HOSPITAL CHRONICLES 2012, 7(4): 202–207

EDITORIAL

The Contribution of Echocardiography in Discerning Responders to Cardiac Resynchronization Therapy

Stamatis Kapetanakis, MD, MRCP

St. Thomas' Hospital, London, UK

ABSTRACT

Cardiac resynchronisation therapy (CRT) has emerged as an effective intervention in chronic heart failure and its use has significantly increased over the last decade. Although the major selection criterion for CRT candidates relates to the QRS duration, clinical results on the assessment of systolic dyssynchrony by various echocardiographic tools are accumulating. It appears clear now that a reproducible method of assessing systolic dyssynchrony is potentially useful if the parameter also predicts a favourable response to CRT. Conventional echocardiographic tools, such as M-Mode, are simple and quick, though may be limited by the lack of ability to assess complex patterns of systolic dyssynchrony in fine details. Newer tools, such as tissue Doppler imaging (TDI) and real-time 3D Echo, appear promising and are becoming readily available in all the high-end echocardiographic machines. Different algorithms for assessing left ventricular mechanical dyssynchrony have been proposed and further prospective, multi-center studies are needed to define a "gold standard" technique and to support the clinical utility of these techniques.

KEY WORDS: *heart failure; echocardiography; biventricular pacing; cardiac resynchronization; left bundle branch block; mechanical dyssynchrony*

Abbreviations

CRT = cardiac resynchronization therapy
ECG = electrocardiogram
LBBB = left bundle branch block
LV = left ventric-le(-ular)
LVMD = left ventricular mechanical dyssynchrony
SDI = systolic dyssynchrony index
SPWMD = septal-to-posterior wall motion delay
TDI = Tissue Doppler Imaging

Correspondence to:
Stam Kapetanakis, MD, St. Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK;
Tel: +44 (0)20 7188 7188;
e-mail: stam66@mac.com

Manuscript received February 17, 2010; Revised manuscript accepted August 24, 2012

INTRODUCTION

Cardiac resynchronization therapy (CRT) has emerged as an effective intervention in chronic heart failure and its use has significantly increased over the last decade. Selection criteria for CRT are widely based on selection criteria from validation trials in biventricular pacing.[1-3] Almost all of these selected patients with low left ventricular (LV) ejection fraction, New York Heart Association (NYHA) class II, III or IV on maximal achievable therapy and prolonged QRS duration as a surrogate marker for left ventricular mechanical dyssynchrony (LVMD).

Experimental data in infra-nodal conduction abnormalities, such as left bundle branch block (LBBB), have demonstrated an abnormal LV contraction pattern, characterised by the separation of the LV into early and late contracting units. Typically, there is early septal contraction with pre-stretch of the lateral LV free wall, followed by late systolic contraction of the lateral wall and stretching of the septum resulting in a very inefficient mechanical contraction often described as "paradoxical". Additionally the presence of LBBB has been clearly linked to worse outcomes in chronic heart failure.[4,5]

*presented in part at the "Athens Cardiology Update 2010" Symposium in Athens on March 26, 2010
Disclosures: The author has received honoraria from Philips Medical Systems for teaching

In heart failure patients however, a large variation in electrical and mechanical activation have been reported with both opposite patterns of contraction and no significant delay in segmental contraction also occurring. Conversely, septal-lateral delays have been noted in patients with normal QRS duration and heart failure. This heterogeneity is likely to be linked to the varying degrees of involvement of conduction pathways and myocardium as well as the underlying pathology.

This may in part explain the variable response to CRT using prolonged QRS duration as a patient selection tool, as almost all studies report a non-responder rate of 20-30%. Given the complexity of instrumentation, the potential risks associated with implantation as well as the medical costs associated with the procedure, many investigators are seeking more reliable markers of response to biventricular pacing. There is now a large body of evidence suggesting that echocardiographic markers of LVMD may be much more accurate than presence of a prolonged QRS in identifying responders. Timing regional contraction by various methods has led to a number of parameters, which have all been shown, at least in single-center studies, to be superior to QRS prolongation in identifying responders, albeit their predictive value could not be confirmed in a multicenter setting and thus they may not be recommended yet as routine selection criteria for CRT beyond current guidelines.[6,7]

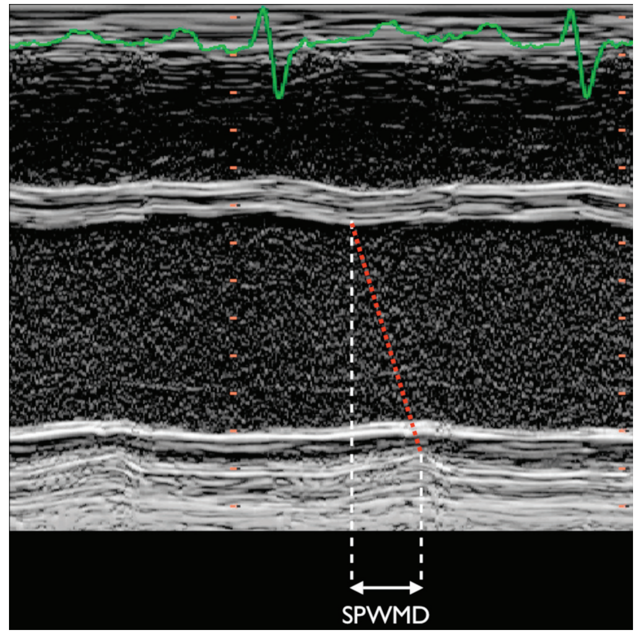

FIGURE 1. Septal to Posterior Wall Motion Delay (SPWMD): Time from peak anteroseptal excursion to peak posterior excursion.

M-MODE AND DOPPLER ECHOCARDIOGRAPHY

M-Mode echocardiography is perhaps the most widely available imaging modality, and is well suited to examine delay in contraction of the basal/mid anteroseptal and posterior segments. Pitzalis and colleagues examined the predictive value of the septal-to-posterior wall motion delay (SPWMD) in 20 patients with predominantly non-ischemic LV dysfunction and found that a SPWMD ≥130 ms had overall accuracy in predicting reverse LV remodelling post CRT of 85%, compared to 65% for presence of prolonged QRS duration (Fig. 1).[8,9]

Doppler echocardiography, also available on all echo platforms, may be used to time onset of blood flow from one chamber to the next relative to the ECG and may be used to assess delay in LV and right ventricular contraction (Fig. 2). In the CARE-HF trial this was used as a diagnostic criterion for LVMD, however its value in predicting response to CRT remains to be determined.[10]

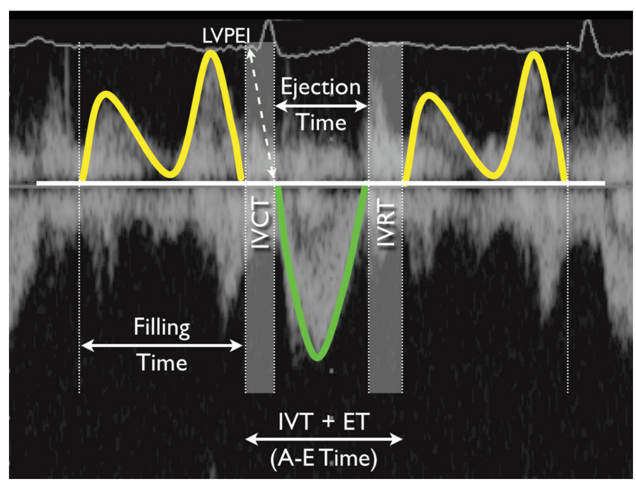

FIGURE 2. Pulsed wave Doppler indices of LV function and dyssynchrony. LV pre-ejection interval (LVPEI)—time from the onset of QRS to the onset of ejection. IVCT = isovolumic contraction time; IVRT = isovolumic relaxation time; Total isovolumic time (t-IVT) = 60 – ([IVCT + IVRT] X Heart rate); Myocardial Performance Index (MPI) = (IVCT + IVRT)/ejection time, or (A-E Time – ET)/ET. LV = left ventric-le(-ular).

TISSUE DOPPLER IMAGING

Tissue Doppler Imaging (TDI) allows timing of regional systolic and diastolic events relative to the QRS complex and provides many potentially useful parameters of LVMD. Through a simple mathematical transformation, regional strain rate and strain can also be derived as measures of regional function and co-ordination. TDI requires high frame rate as the velocity events of myocardium (isometric contraction, peak systolic velocity, diastolic velocities) are brief and may be missed with low frame rate acquisition. TDI may be acquired either with pulsed Doppler or by colour-coding tissue velocities in 2D echocardiography and requires several separate acquisitions taking care to align the longitudinal motion of the region of interest with the ultrasound beams and maintaining high frame rates (Fig. 3). Analysis is performed online or offline to quantify any of a number of measures of LVMD.

Garrigue and colleagues used pulsed TDI to examine the septal to lateral mitral annular delay in patients with prolonged QRS duration and were able to demonstrate that LVMD could even be detected in patients with right bundle branch block and improved significantly with CRT.[11] Colour coded TDI for similar analysis was investigated by Bax and colleagues, who found that a septal-to-lateral delay of ≥60 ms was a strong predictor of response to CRT.[12] However, using just 2 points to assess global LV dyssynchrony has the theoretical disadvantage of underestimating LVMD, particularly if maximal delay occurs in territories other than the septal or lateral walls. Ansalone et al demonstrated that using pulsed TDI in 5 positions predicted improvement in exercise capacity, symptoms and echocardiographic improvement.[13]

Yu and colleagues utilized a more complex model with colour-coded TDI by using the Standard Deviation of Times to peak Systolic velocity (TS) in the 12 non-apical segments (TSSD) and have reported several studies showing both excellent accuracy in predicting outcomes from CRT but also superiority to other methods. In a study of 56 patients examining 18 different 2D echo and TDI parameters, Yu's team found

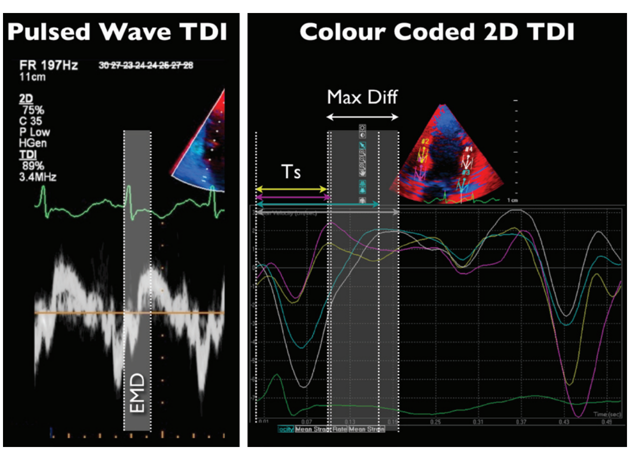

FIGURE 3. Left panel: Pulsed wave tissue Doppler at a basal segment showing a typical velocity trace. Electromechanical delay (EMD) is time from onset of QRS to peak sustained systolic velocity. Some investigators have used time from R-wave instead while others measure time to onset or end of systolic velocity, which may be easier to recognise and therefore are possibly more reproducible. Right panel: Typical TDI velocity trace which may be obtained by either pulsed or colour-coded 2D TDI, illustrating myocardial events: Si: Early systolic velocity, corresponding to isovolumic contraction. Sm: maximum sustained systolic velocity. E' and A': Diastolic events corresponding to E and A waves on transmitral pulsed flow Doppler. TDI = tissue Doppler imaging.

that TSSD was the best predictor of reverse remodelling post CRT with an area under the curve in ROC analysis of 0.94.[14-17]

Strain delay index, defined as the sum of difference between end-systolic and peak-strain across 16 segments, allows for quantification of the wasted contraction or gain of myocardial contractility expected after cardiac resynchronization therapy (CRT). In the MUSIC study, the strain delay index was evaluated in 189 patients receiving CRT[18] and found to be correlated with reverse remodelling (r = 0.61, P <0.0001 for all) in both wide and narrow QRS patients and ischemic and non-ischemic patients. Decrease in strain delay index after CRT was greater in responders. Strain delay index >25% identified responders to CRT (positive and negative predictive value of 80 and 84 %, respectively) with 6% inter-observer variability.

Recent data indicate that classical regional strain pattern analysis may be a more promising predictor and superior to time-to-peak methods.[19] The classical pattern consisted of a region(s) of early systolic stretching and late contraction with early contraction and late stretching in the opposite wall(s). In 67 CRT patients, the presence of a classical pattern showed 91% specificity and 95% sensitivity for response (n=43, 65%) and performed significantly better than time-to-peak parameters in prediction of response to CRT (P <0.001).[19]

LOW-DOSE DOBUTAMINE ECHOCARDIOGRAPHY

Low-dose dobutamine echocardiography was used in 31 patients to evaluate response to CRT.[20] The dobutamine-induced increase in ejection fraction (contractile reserve) was measured, and the most mechanically delayed segment was identified. Those who had a contractile reserve of >20% and a left ventricular lead position concordant with the mechanically delayed segment were significantly more likely to have an echocardiographic response at 6 months (80% vs 29% of those who did not have these parameters, p = 0.018) and had an improved 2-year heart failure hospitalization-free survival rate (90% vs 33%, p = 0.006). In this study the authors concluded that low-dose dobutamine echocardiography provides information that can help to predict responders to CRT. Similarly, in the LODO-CRT trial using a dobutamine stress echocardiography test,[21] multivariable analysis identified left ventricular contractile reserve and interventricular dyssynchrony as independent predictors of CRT response among 221 CRT patients. The concomitant presence of both factors showed 99% specificity and 83% sensitivity in detecting responders.

REAL-TIME 3D ECHO

Real-Time 3D Echo (RT3DE) provides a unique and powerful tool for quantification of LVMD and response to CRT (Fig. 3 & 4). A dataset containing the entire LV is acquired from 4 consecutive cardiac cycles within 4-6 seconds and can be analysed online or offline by creating a model of the LV cavity throughout the cardiac cycle; by dividing the global volume into 16 or 17 sub-volumes corresponding to the standard myocardial

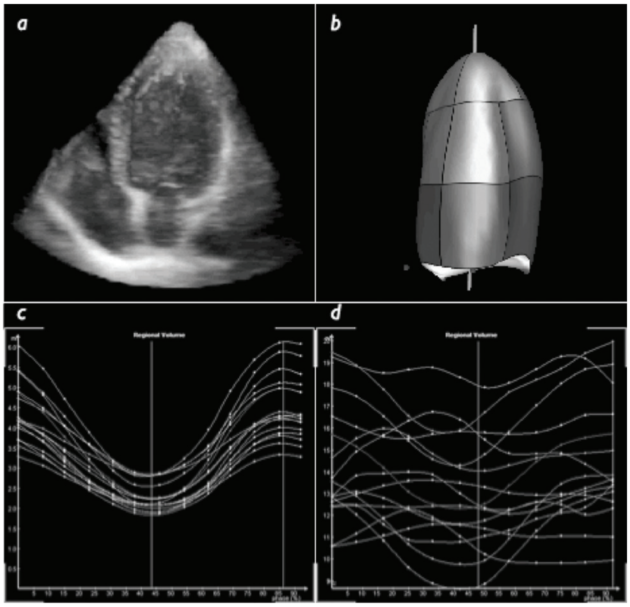

FIGURE 4. Top row: 3D Echo cropped into a 4-chamber view (left) and volumetric analysis (right). Lower row: Based on volumetric analysis, regional time-volume curves can be derived for each standard myocardial segment. A normal, synchronous ventricle (left) contrasts strongly with a dyssynchronous ventricle with severe dysfunction (right).

segments, time-volume curves for each segment can be used to assess the time to segmental contraction.

Kapetanakis et al used the standard deviation of times to peak segmental contraction corrected for the R-R interval (Systolic Dyssynchrony Index, SDI) in a cross-sectional study of 89 healthy volunteers and 174 patients and demonstrated that in keeping with previous studies, dyssynchrony was independent of QRS duration and could be reproducibly quantified in patients with LV dysfunction.[22,23] A subgroup of patients underwent CRT with standard indications and the SDI was the only predictor in multivariate analysis to predict responders. Similar findings were reported more recently by other investigators.[24-28]

Using the same volumetric analysis the mathematical model of the LV cavity may be divided into 800 sub-volumes and the times to minimum volume (peak contraction) for each volume may be represented as a parametric display, providing a high resolution display of mechanical delay as a static image. What is perhaps more useful is Contraction Front Mapping, a dynamic display of how every point in the LV reaches peak contraction. Emerging data suggest that this to visually assess patterns of mechanical contraction is also a useful way to assess suitability for CRT, which may be used alongside temporal measures of dyssynchrony.

CONCLUSION

Clinical results on the assessment of systolic dyssynchrony by various echocardiographic tools are accumulating. It appears clear now that a reproducible method of assessing

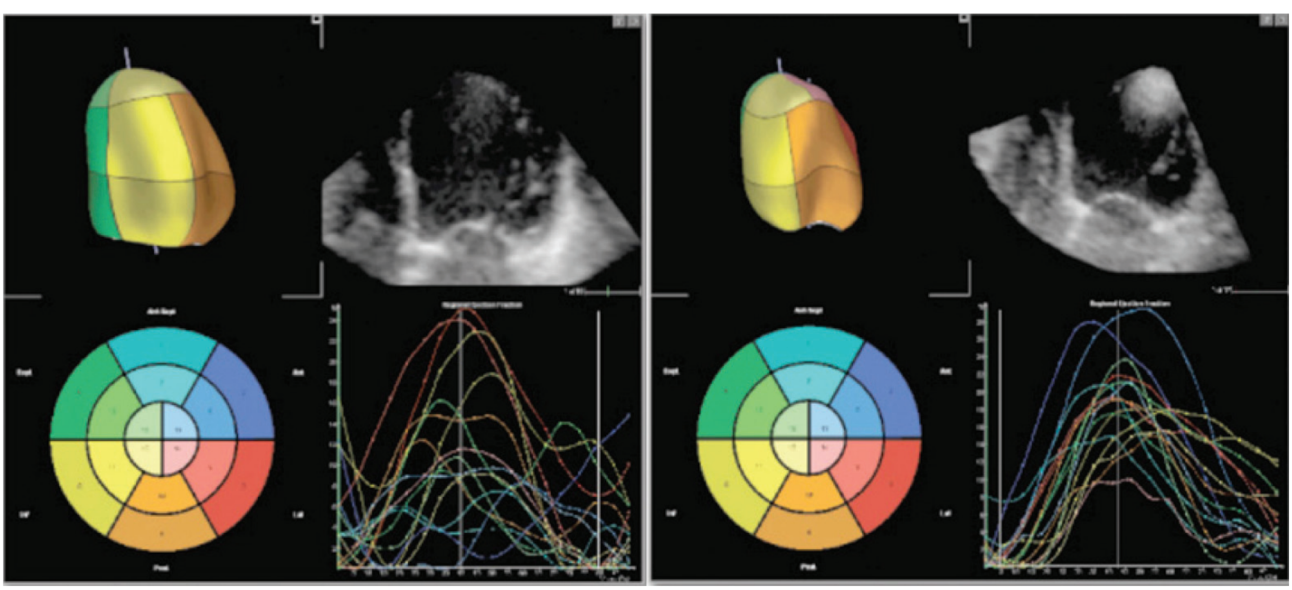

FIGURE 5. 3D Echo and volumetric quantification in a patient pre and post CRT. Prior to CRT there is wide dispersion of times to minimum regional volumes (regional contraction) and a high SDI. Post CRT, there is significant improvement in synchronicity of regional contraction with much less dispersion of times to minimum volume and lower SDI. CRT = cardiac resynchronization therapy; SDI = systolic dyssynchrony index.

systolic dyssynchrony is potentially useful if the parameter also predicts a favourable response to CRT. Conventional echocardiographic tools, such as M-Mode, are simple and quick, though may be limited by the lack of ability to assess complex patterns of systolic dyssynchrony in fine details.[29] Newer tools, such as TDI and Real-Time 3D Echo, appear promising and are becoming readily available in all the high-end echocardiographic machines. Different algorithms for assessing LVMD have been proposed and further prospective, multi-center studies are needed to define a "gold standard" technique and to support the clinical utility of these techniques. For now, intraventricular dyssynchrony measured between the septum and left ventricular free wall may be our best tool to discern CRT responders,[7] although data are emerging that classical regional strain pattern analysis, consisted of a region(s) of early systolic stretching and late contraction with early contraction and late stretching in the opposite wall(s), may be a more promising predictor and superior to time-to-peak methods.[19] Although there is no consensus yet with regards to a single ideal echocardiographic parameter to define mechanical dyssynchrony and accurately predict response to CRT, it appears that there may be a consensus that the presence of less baseline left ventricular mechanical dyssynchrony, as assessed via echocardiography, predicts nonresponders. Indeed, many studies have demonstrated the predictive value of echocardiographically assessed LV mechanical dyssynchrony with sensitivities and specificities near 80% to 90%. Thus, it appears that LV mechanical dyssynchrony is an independent predictor of response to CRT; despite similar QRS complex durations, nonresponder patients show significantly less LV mechanical dyssynchrony than responder patients.[30]

REFERENCES

1. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003;289:2685-2694.
2. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002;40:111-118.
3. Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E. Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling. *Circulation* 2002;105:1304-1310.
4. Cowie MR, Mosterd A, Wood DA, et al. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-225.
5. Kearney MT, Zaman A, Eckberg DL, et al. Cardiac size, autonomic function, and 5-year follow-up of chronic heart failure patients with severe prolongation of ventricular activation. *J Card Fail* 2003;9:93-99.
6. Chung E, Leon A, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;117:2608–2616.
7. Seo Y, Ito H, Nakatani S, et al; J-CRT investigators. The role of echocardiography in predicting responders to cardiac resynchronization therapy. *Circ J* 2011;75:1156-1163.
8. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol* 2002;40:1615-1622.
9. Pitzalis MV, Iacoviello M, Romito R, et al. Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy. *J Am Coll Cardiol* 2005;45:65-69.
10. Cleland JG, Daubert JC, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;27:1928-1932.
11. Garrigue S, Jais P, Espil G, et al. Comparison of chronic biventricular pacing between epicardial and endocardial left ventricular stimulation using Doppler tissue imaging in patients with heart failure. *Am J Cardiol* 2001;88:858-862.
12. 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.
13. 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.
14. 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.
15. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. 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.
16. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart* 2003;89:54-60.
17. Yu CM, Bax JJ, Monaghan M, Nihoyannopoulos P. Echocardiographic evaluation of cardiac dyssynchrony for predicting a favourable response to cardiac resynchronisation therapy. *Heart* 2004;90 Suppl 6:vi17-22.
18. Lim P, Donal E, Lafitte S, et al. Multicentre study using strain delay index for predicting response to cardiac resynchronization therapy (MUSIC study). *Eur J Heart Fail* 2011;13:984-991.
19. Risum N, Jons C, Olsen NT, et al. Simple regional strain pattern analysis to predict response to cardiac resynchronization therapy: rationale, initial results, and advantages. *Am Heart J* 2012;163:697-704.
20. Altman RK, McCarty D, Chen-Tournoux AA, et al. Usefulness of low-dose dobutamine echocardiography to predict response and outcome in patients undergoing cardiac resynchronization

therapy. *Am J Cardiol* 2011;108:252-257.
21. Gasparini M, Muto C, Iacopino S, et al. Low-dose dobutamine test associated with interventricular dyssynchrony: a useful tool to identify cardiac resynchronization therapy responders: data from the LOw dose DObutamine stress-echo test in Cardiac Resynchronization Therapy (LODO-CRT) phase 2 study. *Am Heart J* 2012;163:422-429.
22. Kapetanakis S, Cooklin M, Monaghan MJ. Mechanical resynchronisation in biventricular pacing illustrated by real time transthoracic three dimensional echocardiography. *Heart* 2004;90:482.
23. Kapetanakis S, Kearney MT, Siva A, Gall N, Cooklin M, Monaghan MJ. Real-time three-dimensional echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony. *Circulation* 2005;112:992-1000.
24. Soliman OII, Geleijnse ML, Theuns DAMJ, et al. Usefulness of left ventricular systolic dyssynchrony by real-time three-dimensional echocardiography to predict long-term response to cardiac resynchronization therapy. *Am J Cardiol* 2009;103:1586-1591.
25. Soliman OII, van Dalen BM, Nemes A, et al. Quantification of left ventricular systolic dyssynchrony by real-time three-dimensional echocardiography. *J Am Soc Echocardiogr* 2009;22:232-239.
26. Delgado V, Sitges M, Vidal B, et al. Assessment of left ventricular dyssynchrony by real-time three-dimensional echocardiography. *Rev Esp Cardiol* 2008;61:825-834.
27. Lau C, Abdel-Qadir HM, Lashevsky I, Hansen M, Crystal E, Joyner C. Utility of three-dimensional echocardiography in assessing and predicting response to cardiac resynchronization therapy. *Can J Cardiol* 2010;26:475-480.
28. Tani T, Sumida T, Tanabe K, et al. Left ventricular systolic dyssynchrony index by three-dimensional echocardiography in patients with decreased left ventricular function: comparison with tissue Doppler echocardiography. *Echocardiography* 2012;29:346-352.
29. Petrovic M, Petrovic MT, Milasinovic G, et al. Prediction of a good response to cardiac resynchronization therapy in patients with severe dilated cardiomyopathy: could conventional echocardiography be the answer after all? *Echocardiography* 2012;29:267-275.
30. Shanks M, Delgado V, Ng ACT, et al. Clinical and echocardiographic predictors of nonresponse to cardiac resynchronization therapy. *Am Heart J* 2011;161:552-557.