The Heart Surgery Forum #2009-1129
12 (6), 2009 [Epub December 2009]
doi: 10.1532/HSF98.20091129

Online address: http://cardenjennings.metapress.com

Detecting Volume Responders prior to Implantation of a Cardiac Resynchronization Therapy Device via Minithoracotomy: The Septal Flash as a Predictor of Immediate Left Ventricular Reverse Remodeling

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ABSTRACT

Background: Although cardiac resynchronization therapy (CRT) is well established as an adjunctive heart failure treatment, a 30% rate of nonresponders poses a challenge to improve the detection of potential responders prior to device implantation. A previously proposed mechanism-based approach to patient selection suggests in part that the septal flash is a sign of intraventricular dyssynchrony, which is predictive of CRT responsiveness.

Methods: In this pilot study, data from 5 consecutive patients (2 women and 3 men; mean ± SD age, 62 ± 9 years) referred for CRT device implantation via a minithoracotomy were analyzed. Intraoperative transthoracic and/or transesophageal echocardiography data, as well as Doppler myocardial imaging data, were acquired before and after CRT device activation. The septal flash was defined as an early ventricular inward and outward septal motion within the isovolumic contraction period and was imaged with gray-scale imaging or tissue Doppler color M-mode. Reverse remodeling was defined as a reduction in the left ventricular end-systolic volume (LVESV) of ≥10%. The right atrial and right ventricular leads were placed transvenously, and the LV screw-in lead was positioned epicardially on the lateral wall.

Results: The septal flash was detected preoperatively in all patients and resolved immediately after the onset of biventricular pacing. Immediately following pacemaker activation, we measured a significant reduction in the LVESV (248 ± 99 mL versus 190 ± 100 mL, $P = .01$) and an increase in the ejection fraction (19% ± 5% versus 28% ± 5%, $P = .01$) in all patients. Likewise, a significant increase in the postactivation dP/dt (rate of LV pressure change) measured noninvasively from the mitral regurgitation trace was noted in all patients (298.6 ± 58.0 mm Hg/s versus 601.7 ± 111.2 mm Hg/s, $P = .001$).

Conclusion: The preoperative presence of the septal flash is a valid predictor of the response to CRT. Immediately after CRT device activation, the septal flash disappears, and LV reverse remodeling and an increase in contractility are observed.

Presented at the 6th Annual Meeting of the Euro-Asian Bridge, Dubrovnik, Croatia, April 27-28, 2009.

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INTRODUCTION

Although cardiac resynchronization therapy (CRT) is well established as an adjunctive heart failure treatment, the 30% rate of nonresponders poses a challenge to better define potential candidates before device implantation [Cleland 2005]. Several echocardiographic parameters for predicting CRT responders have been proposed. Most of these parameters are based on measurements of time intervals between velocities of the segments of the left ventricular (LV) walls, but they have been shown to add no further benefit for predicting the response to CRT [Chung 2008]. A recently proposed mechanism-based approach to patient selection is based on multiple independent mechanisms, the correction of which leads to CRT response [Parsai 2009a, 2009b]. Along with atrioventricular (AV) and interventricular dyssynchrony, the septal flash has been defined as an echocardiographic sign of LV intraventricular dyssynchrony that occurs as a mechanical consequence of left bundle branch block (LBBB)-induced activation of the LV. Furthermore, the disappearance of the septal flash after CRT implantation, which occurs in almost 90% of patients at a median follow-up of 6 months, has been shown to provide high sensitivity and specificity in detecting the response to CRT.

We hypothesized that the immediate response to CRT implantation observed from the point of LV intraventricular dyssynchrony can be detected/predicted by resolution of the septal flash (immediately following device activation), thus demonstrating that the presence of a septal flash prior to CRT pacing is a direct consequence of early septal activation in LBBB, which is correctable by biventricular pacing.

METHODS

Patients

In this pilot study, we studied 5 consecutive patents referred for CRT pacemaker implantation by means of a left anterior minithoracotomy. These patients underwent a preoperative echocardiographic dyssynchrony-screening study,

which is routinely performed in our center, that identified them as potential CRT responders on the basis of the presence of the septal flash. The group consisted of 3 male and 2 female patients (mean ± SD age, 62 ± 9 years). All patients fulfilled the current guideline criteria for CRT device implantation (ejection fraction [EF] <35%, QRS duration >120 milliseconds, New York Heart Association class III-IV, undergoing optimal pharmacotherapy) [Hunt 2005]. All patients underwent coronary angiography evaluation prior to CRT device implantation to exclude significant obstructive coronary artery disease.

Informed, signed consent was obtained from all patients, and the study was conducted in accordance with the ethics guidelines of the hospital.

Echocardiographic Imaging

Standard cardiac ultrasound data were acquired intraoperatively before and after CRT device implantation by means of a Vivid 7 ultrasound scanner equipped with a 2.5-MHz phased-array transducer (GE Healthcare, Horten, Norway). The postactivation echocardiography sequences were obtained after AV interval optimization was performed, as described below.

Standard 2-dimensional data, spectral Doppler flows, and myocardial velocity data were obtained from the parasternal and apical views. The echocardiographic data were obtained for 3 complete cardiac cycles. In patients with lower-quality transthoracic views, the intraoperative study was extended with a transesophageal echocardiography (TEE) study (6-MHz transducer; GE Healthcare) with the mid-esophageal and transgastric views.

Offline analysis was performed with dedicated software (EchoPAC; GE Healthcare). LV size was measured from the M-mode images [Devereux 1986; Schiller 1989]. The LVEF and LV volumes were measured by the Simpson biplane method from the apical 4- and 2-chamber views [Schiller 1989]. Pulse wave Doppler traces of the LV outflow acquired from the 4-chamber view were analyzed by planimetry of the Doppler envelope to obtain the stroke volume, which was calculated by multiplying the LV outflow tract (LVOT) velocity time integral by the LVOT area (the LVOT diameter was measured from the 2-dimensional image of the parasternal long axis). In addition, cardiac output was calculated as the product of the stroke volume and heart rate. Transmitral flow velocities were obtained by positioning the pulse wave sample volume at the tips of the mitral leaflets in the 4-chamber view. dP/dt (the rate of change in LV pressure) was measured from the continuous wave traces of mitral regurgitation, from which the presystolic mitral regurgitation was assessed as well (when available) [Bargiggia 1989; Chung 1992].

Velocity data were acquired by Doppler myocardial imaging (DMI) as data superimposed on the underlying 2-dimensional gray-scale image. The necessary high frame rate was obtained by optimizing the angle of insonation and the depth of imaging, as previously described [Weidemann 2001]. Special attention was paid to avoid aliasing within the image by adjusting the values of the pulse-repetition frequency (between 2.0 and 2.5 kHz).

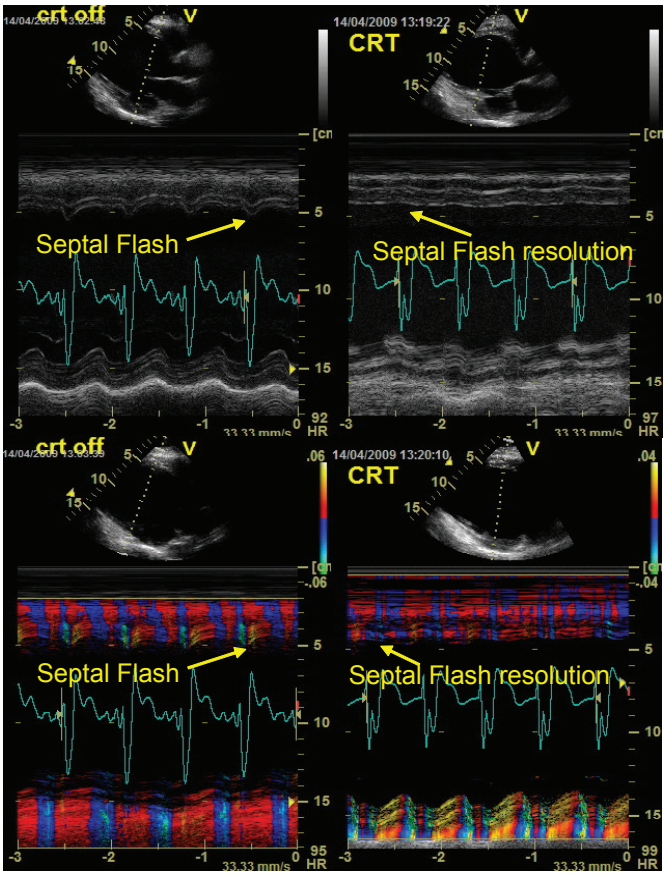

Figure 1. The septal flash, ie, early septal thickening/thinning (occurring within the duration of the QRS complex), visualized on the parasternal long-axis view with gray scale (top left) or by tissue Doppler color M-mode (bottom left), in which the flash is imaged as a rapid change in color during the isovolumic contraction time. Resolution of the septal flash is seen immediately after implantation of the cardiac resynchronization therapy (CRT) device (top and bottom, right).

The early septal fast inward/outward motion (thickening/thinning), ie, the septal flash, was visualized on the parasternal short- or long-axis view with either gray scale or tissue Doppler color M-mode, in which the septal flash was imaged as a rapid change in color during the isovolumic contraction time (IVCT) (Figure 1, left). The amplitude of this septal motion was measured as the maximal excursion in the parasternal (or transgastric, in cases of TEE imaging) short- or long-axis view or as a transverse M-mode in an apical 4-chamber view. Furthermore, the septal flash was identified on the DMI radial velocity data as an early, fast, and short-lived negative declination shortly after the QRS onset, where its peak velocity was measured [Parsai 2009a, 2009b].

Minithoracotomy and CRT Device Optimization

The right atrial and ventricular leads were placed transvenously. Actual placement of the LV lead was performed through a left anterior minithoracotomy, with the LV screw-in lead positioned epicardially on the LV lateral wall.

Basic Clinical and Echocardiographic Measurements*

	Before CRT Device Implantation	After CRT Device Implantation	*P*
SBP, mm Hg	111 ± 7	115 ± 13	NS
DBP, mm Hg	67 ± 8	66 ± 9	NS
HR, /min	67 ± 8	74 ± 13	NS
LVIDd, cm	7.6 ± 1.3	7.2 ± 1.2	.01
LVIDs, cm	6.6 ± 1.4	6.2 ± 1.1	.05
LVESV, mL	248 ± 99	180 ± 89	.01
LVEDV, mL	302 ± 109	247 ± 107	.01
EF, %	19 ± 5	28 ± 5	.01
MR dP/dt	299 ± 58	602 ± 111	.001
Septal flash, mm	10.2 ± 6.9	1.5 ± 0.7	.02
Septal flash, cm/s	4.8 ± 2.3	1.4 ± 0.2	.01
IVCT, ms	181 ± 23	61 ± 51	.001
IVRT, ms	147 ± 109	109 ± 75	NS
IVD, ms	60 ± 39	29 ± 11	NS
SV, mL	59.0 ± 6.2	66.8 ± 14.1	NS
CO, mL	4.5 ± 0.8	4.7 ± 1.0	NS

*CRT indicates cardiac resynchronization therapy; SBP, systolic blood pressure; NS, not statistically significant; DBP, diastolic blood pressure; HR, heart rate; LVIDd, left ventricular internal diastolic dimension at end-diastole; LVIDs, left ventricular internal diastolic dimension at end-systole; LVESV, left ventricular volume at end-systole; LVEDV, left ventricular volume at end-diastole; EF, ejection fraction; MR dP/dt, change in pressure over time derived from the mitral regurgitation jet; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; IVD, interventricular delay; SV, stroke volume; CO, cardiac output.

Immediately after CRT device activation, a simplified AV-delay screening was performed. In cases of a truncated or absent transmitral A wave (indicating too short of an AV delay) or a merged E and A wave (indicating too long of an AV delay), the initial AV optimization was performed with the iterative method.

Statistical Analysis

The data for continuous variables are expressed as the mean ± SD, and the data for pre- and postimplantation groups were compared with a paired *t* test. Categorical variables are expressed as percentages. For categorical variables, group comparisons were made with the chi-square test. Results with *P* values <.05 were considered statistically significant.

RESULTS

Patient Characteristics

During an extensive diagnostic investigation of the etiology of heart failure, significant coronary artery disease was detected by coronary angiography in only 1 of 5 patients. This patient underwent a percutaneous coronary intervention. Therefore, coronary artery disease was absent or resolved in all patients at least 1 year prior to CRT. The diagnosis for the remaining patients (80%) was idiopathic dilated cardiomyopathy. Neither the values for systolic and diastolic blood pressures nor those for the heart rate before CRT device implantation differed significantly from the values after device implantation (Table). All patients were in sinus rhythm before and after the procedure. The duration of the QRS interval decreased significantly after CRT (182 ± 36 milliseconds versus 136 ± 22 milliseconds, *P* = .05). The mean duration of the PR interval was reduced by biventricular pacing as well (184 ± 43 milliseconds versus 138 ± 17 milliseconds, not statistically significant).

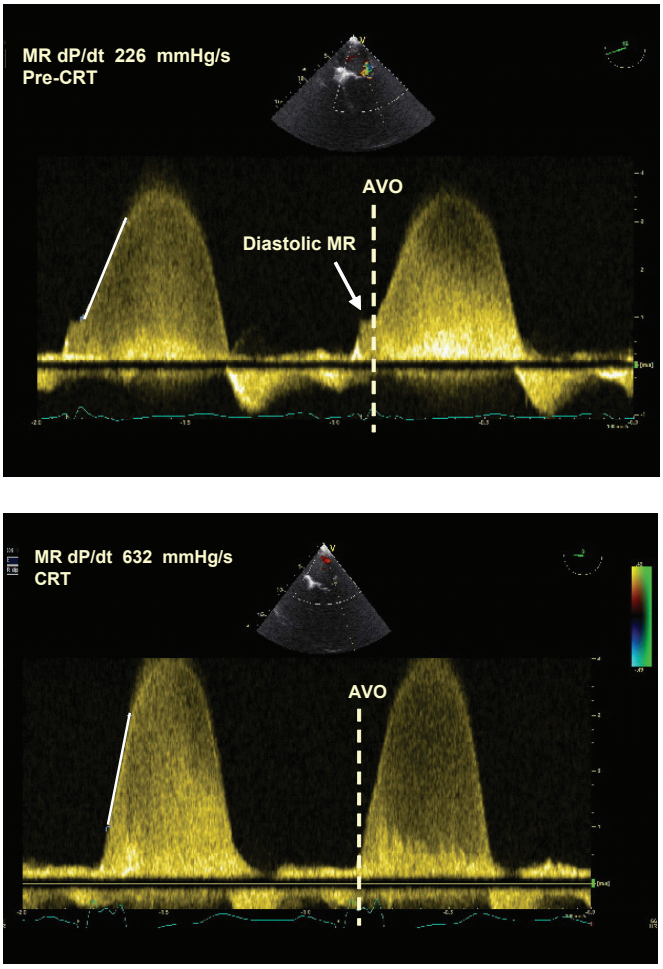

Figure 2. Transesophageal echocardiography imaging of significant improvement in dP/dt values derived from the mitral regurgitation (MR) trace before (top) and immediately after (bottom) implantation of the cardiac resynchronization therapy (CRT) device. Furthermore, presystolic MR present before biventricular pacing because of a long atrioventricular delay (top, arrow) is resolved by CRT (bottom). AVO, aortic valve opening.

Echocardiographic Imaging

The Table summarizes the echocardiographic measurements. Significant reductions in the LV end-diastolic

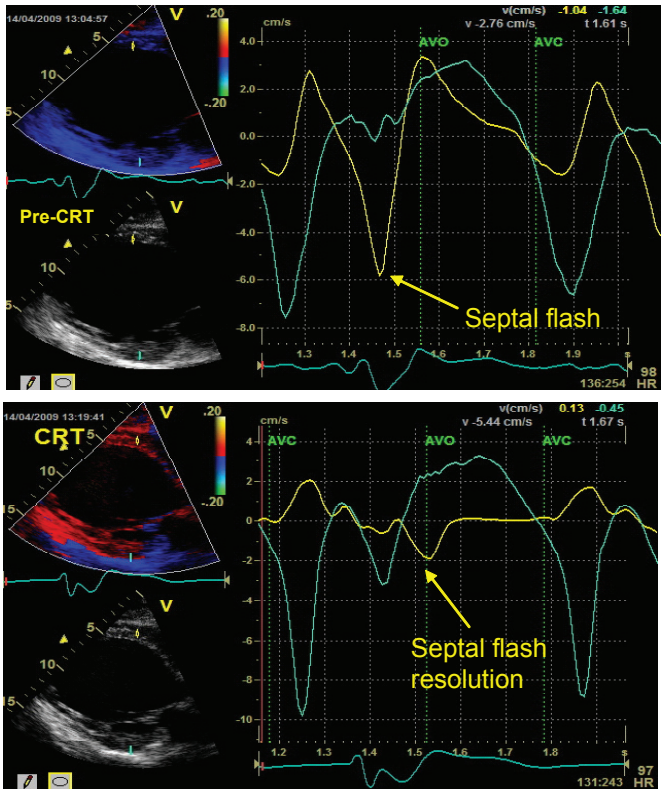

Figure 3. The septal flash seen in the preimplantation radial velocity data from Doppler myocardial imaging is an early, fast, and short-lived negative declination that occurs shortly after the QRS onset (top). The septal flash is immediately resolved by cardiac resynchronization therapy (CRT), which normalizes the radial velocities, which become mirrored (bottom).

dimension (7.6 ± 1.3 cm versus 7.2 ± 1.2 cm, P = .01), the end-systolic volume (248 ± 99 mL versus 180 ± 89 mL, P = .01), and the end-diastolic volume (302 ± 109 mL versus 247 ± 107 mL, P = .01) were noted immediately after activation of the CRT device. Reverse remodeling, defined as a reduction in the LV end-systolic volume (LVESV) of ≥10% [Yu 2005], was found in all patients (mean LVESV reduction after CRT device activation, 27% ± 13%; range, 16%-46%). An immediate increase in the EF was noted in all patients as well (mean ΔEF, 9% ± 6%; range, 4%-19%). Furthermore, the dP/dt obtained noninvasively from the mitral regurgitation trace (obtainable from 4 of 5 patients) showed immediate improvement after CRT device activation in all of these patients (mean ΔdP/dt, 303.2 ± 64.2 mm Hg/s; range, 213-363.2 mm Hg/s) (Figure 2). Increases in stroke volume and cardiac output were noted after CRT device activation, although the increases were not statistically significant. Three (60%) of the 5 patients had moderate or severe mitral regurgitation preoperatively, which was immediately reduced by at least 1 grade after CRT device activation.

The septal flash was detected before CRT device activation in all patients and was diminished immediately after the onset of biventricular pacing by a mean of 80% (which was measured from the amplitude of this early, rapid septal motion imaged by gray scale or by tissue Doppler color M-mode), leading to a normalization of septal motion (Figure 1). Likewise, the peak velocity of the septal flash measured from the DMI radial velocity data sets was decreased in the entire study group as well (mean decrease, 70%; Table, Figure 3).

Significant interventricular dyssynchrony (expressed as a delay of ≥40 milliseconds between the left and right ventricular preejection periods measured from the aortic and pulmonary outflow Doppler velocity traces, respectively) was present in 60% (3 of 5) patients and was resolved by biventricular pacing in all cases.

A significantly prolonged IVCT found before activation of the CRT device was significantly reduced by CRT (181 ± 23 milliseconds versus 61 ± 51 milliseconds, P < .001). The isovolumic relaxation time was generally shorter than the IVCT before pacing, when it was somewhat prolonged, although without statistical significance.

Assessment of the transmitral traces before the onset of biventricular pacing showed an absence of significant AV dyssynchrony in 2 patients, whereas a filling pattern corresponding to a prolonged AV delay was revealed in the other 2 patients (fusion of the transmitral E and A wave and presence of presystolic mitral regurgitation). This pattern was resolved by CRT in one of these patients, and the other had persistent sinus tachycardia intraoperatively, presumably causing the ongoing E and A wave fusion after CRT device activation (regardless of attempts to optimize the AV delay). Finally, 1 patient had signs of restrictive filling prior to biventricular pacing that reverted to pseudonormal filling after CRT device activation.

DISCUSSION

In this study, we have shown that patients who fulfilled the guideline criteria for CRT device implantation and who presented with a septal flash as a marker of intraventricular dyssynchrony showed an acute volume response as well as contractility recruitment immediately after activation of the CRT device.

Ventricular remodeling is in the first instance a response to an inherent problem within either the myocardium or the environment in which it has to work and is a compensatory attempt to preserve the heart's function. In the long term, imminent mechanical disadvantages within this abnormal situation will lead to irreversible myocardial damage and then to ventricular dysfunction and heart failure [Bijnens 2009]. With the new approaches to treatment available for heart failure patients, reverse remodeling is emerging as a new entity for patients for whom progressive LV dilatation and deterioration in contractile function show a partial reversibility instead of stagnation [Sutton 2007].

A substantial number of studies that assessed survival and clinical response (change in New York Heart Association class, exercise capacity, and quality of life) have acknowledged the benefits of CRT, whereas the current knowledge on the mechanisms and effects of the volume response is far less evident.

Generally, CRT leads to a significant decrease in LV size (optimally assessed by measuring LV volumes), as well as an increase in the LVEF [Linde 2002; Yu 2002; Molhoek 2004; Cleland 2005]. Various time periods have been chosen for patient follow-up for documenting signs of reverse remodeling. These periods range from as early as 1 month to 18 months, when LV reverse remodeling and associated clinical improvement are sustained [Linde 2002; Abraham 2003; Molhoek 2004; Cleland 2005]. Recently published long-term results from the Cardiac Resynchronization in Heart Failure (CARE-HF) trial reported on the long-term effects of CRT on LV reverse remodeling [Ghio 2009]. After a mean study period of 29 months after CRT device implantation, CRT was demonstrated to induce sustained LV reverse remodeling, with the most marked effects occurring within the first 3 to 9 months (the earliest follow-up being 3 months after device implantation) and further improvement occurring at subsequent assessments.

The onset of reverse remodeling induced by CRT is not well documented, however. In the present study, we have demonstrated that in patients with true LBBB-induced intraventricular dyssynchrony (as defined by the septal flash), reverse remodeling occurs immediately after the activation of biventricular pacing. All patients within this group had preoperative evidence of the septal flash (a marker of intraventricular dyssynchrony) that was promptly abolished by biventricular pacing.

The preoperative presence of the septal flash was thought to be a direct mechanical consequence of LBBB-induced early septal activation that develops force and shortens against the opposite lateral wall, which is still latent. Because the septum is contracting against a reduced load, it will move faster than normally, resulting in the septal flash. The septum thus pulls the lateral wall until the latter becomes electrically activated, at which point the lateral wall starts to contract and then begins to influence the septum, resulting in a "rocking" apical motion in the ejection phase [Bijnens 2009; Parsai 2009b].

Besides a prompt, significant decrease in LV volumes and a concomitant increase in the EF, we also observed a marked increase in the noninvasively obtained dP/dt in this study. This increase reflects a direct, positive influence of CRT on LV contractility.

CONCLUSION

In this group of patients with overt heart failure and LBBB, immediate reverse remodeling (volume response) to biventricular pacing occurred in all patients after CRT device activation. The reverse remodeling appears to be a direct effect of correcting the underlying conduction abnormality and its mechanical consequence, which can readily be imaged by echocardiography as the septal flash.

ACKNOWLEDGMENTS

This work was partially financed by the Ministry of Science, Education and Sport of the Republic of Croatia (projects nos. 108-1081875-1991 [M. Čikeš] and 108-1081875-1993 [D. Miličić]), as well as by the Spanish Industrial and Technological Development Centre (CDTI) under the CENIT Programme (CDTEAM Project) and the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 224495 (euHeart project) (B. Bijnens).

REFERENCES

Abraham WT, Leon AR, Young JB. 2003. Benefits of cardiac resynchronization therapy sustained for 18 months: results from the MIRACLE program [abstract]. Circulation 108(suppl IV):IV-629. Abstract 2859.

Bargiggia GS, Bertucci C, Recusani F, et al. 1989. A new method for estimating left ventricular dP/dt by continuous wave Doppler echocardiography: validation studies at cardiac catheterization. Circulation 80:1287-92.

Bijnens BH, Cikes M, Claus P, Sutherland GR. 2009. Velocity and deformation for the assessment of myocardial dysfunction. Eur J Echocardiogr 10:216-26.

Chung ES, Leon AR, Tavazzi L, et al. 2008. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 117:2608-16.

Chung N, Nishimura RA, Holmes DR Jr, Tajik AJ. 1992. Measurement of left ventricular dP/dt by simultaneous Doppler echocardiography and cardiac catheterization. J Am Soc Echocardiogr 5:147-52.

Cleland JGF, Daubert J-C, Erdmann E, et al, for the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. 2005. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 352:1539-49.

Devereux RB, Alonso DR, Lutas EM, et al. 1986. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 57:450-8.

Ghio S, Freemantle N, Scelsi L, et al. 2009. Long-term left ventricular reverse remodelling with cardiac resynchronization therapy: results from the CARE-HF trial. Eur J Heart Fail 11:480-8.

Hunt SA, Abraham WT, Chin MH, et al, American College of Cardiology; American Heart Association Task Force on Practice Guidelines, American College of Chest Physicians, International Society for Heart and Lung Transplantation, Heart Rhythm Society. 2005. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 112:e154-235.

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

Molhoek SG, Bax JJ, van Erven L, et al. 2004. Comparison of benefits from cardiac resynchronization therapy in patients with ischemic cardiomyopathy versus idiopathic dilated cardiomyopathy. Am J Cardiol 93:860-3.

Parsai C, Baltabaeva A, Anderson L, Chaparro M, Bijnens B, Sutherland GR. 2009. Low-dose dobutamine stress echo to quantify the degree of remodelling after cardiac resynchronization therapy. Eur Heart J 30:950-8.

Parsai C, Bijnens B, Sutherland GR, et al. 2009. Toward understanding response to cardiac resynchronization therapy: left ventricular dyssynchrony is only one of multiple mechanisms. Eur Heart J 30:940-9.

Schiller NB, Shah PM, Crawford M, et al. 1989. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 2:358-67.

Sutton MS, Keane MG. 2007. Reverse remodelling in heart failure with cardiac resynchronisation therapy. Heart 93:167-71.

Weidemann F, Kowalski M, D'hooge J, Bijnens B, Sutherland GR. 2001. Doppler myocardial imaging. A new tool to assess regional inhomogeneity in cardiac function. Basic Res Cardiol 96:595-605.

Yu CM, Bleeker GB, Fung JW, et al. 2005. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. Circulation 112:1580-6.

Yu CM, Chau E, Sanderson JE, et al. 2002. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 105:438-45.