5-9] In CRT's original assumption, a wide QRS, a marker of electrical DYS, is correlated with mechanical ventricular DYS. While this may be correct, it is worth mentioning that some patients with wide QRS do not suffer from prominent mechanical ventricular DYS, and conversely, that some patients with narrow QRS may be candidates for CRT due to significant mechanical DYS.[10] Further more, Bordachar et al.[42] have recently shown that QRS duration dose not reliably predict the ventricular DYS in patients with RV- based pacing.

On the other hand, although short-term experimental studies have shown that the patients with wider QRS complexes have a greater immediate mechanical response to CRT,[11-15] most long-term studies have shown that QRS duration dose not predict response to CRT; and QRS narrowing does not predict functional improvement following CRT,[16-22] although in some studies the opposite has been observed.[23-24] In addition, in Ansalone's series,[20] 10 percent of CRT recipients experienced worsening of symptoms and mechanical DYS. The above-mentioned issues may explain (at least in part) the relatively high percentage of NR patients who have been selected for CRT based on QRS duration as a surrogate for mechanical ventricular DYS (Table I). Thus, direct assessment of mechanical ventricular DYS may have greater accuracy in patient selection for CRT and help to reduce the number of NR.

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This review overviews the CRT and presents recent studies on predictors of long-term response and its impact on patient selection for CRT.

**Table 1: Factors that can increase the number of non - responders to CRT**

- Improper patient selection (improper assessment of DYS)
- Inadequate medical therapy
- Progression of underlying cardiac disease
- Persistent or worsening dyssynchrony after CRT
- Improper lead (RV and/or LV) position
- Improper AV and V-V interval programming (V-V interval optimization may by possible by using indices of mechanical DYS)
- Lack of regular follow- up and device reprogramming

### *Cardiac Resynchronization Therapy: Overview*

CRT is indicated in selected patients with heart failure. It is estimated that as high as 15-20% of patients with heart failure are candidates for this therapy based on the current guidelines. Currently patients with New York Heart Association Class III-IV despite optimal drug therapy who have LVEF ≤ 35%, QRS duration > 130 ms, and LV end diastolic dimension ≥ 55 mm, are candidates for BiV pacing. The first BiV pacing system was implanted in 1994 and approved by the Food and Drug Administration in 2001.[43] CRT restores contractile synchrony in hearts with mechanical DYS due to conduction delay. This is achieved by stimulating the most delayed segment of the ventricle so it can contract in synchrony with the other territories. Two leads, one in the left ventricle (LV) and one in the RV, are used in CRT. These leads are paced simultaneously, or with a small delay. CRT can restore synchrony and improve cardiac performance without increased myocardial oxygen consumption. CRT improves patient's quality of life as shown by enhanced exercise capacity and reduced hospitalization. The recently conducted "Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure" (COMPANION) trial and meta-analyses suggest that CRT has a mortality benefit, particularly when combined with a defibrillator. To date, the widely accepted criteria for DYS are based on QRS duration, but in the near future, the assessment of mechanical DYS may play an important role in the selection and follow-up of patients and the optimization of the therapy.

Ventricular DYS induced by conduction abnormality or RV pacing generates changes in ventricular loading condition, alters myocardial blood flow and causes a non-uniform myocardial metabolism.[44] In addition, experimental evidence suggests that stress kinase is significantly increased in late activated region and phospholamban is significantly decreased.[46] In addition $Ca^{2+}$-ATPase in sarcoplasmic reticulum is decreased in early activated region.[47] Ventricular DYS induces changes in contractile and noncontractile myocardial cellular elements and extracellular matrix and therefore accelerates the process of ventricular remodeling. In conclusion, ventricular DYS contributes to ventricular dilation and failure. Whether ventricular DYS is the cause and/or consequence of heart failure is still under some debate.[45]

CRT targets four level of mechanical DYS in the failing heart which includes: (1) AV DYS, (2) Interventricular DYS, (3) Intraventricular DYS and (4) Intramural DYS.[48] CRT, by synchronizing the cardiac function at the above-mentioned levels, restores coordinated ventricular contraction. This in turn improves LV loading condition, myocardial metabolic efficiency, systolic function and contractility with no or slight positive effect on myocardial diastolic function.[11,12] Pacing from lateral wall especially close to the posterior papillary muscle decreases systolic and presystolic MR.[49] When combined, these various effects of CRT improve the cardiac function and symptoms of heart failure. In addition CRT, through the above-mentioned mechanisms, induces reverse remodeling of the failing LV. Therefore,

after a period of CRT, contractility improves and LV size decreases. Reverse remodeling even renders LV sizes normal in some patients.

### *Definition of Responder and Non-Responder*

The definition of responder has been a major setback in predicting the long-term response to CRT. Different studies have used different criteria for positive response to CRT [22, 23, 25-27] (Table II).

**Table II: Different definitions of positive response to CRT**

| Reference | Definition of Responder |
|---|---|
| Alonso [23] | Improved symptoms at least one NYHA class down and at least 10% increase in peak $V_{O2}$ for at least 6 months |
| Reuter [22] | Improved symptoms and NYHA class with decrease in the QOL* score |
| Cazeau [25] | Improved NYHA class associated with improved echocardiographic derived indices of DYS (see text) |
| Pizalis [26] | Reduction in LV end systolic volume index ≥ 15% |
| Nelson [27] | Improvement of more than 25% in LV dP/dt max |

* Quality of life

A consensus on definition of positive response to CRT is needed to better identify the potential candidates of CRT and assess the outcome in different clinical trials. The data from COMPANION study[44] revealed that in patients who just received optimum medical therapy, systolic blood pressure decreased progressively which is a marker for progression of underlying heart disease. This phenomenon was not observed in CRT group. Thus stabilization of patients even without symptomatic improvement (currently classified as non-responder patients) may be considered at least to some extent a benefit rather than failure of CRT.

### *Predictors of Long-Term Response*

Based on limitations of QRS duration, various recent studies have assessed different indices of ventricular mechanical DYS in CRT candidates as predictors of long-term response [21, 25-32] (Table III).

**Table III: Predictors of long-term response to CRT**

| Reference | Variable | Findings |
|---|---|---|
| Saxon [21] | Myocardial performance index (MPI) | The degree of abnormality of the Doppler-derived MPI strongly predicts a remodeling response with long-term CRT |
| Cazeau [25] | LV pre-ejection interval (LPEI)<br>Interventricular delay (IVD)<br>LV filling time (LVFT) | LPEI ≥ 140 ms, with or without IVD ≥ 40 ms; LVFT < 40% of cardiac cycle; and overlap between the end of lateral wall contraction and onset of LV filling were predictors of response to CRT |
| Pizalis [26] | Septal posterior wall motion delay (SPWMD) | In patients with advanced CHF and LBBB, baseline SPWMD is a good predictor of the occurrence of reverse remodeling after CRT, thus suggesting its usefulness in identifying patients likely to benefit from BiV pacing. |
| Nelson [27] | Mechanical dyssynchrony measured by tagged MRI; QRS duration; and LV dP/dt max | Mechanical dyssynchrony measured by MRI is a key predictor for pacing efficacy in DCM; and combining information about QRS (i.e. QRS duration > 155 ms), and basal dP/dt max (< 700) provides an excellent tool to identify maximal responders. |
| Breithardt [28] | Lateral septal (LS) wall contraction phase difference assessed by echocardiography | This study provides a noninvasive screening method for patients with CHF, so that those likely to have increased contractile function with CRT can be selected and so that CRT after implantation can be optimized. Baseline asynchrony indicated by LS > 25° predicts a contractile function benefit from CRT |
| Søgaard [29] | Delayed longitudinal contraction (DLC) detected by tissue Doppler imaging (TDI) | The extent of the LV base segments displaying DLC, detected by TDI before pacemaker implantation, predicted long-term efficacy of CRT. The QRS duration failed to predict CRT efficacy. |
| Yu [30, 31] | Dyssynchrony Index (DI)= SD of LV 12 segment time to peak myocardial systolic contraction measured by TDI | A preimplant dyssynchrony index of 32.6 ms (2 SDs from mean of 88 normal controls) was able to totally segregate responders from non-responders of BiV. |
| Breithardt [32] | TDI-derived strain rate imaging (SRI) | SRI might provide the optimal noninvasive approach to determine the nature of baseline regional contractile DYS and to assess the changes with pacing to define better patient selection criteria for CRT. |
| Bax[40] | Intra LV DYS assessed by TDI | Septal lateral wall delay≥60 ms was the only predictor of improvement in LVEF. |

These studies have provoked a re-evaluation of the correlation between electrical DYS (QRS duration) and mechanical ventricular DYS and have shown that the larger the mechanical ventricular DYS, no matter how it is measured, the larger the benefit from CRT. So, direct assessment of ventricular DYS may increase the accuracy of patient selection for CRT and reduces the number of NR. Cazeau and his colleagues [25] have recently reported the results of the first prospective study on selection of candidates for CRT based on mechanical rather than electrical criteria. They included 66 patients with LVEF≤ 35%; NYHA functional class III or IV despite optimum medical therapy; and one or more of the following echocardiographic criteria of AV, inter- and intraventricular DYS: (a) left ventricular filling time < 40% of the cardiac cycle; (b) Left pre-ejection interval >140 ms with or without interventricular delay >40 ms; and (c) presence of overlap between the end of lateral wall contraction and onset of LV filling. An immediate positive response (see Table II for the definition) was observed in 85% of patients with partial or complete improvement of above mentioned echo-derived parameters of ventricular mechanical DYS. This marked improvement is encouraging, but must be interpreted carefully, because these results were observed in the immediate postoperative follow up, in an uncontrolled study design. Direct assessment of ventricular mechanical DYS could also help to select the best timing delay between RV and LV stimulation by minimizing post implant indices of inter- and intraventricular DYS (Table III). Further prospective studies are needed to assess and compare different criteria for patient selection in CRT.

***Effect of Pacing Site on Response to Cardiac Resynchronization***

Initial reports suggested that stimulation site in the left ventricle (LV) may play an important role in the response to CRT. These studies have suggested that the LV lateral wall is the "preferred site" for CRT in patients with wide QRS and LBBB, since the best acute hemodynamic results were obtained by stimulating the LV lateral wall.[33, 34] Butter [35] showed that in 30 patients, 18 with dilated cardiomyopathy (DCM) and 12 with coronary heart disease (CAD), CRT with LV free wall stimulation produced significantly better LV systolic performance (LV dP/dt max) compared with anterior stimulation, regardless of mode of pacing (univentricular or BiV). They suggested that further studies are necessary to prove the clinical superiority of the LV free wall as a preferred site for long-term CRT and its outcome. Ansalone[36] compared the efficacy of BiV at the most delayed wall (assessed by tissue Doppler imaging) of the LV and at other LV walls in 31 patients with DCM. They found that lateral wall was the most delayed site in 60%, and anterior wall in 40% of patients. Myocardial performance index, LV end systolic volume index (LVESVi), LVEF, and exercise load improved significantly in all patients. However, the greatest improvement was found in those who paced at the most delayed site. However, they observed no deference between concordant and discordant groups in long-term improvement of NYHA functional class. Søgaard[29] evaluated the correlation between etiology of heart failure and the location of the most delayed segments assessed by TDI. In CAD patients (n=11), the most delayed segments were anteroseptal (10/11) whereas in DCM patients (n=9) they were lateral (8/9). Ansalone[4] in his recent review suggested that (a) according to the anatomic distribution of the left bundle branch

fascicles, the greatest delay can be located at the inferior wall, the lateral wall, or the posterior wall; (this finding was also recently confirmed[41]) (b) we cannot say whether it could be more effective to pace the most delayed or the most dyskinetic region; and (c) the beneficial effect of CRT on LV volume and dimension did not correlate with acute hemodynamic parameters and/or improvement of functional class. Gasparini [37] performed the largest single center, long-term study that evaluated the effect of different pacing sites in 158 patients treated with CRT. Their data surprisingly showed that LVEF, LVESVi, and exercise load improved significantly during long-term follow up, regardless of LV pacing site. Further prospective large-scale studies are necessary to resolve the controversies surrounding this issue. Two recently published trials[38, 39] have added new controversies regarding whether BiV and LV pacing gave similar beneficial effects. In PATH-CHFII study[38] patients with QRSd between 120-150 ms failed to benefit from LV pacing based CRT while in Achili et al.[39] study in 52 patients, who were chosen for CRT based on echocardiographic criteria, BiV pacing improved NYHA class, LVEF, LVESd, LVEDd and MR in all patients regardless of QRS duration and there was no difference in the magnitude of benefit in patients with QRSd≥120 ms compared to those with QRSd<120ms. Weather different mode of pacing or different selection criteria resulted in this discrepancy is not clear and warrants further studies.

### *Unresolved Issues and Future Directions*

Although much has been learned over the past several years regarding patient selection in CRT, there are major unresolved issues. First, a consensus definition of responder is lacking and is of paramount importance for patient selection. New methods examining regional DYS hold promise for generating a DYS index that could improve patient selection compared to present more indirect methods, but optimal method(s) for assessment of mechanical ventricular DYS and their role in prospective identification of responders are still unresolved issues. The optimal method of therapy itself is unresolved. Questions remain as whether BiV stimulation is needed, whether multisite left-heart stimulation would enhance the efficacy, whether lateral wall is the best LV pacing site or, where the optimal location of RV pacing is, and what the best timing delay is between RV and LV stimulation. Resolving these issues will help to better identify potential candidates for CRT.

## References


1. Ritter, P: Editorial *PACE*. 2003; 26: 136.
2. Auricchio A, Spinelli, JC: The promise of resynchronization therapy. Who (and how many) will benefit? CEPR 2003;7:17-26.
3. Galizio N, Pesce R, Valero E, et al: Which patients with congestive heart failure may benefit from biventricular pacing? PACE 2003; 26: 158–161.
4. Ansalone G, Giannantoni P, Ricci R, et al: Biventricular pacing in heart failure: back to basics in the pathophysiology of left bundle branch block to reduce the number of non-responders. Am J Cardiol 2003; 91: 55F–61F.
5. 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: 873–80.
6. Abraham WT: Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). J Card Fail 2000; 6: 369–80.

7. Abraham WT: Late breaking clinical trials: results from late breaking clinical trial sessions at ACC 2001. J Am Coll Cardiol 2001; 38: 604–5.

8. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S: Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in Cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002; 40: 111-8.

9. Auricchio A, Stellbrink C, Sack S, et al: For Pacing Therapies in Congestive Heart Failure (PATH-CHF) Study Group. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002; 39: 2026-33.

10. Yu CM, Yang H, Lau CP, et al: Regional left ventricle mechanical asynchrony in patients with heart disease and normal QRS duration: implication for biventricular pacing therapy. PACE 2003; 26: 562-570.

11. 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: The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Circulation 1999; 99: 2993–3001.

12. Kass DA, Chen CH, Curry C, Talbot M, Berger R, Fetics B, et al: Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation 1999; 99: 1567–73.

13. Nelson GS, Curry CW, Wyman BT, et al: Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000; 101: 2703–9.

14. Alonso C, Leclercq C, Victor F, et al: Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. Am J Cardiol 1999; 84: 1417–21.

15. Burkhoff D, Oikawa RY, Sagawa K: Influence of pacing site on canine left ventricular contraction. Am J Physiol 1986; 251: H428–35.

16. Anselme F, Savoure A, Schuster I: Is QRS duration a good predictor of right to left ventricular asynchrony? Comparison with conventional Doppler and tissue Doppler imaging criteria. (abstract). PACE 2002; 25: 528.

17. Garrigue S, Bader H, Reuter S: QRS duration and morphology are not reliable parameters to identify heart failure patients with left ventricular dyssynchrony: An Echocardiographic doppler tissue imaging study. (abstract) PACE 2002; 25: 547.

18. Kass DA: Ventricular dyssynchrony and mechanisms of resynchronization therapy. Eur Heart J 2002; 4:D23–D30.

19. Zardini M, Tritto M, Bargiggia G, et al: on behalf of the InSync Italian Registry Investigators: The InSync Italian Registry: analysis of clinical outcome and considerations on the selection of candidates to left ventricular resynchronisation. Eur Heart J 2000; 2: J16–J22.

20. Ansalone G, Giannantoni P, Ricci R, et al: Doppler myocardial imaging in patients with heart failure receiving biventricular pacing treatment. Am Heart J 2001; 142:881–896.

21. Saxon LA, De Marco T, Schafer J, et al: Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling. Circulation 2002; 105: 1304-1310

22. Reuter S, Garrigue S, Barold SS, et al: Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure. Am J Cardiol 2002; 89: 346-350.

23. Alonso C, Leclercq C, Victor F, et al: Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. Am J Cardiol 1999; 84: 1417-1421.

24. Kim WY, Sogaard P, Mortensen PT, et al: Three-dimensional echocardiography documents haemodynamic improvement by biventricular pacing in patients with severe heart failure. Heart 2001; 85: 514-520.

25. Cazeau S, Bordachar P, Jauvert G, et al: Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: a prospective study. PACE 2003; 26:137–143.

26. Pitzalis MV, Iacoviello M, Romito R, et al: Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol 2002; 40: 1615–22.

27. Nelson GS, Curry CW, Wyman BT, et al: Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000; 101: 2703-2709.

28. Breithardt OA, Stellbrink C, Kramer AP, et al: Echocardiographic quantification of left ventricular asynchrony predicts an acute hemodynamic benefit of cardiac resynchronization therapy. J Am Coll *Cardiol* 2002; 40: 536–45.

29. Sogaard P, Egeblad H, Kim WY, et al: Tissue doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. J Am Coll Cardiol 2002; 40: 723–30.

30. Yu CM, Fung WH, Lin H et al: Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 2003; 91: 684–688.

31. Yu CM, Chau E, Sanderson JE, et al: Tissue doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105: 438-445.

32. Breithardt OA, Stellbrink C, Herbots L, et al: Cardiac resynchronization therapy can reverse abnormal myocardial strain distribution in patients with heart failure and left bundle branch block. J Am Coll Cardiol 2003; 42: 486 –94.

33. Auricchio A, Klein H, Tockman B, et al: Transvenous biventricular pacing for heart failure: can the obstacles be overcome? Am J Cardiol 1999; 83:136D–142D.

34. 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.

35. Butter C, Auricchio A, Stellbrink C, et al: on behalf of Pacing Therapy for Chronic Heart Failure II (PATH-CHF-II) Study Group: Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001; 104: 3026-3029.

36. Ansalone G, Giannantoni P, Ricci R, et al: Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. J Am Coll Cardiol 2002; 39: 489 –99.

37. Gasparini P, Mantica M, Galimberti P, et al: Is the left ventricular lateral wall the best lead implantation site for cardiac resynchronization therapy? PACE 2003; 26: 162–168.

38. Auricchio A, Stellbrink C, Butter C, et al: Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. J Am Coll Cardiol 2003; 42: 2109 –16.

39. Achilli A, Sassara M, Ficili S: Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and “narrow” QRS. J Am Coll Cardiol 2003; 42: 2117–24.

40. Bax JJ, Marwick TH, Molhoek SG, et al: Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure Before pacemaker implantation. Am J Cardiol 2003; 92: 1238–1240.

41. Fung JW-H, Yu CM, Yip G, et al: Variable left ventricular activation pattern in patients with heart failure and left bundle branch block. Heart 2004; 90: 17–19.

42. Bordachar P, Garrigue S, Lafitte S, et al: Interventricular and intra-left ventricular electromechanical delays in right ventricular paced patients with heart failure: implications for upgrading to biventricular stimulation. Heart 2003; 89: 1401–1405.

43. Leclercq C, Hare JM: Ventricular resynchronization: current state of the art. Circulation 2004; 109: 296-299.

44. Auricchio A, Abraham WT: Cardiac Resynchronization Therapy: Current State of the Art Cost Versus Benefit. Circulation 2004; 109: 300 –307.

45. Willerson JT, Kereiakes DJ: Cardiac resynchronization therapy helpful now in selected patients with CHF. Circulation 2004; 109: 308 –309.

46. Kajstura J, Zhang X, Szoke E, et al. The cellular basis of pacing-induced dilated cardiomyopathy: myocyte cell loss and myocyte cellular reactive hypertrophy. Circulation 1995; 92: 2306–2317.

47. Spragg DD, Leclercq, Loghmani M, et al. Regional alterations in protein expression in the dyssynchronous failing heart. *Circulation*. 2003;108: 929–932.

48. Auricchio A, Fantoni C, Regoli F, et al: Characterization of left ventricular activation in patients with heart failure and left bundle branch block. Circulation In press.

49. 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: 3273–3277.