Evaluation of dyssynchrony: other techniques

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Introduction

According to the currently accepted paradigm underpinning cardiac resynchronization therapy (CRT), cardiac dyssynchrony contributes to the syndrome of heart failure and its correction leads to a clinical benefit. The first testament to this paradigm was provided by Cazeau et al, who in 1994 reported on the dramatic clinical improvement of a 54 year old man who was treated with four-chamber pacing. (1) In an acute haemodynamic study, Leclerq et al subsequently showed that temporary cardiac resynchronisation therapy (CRT) using biventricular pacing led to an increase in left ventricular (LV) output and to a decrease in pulmonary capillary wedge pressure. (2) Reporting on 27 patients with end-stage heart failure, Auricchio et al showed that CRT led to an increase in aortic pulse pressure and LV dP/dt, which reversed immediately after pacing was withdrawn. (3) The Multisite Stimulation in Cardiomyopathies (MUSTIC) study, a single-blind, cross over study of 67 patients, showed that CRT dramatically reduced heart failure hospitalizations and improved NYHA class, as well as quality of life, exercise distance and peak oxygen uptake. (4) The major outcome trial of CRT-pacing (CRT-P), the Cardiac Resynchronization in Heart Failure (CARE-HF) study, showed that this therapy led to a 36% relative reduction in total mortality. (5) The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) study showed that addition of a cardioverter defibrillator to CRT-P (CRT-D) also led to a mortality benefit. (6)

Several mechanisms have hitherto been offered as possible explanations for the beneficial effects of CRT. The diastolic ventricular interaction, which is demonstrable in patients with heart failure, (7) is relieved by both biventricular and LV pacing. (8) In addition, CRT reduces functional mitral regurgitation, acutely as well as in the long term. (9-11) The roles of blood flow, (12) heart failure aetiology, (13) myocardial viability (14), location of myocardial scarring, (15) and atrial rhythm (16,17) have also been explored. The most intuitive mechanism by which CRT confers a benefit, however, is through correction of dyssynchrony. Whilst echocardiography is the most widely studied imaging modality in relation to the assessment of cardiac dyssynchrony, other techniques are emerging. This review focuses on the assessment of cardiac dyssychrony using techniques other than echocardiography.

Definition of response to CRT

For a test to be clinically meaningful, it must prove its value when evaluated against clinically meaningful parameters, such as symptoms, morbidity and mortality. Because mortality is not always a practicable outcome measure in studies other than large outcome trials, surrogate measures, such as reverse LV remodelling, have found popularity in smaller studies.

To compound the issue of what constitutes a response to a given treatment, a symptomatic is not necessarily associated with a survival benefit. At the extremes, chemotherapy for the treatment of cancer is intended for a survival benefit, but it rarely carries a symptomatic benefit. On the other hand, palliative treatments usually provide symptom relief, but not a survival advantage. In this respect, data from the CARE-HF study suggests that all patients treated with CRT improve relative to those treated with medical therapy alone. (18) On the other hand, other studies have shown that there is a discordance between benefit in terms of symptoms and of surrogate measures of a survival benefit, such as reverse LV remodeling. (19) It is important, therefore, to qualify whether 'responder rate' relates to a survival benefit or a symptomatic benefit, or both. This issue of definition of response applies to most studies of CRT.

As a further limitation, the term 'responder' does not incorporate a measure of the degree with which a treatment prevents deterioration, unless it is compared with placebo. After publication of clinical guidelines, however, CRT cannot be compared to placebo. For this reason, the responder rate quoted in studies other than the CARE-HF and the COMPANION study do not, therefore, reflect the effects of CRT in preventing clinical deterioration, as would be expected from the natural history of heart failure. This is an important factor to take into account in interpreting the findings of CRT studies.

Echocardiography

Echocardiographic studies of the response to CRT have focused on surrogate measures of mortality, the most popular of which is reverse LV remodelling. Several groups have employed tissue Doppler imaging (TDI)-derived measures of the temporal dispersion of the time-to-peak velocity of myocardial segments as a predictor of response to CRT. (20-23) Together, these studies have supported the notion that demonstration of cardiac dyssynchrony prior to implantation is a requirement for a benefit from CRT. (24, 25)

The Predictors of Response to CRT (PROSPECT) study was the first multicentre study to evaluate echocardiography as a predictor of response to CRT. (26) Although concerns have been raised

about the quality of data acquisition, data collection and study design, (27) the authors of the original publication concluded that no single echocardiographic measure could be recommended in the selection of patients for CRT. On this basis, the American Society of Echocardiography has recommended that echocardiographic measures of dyssynchrony should not be used in selecting patients for CRT. (28) Apart from the United Kingdom National Institute of Clinical Excellence, no clinical guideline group has adopted echocardiography in selecting patients for CRT.

The PROSPECT study has stimulated a recapitulation of the role of echocardiographic measures of dyssynchrony in selecting patients for CRT. In a recent review, Marwick referred to the numerous dyssynchrony measures as the tower of Babel. (29) In his review, Marwick alludes to the limitations of TDI in measuring dyssynchrony. He also refers to the clinical impracticality of the numerous techniques used to quantify dyssynchrony. In this regard, some anomalies of definition have arisen. Various groups have shown, for example, that even healthy controls have dyssynchrony. (30-33) Others have shown that some patients with heart failure and broad QRS do not satisfy the echocardiographic criteria for dyssynchrony. (34) Whilst echocardiography boasts of exquisitively high temporal resolution, this may actually work against it, as it also increases ‘noise’. (35) After a decade of research, there is no consensus with regard to the role of echocardiography in the quantification of dyssynchrony for the purposes of selecting patients for CRT.

Nuclear imaging

Myocardial scintigraphy allows measurement of ventricular volumes, myocardial perfusion as well as myocardial motion. To evaluate the prognostic value of interventricular and intraventricular dyssynchrony, Fauchier et al studied 103 patients with non-ischaemic cardiomyopathy, 25% of whom had a left bundle branch block (LBBB). (36) Fourier phase analysis of equilibrium radionuclide angiographic data was performed for both right and left ventricles. (**Fig.1**) The difference between the mean phase of left and right ventricles was taken as a measure of interventricular dyssynchrony, whereas the standard deviations of the mean phase in each ventricle was taken as a measure of intraventricular dyssynchrony. The authors found that over a mean follow-up of 27 months, the standard deviation of the LV and right ventricular mean phase (intraventricualr dyssynchrony) predicted cardiac events. Among 13 potential predictors of cardiac events on univariate analyses, a high standard deviation of the LV mean phase (intraventricular dyssynchrony) and a high pulmonary capillary wedge pressure emerged as independent predictors of cardiac events in multivariate analyses.

Figure 1

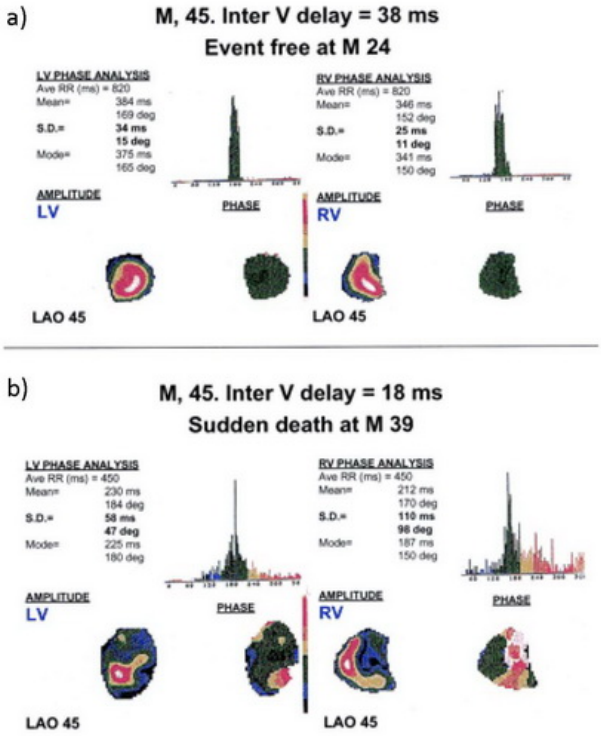

Figure 1. Phase analysis of radionuclide ventriculography data. The images show the ventriculograms obtained from the left and right ventricles. (a) shows a mean phase of 384 ms for the left ventricle and 346 ms for the right ventricle, which amounts to a phase difference of 38 ms; (b) shows a mean phase of 230 ms for the left ventricle and 212 ms for the right ventricle, which amounts to a mean difference of 18 ms. Reproduced with permission from Fauchier et al. (36)

Henneman et al used phase analysis of gated myocardial perfusion single photon computed tomography (SPECT) to assess intraventricular dyssynchrony. Four indices of dyssynchrony derived from the phase analysis were found to correlate well with septal-to-posterior wall motion delay on TDI. (37) In another study of 42 patients undergoing CRT, the same group found that the standard deviation of a phase angle of 42º on SPECT was the best predictor of improvement in NYHA class (by ≥1) at six months (area under the receiver operator characteristic curve of 0.81). (38) Other groups have found that SPECT-derived measures of mechanical dyssynchrony have low intra-observer and inter-observer variabilities. (39)

As well as providing measures of mechanical dyssynchrony, SPECT also permits assessment of myocardial perfusion and myocardial viability, factors which are known to be important in the response to CRT. (14,15,40,41). In a study of 20 patients, Sciagra et al showed that, compared with patients with no perfusion defects, patients with perfusion defects affecting ≥50% of the myocardial wall on SPECT had a worse quality of life and six-minute walking distance 3 months after CRT device implantation. (42). Whilst symptomatic benefit was observed in patients with and without perfusion defects, those with perfusion defects did not exhibit reverse LV remodelling. In a study of 51 patients with heart failure due to ischaemic cardiomyopathy, Ypenburg et al also showed a relationship between the response to CRT and the extent of viable myocardium and scar tissue. Furthermore, up to the 29% with transmural scar tissue (< 50% tracer activity) in the region of the LV pacing lead showed no improvement after 6 months of CRT. (43) In a retrospective study of 51 patients, Adelstein et al. showed that a low myocardial perfusion score and the average scar density in the segments immediately adjacent to the LV lead were significantly lower response in responders versus non-responders to CRT (response defined as a≥15% increase in LVEF). (44)

Nuclear imaging permits assessment of patients with poor echocardiographic windows. Disadvantages, however, include a low spatial and temporal resolution and the use of radiation.

Computerised tomography

Contrast-enhanced ventriculography using currently available computed tomography (CT) allows adequate delineation of myocardial borders throughout the cardiac cycle, thus making it a potential imaging modality for the assessment of mechanical dyssynchrony. Truong et al studies 38 patients undergoing CRT using 64-slice CT. (45) Endocardial and epicardial borders were contoured throughout the cardiac cycle, with each cycle divided into 10 phases. The dyssynchrony index was defined as the standard deviation of the time to maximal wall thickness for each myocardial segment. The mean dyssynchrony index was 152 ± 44 ms for patients with heart failure and a wide QRS duration 65 ± 12 ms for age-matched controls. The authors found excellent agreement between the two independent observers. Whilst this dyssynchrony index has not been evaluated against the outcome of CRT, a good agreement with speckle tracking has been shown. (45)

Cardiovascular magnetic resonance

Cardiovascular magnetic resonance (CMR) has gained widespread acceptance as the gold standard investigation for the *in vivo* quantification of ventricular volumes. Recently, CMR has been applied to the assessment of mechanical dyssynchrony. As with other imaging modalities, dyssynchrony can be measured in terms of the temporal dispersion of myocardial motion. Chalil et

al have recently used the standard deviation of the time to peak wall motion in myocardial segments as a measure of dyssynchrony (**Fig. 2)**. (46) Compared with tissue Doppler measures of dyssynchrony, the so-called CMR tissue synchronisation index (CMR-TSI) emerged as a good discriminator between healthy controls and patients with heart failure **Fig. 3**). Furthermore, the CMR-TSI was identified as a powerful independent predictor of morbidity and mortality after CRT: patients with a CMR-TSI ≥ 110 ms were 3.8 times more likely to die from cardiovascular causes, compared with patients with a CMR-TSI<110 ms. These findings support the use of dyssynchrony assessment using CMR in the risk-stratification of patients undergoing CRT.

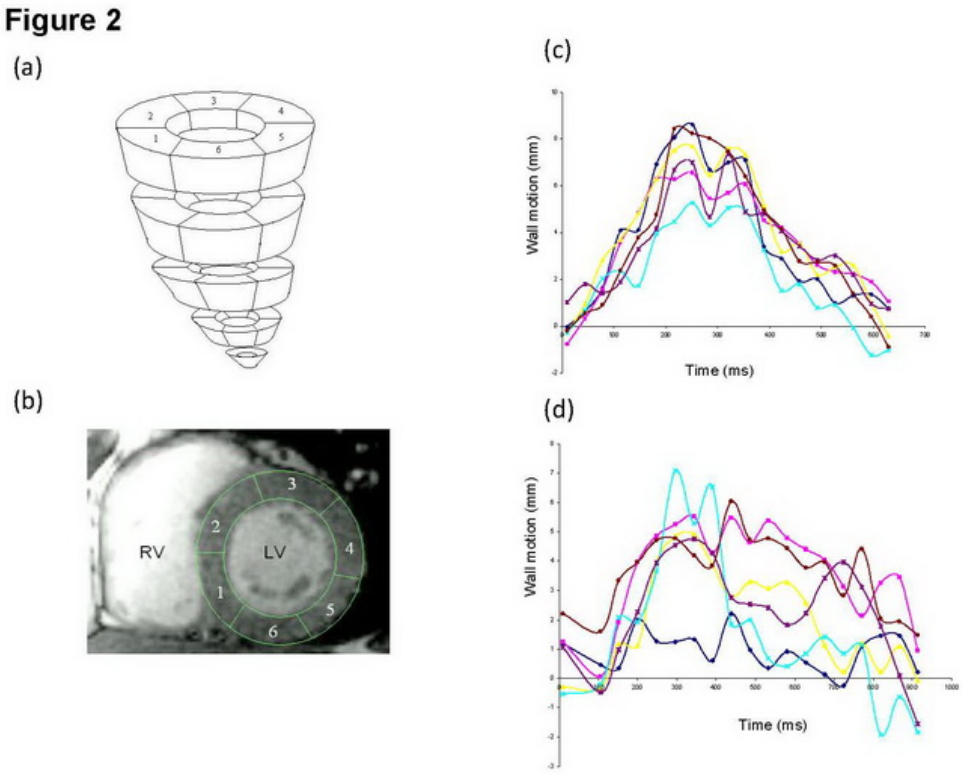

Figure 2: Assessing dyssynchrony using wall motion obtained using cardiovascular magnetic resonance. (a) shows the left ventricle sliced into slices from the base (top) to apex (bottom), with each slice consisting of 6 segments; (b) shows the left ventricle in short axis, with manual contouring of the left ventricular epicardial and endocardial borders; (c) shows wall motion plotted against time in a healthy control; (d) shows wall motion plotted against time in a patient with heart failure and a left bundle branch block (LBBB). Reproduced with permission from Chalil et al. (46)

Figure 3

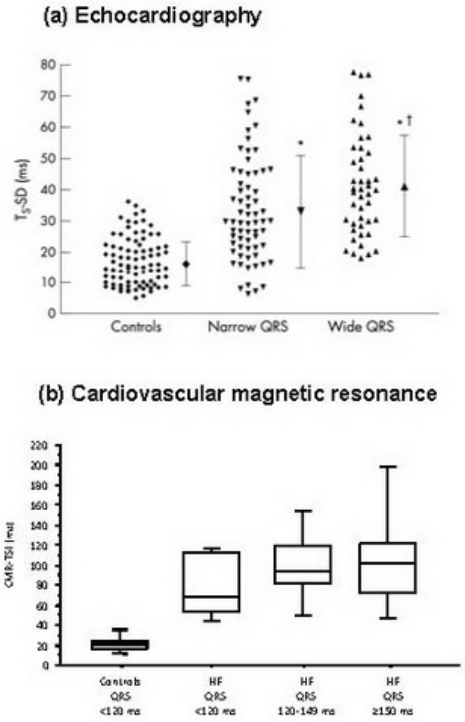

Figure 3: Assessing dyssynchrony in heart failure vs controls. (a) The standard deviation of the time-to-peak velocity in 12 myocardial segments derived from tissue Doppler imaging in healthy controls and in patients with heart failure, with a QRS duration 120 ms and ≥120 ms. [reproduced with permission from Yu CM et al (23)]; (b) standard deviation of the time to peak inward wall motion (CMR-TSI) in healthy controls and in patients with heart failure with varying QRS durations. (reproduced with permission from Chalil et al (46). Note the lack of overlap in CMR-TSI between healthy controls and patients with heart failure.

Other CMR methods for assessing cardiac dyssynchrony have emerged. Myocardial tagging, which is the gold-standard technique for assessing myocardial motion, permits assessment of wall motion as well as strain in circumferential, radial and longitudinal directions. (47,48) (**Fig. 4**) Strain-coded CMR provides real-time quantitative strain measurement, which is applicable to a rapid assessment of LV dyssynchrony. (47) Helm et al have recently developed a method for assessing dyssynchrony using three-dimensional tagged CMR. (49) Velocity-encoded CMR has recently

been shown to have an excellent agreement with TDI. (50) Although useful experimentally, these techniques have not been validated against the clinical outcome of CRT. Their application in clinical practice is therefore limited.

Figure 4

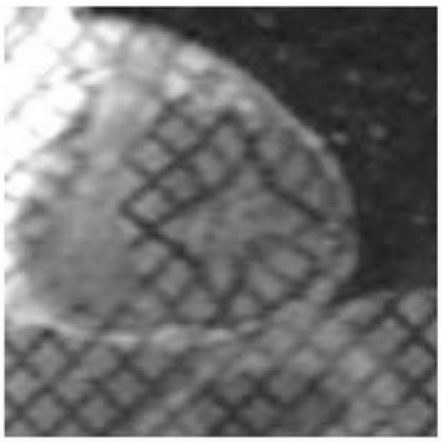

Figure 4. Example of cardiovascular magnetic resonance tags superimposed on a short axis image of the left ventricle. The linear tags (low signal) label areas of the myocardium throughout the cardiac cycle. The lines appear ‘stretched’ during systole. Tracking of tagged myocardium using specialised software allows determination of wall motion and strain in longitudinal, circumferential and radial directions.

Endocardial mapping

At its simplest, QRS duration of the 12-lead ECG provides a crude measure of electrical dyssynchrony. The distribution of myocardial activation, however, is best studied using intracardiac techniques, such as endocardial mapping. Using this technique, Auricchio’s group have shown that, in normal hearts, the sites of latest activation are the posterobasal and posterolateral segments. (51) In patients with heart failure and a left bundle branch block (LBBB), ventricular

activation follows an U-shaped pattern, turning around the apex and inferior wall before it reaches the posterolateral segments. (51) The pattern of ventricular activation in LBBB is highly variable, (52) but the response to CRT appears to be greatest in patients with evidence of conduction block, rather than in patients with homogenous activation. (53)

By identifying the zone of latest activation, non-contact mapping also provides information about the best site for LV lead deployment. (54) Lambiase et al studied 10 patients with heart failure with endocardial mapping. (55) They hypothesised that failure to respond to CRT results from pacing areas of slow conduction, whereas deploying the lead in a site of normal activation results in an improved haemodynamic response. In this acute study, patients underwent non-contact mapping during intrinsic sinus rhythm and during paced rhythm. A roving LV catheter was used to pace the LV during biventricular pacing. In patients with ischaemic cardiomyopathy, a zone of slow conduction was found around the coronary sinus, with a velocity 73% slower than the LV lateral free wall. Pacing the area of normal activation rather than a zone of slow conduction resulted in a 22% rise in maximum dP/dt, which represented a 15% increase in cardiac output. This study showed how non-contact mapping can be used to direct optimal LV lead deployment. A limitation of endocardial mapping studies is that the LV lead is normally in contact with the epicardium. It is uncertain whether the findings of endocardial mapping studies can be extrapolated to the epicardium.

Conclusions

Echocardiography is the most widely studied modality for the assessment of mechanical dyssynchrony. Whilst various measures of dyssynchrony have been proven to predict the outcome of CRT is single-centre studies, they have proven to be of limited clinical applicability in a large multicentre study. Further refinements in the echocardiographic techniques and their application to the selection of candidates for CRT are required. Other imaging techniques using CMR, radionuclide scintigraphy and CT have an evolving potential in the selection of patients for this therapy. Either alone or in combination with electrical mapping, such techniques can be used to derive global and regional measures of mechanical dyssynchrony, which may be useful in selecting patients for CRT as well as in guiding LV lead deployment. Adequate evaluation of these modalities against clinically meaningful endpoints is required before introducing them into the clinical arena.

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