

Cardiac Resynchronisation Therapy: The Role of Echocardiography in Patient Selection and Follow-up

Author: Shirley Middlemost

Private Cardiologist, MBBCH, FCP(SA), PHD(WITS), FACC

Address for correspondence:

Dr S Middlemost
Vergelegen Mediclinic
Main Road
Somerset West
7130

Email:

shirley@helderbergheart.co.za

ABSTRACT Resynchronisation of segmental left ventricular mechanics as well as re-coordination of both atrioventricular and interventricular mechanics are potential mechanisms for the clinical improvement observed in patients undergoing cardiac resynchronisation therapy (CRT) for heart failure. Resynchronisation therapy is approved in patients with refractory heart failure symptoms despite optimal medical therapy. The presence of a prolonged QRS duration has been the main criterion used to identify ventricular dyssynchrony. However, based on the current selection criteria, about 20% to 30% of patients do not improve after biventricular pacing. Using echocardiography, dyssynchrony may be absent in some heart failure patients with a wide QRS, or present in those with a normal QRS interval.

Echocardiography, and especially the more sophisticated techniques based on Tissue Doppler Imaging, may improve patient selection by identifying inter- and intra-ventricular dyssynchrony. Echocardiography can also be used to optimise lead placement. Following pacemaker implantation, various echocardiographic techniques can be used to ensure optimal cardiac resynchronisation and to monitor improvements in left ventricular function and hemodynamics. In this review, the different echocardiographic approaches to predict patient response to CRT are discussed. In addition, the use of echocardiography to guide lead positioning and to optimise pacemaker settings following pacemaker implantation is discussed.

Heart failure is the major cause of mortality, morbidity and hospitalisation in patients age > 60 years⁽¹⁾. Despite major advances in medical therapy, morbidity and mortality remain high. Cardiac resynchronisation therapy (CRT) has been found to provide significant clinical benefit in patients with impaired left ventricular (LV) function, prolonged QRS duration and New York Heart Association (NYHA) functional class III/IV heart failure despite optimal drug therapy^(2,3). Studies have shown that CRT improves NYHA functional class, exercise capacity, quality of life and LV systolic function. This is accompanied by a reduction in hospitalisation and a significant improvement in survival, as confirmed in the CARE-HF study⁽⁴⁾.

Despite these astonishing results, clinicians have only begun to understand the mechanisms responsible for improvement. Clinicians are struggling to identify those most and least likely to derive benefit from CRT and continue to perfect the technique. Currently, patients who remain significantly symptomatic despite optimal medical therapy are selected mainly on electrocardiogram (ECG) criteria (QRS interval > 120ms)⁽⁵⁾. However, using these selection criteria, about 20% to 30% of patients do not respond to CRT. Different factors may influence the ability of CRT to improve clinical outcome, such as patient selection, device programming, lead position and various arrhythmias that result in intermittent CRT delivery.

A major limitation has been the utilisation of the QRS duration as the only marker for dyssynchrony. However, substantial mechanical dyssynchrony, a major predictor of response to CRT, is not necessarily related to electrical dyssynchrony^(6,7). QRS width often does not change following CRT and evidence is conflicting as to whether baseline QRS width predicts who will respond to CRT⁽⁸⁾. In addition, substantial dyssynchrony may be present in heart failure patients with a normal QRS^(9,10). The presence of LBBB may only identify about half of all patients with mechanical dyssynchrony^(8,11).

Mechanical dyssynchrony is complex and should be evaluated at 3 levels. These include:

1. Atrioventricular (AV) dyssynchrony, which results in delayed contraction between the atria and the ventricles. This may produce systolic mitral and tricuspid regurgitation. When the AV delay is excessive, a gap occurs between the end of atrial filling (A wave) and the beginning of left ventricular contraction. During this delay, the mitral valve closes passively (soft first heart sound), as the left atrial pressure falls below LV pressure during late diastole, so that diastolic mitral regurgitation may occur. The shortened ventricular filling time limits net diastolic stroke volume⁽¹²⁾. Atrial systole occurs during early passive filling and this further reduces LV filling⁽¹³⁾. When the AV delay is too short, the left atrial systolic peak pressure occurs after the onset of LV systole. As a result, the left atrial contraction is not able to open the mitral valve because LV pressure greatly exceeds the left atrial peak pressure. The mean left atrial pressure is increased, with possible symptoms of pulmonary congestion.
2. Interventricular dyssynchrony, which is associated with an earlier onset of right ventricular (RV) contraction and ejection, during the LV end-diastolic period. The higher RV pressure displaces the septum into the LV, resulting in decreased mechanical performance⁽¹⁴⁾.

3. Intraventricular dyssynchrony, which is associated with a reduction in ventricular performance and global LV ejection fraction⁽¹⁵⁾. There is wasted work with either early or delayed regional myocardial contraction. The latter may even be delayed to early diastole⁽¹⁶⁾. The early contraction occurs when pressure is low and does not lead to ejection. The late contraction occurs at higher stresses and results in paradoxical stretch of any earlier contracting segments. The net result is a decline in systolic performance⁽¹⁷⁾. Delayed early relaxation shortens LV filling time, whilst delayed papillary muscle contraction contributes to mitral regurgitation.

Considering the limitations of conventional ECG, various echocardiographic techniques, some quite novel, have been developed to determine the extent of mechanical dyssynchrony. These include conventional 2-dimensional (2D) and Doppler echocardiography and newer Tissue Doppler methods. There is currently no consensus on the definition of echocardiographically measured dyssynchrony.

CONVENTIONAL ECHOCARDIOGRAPHY

Pitzalis and colleagues utilized standard M-mode echocardiography to measure the extent of septal-to-lateral wall motion delay as derived from the parasternal short-axis view⁽⁸⁾. A delay >130ms has been

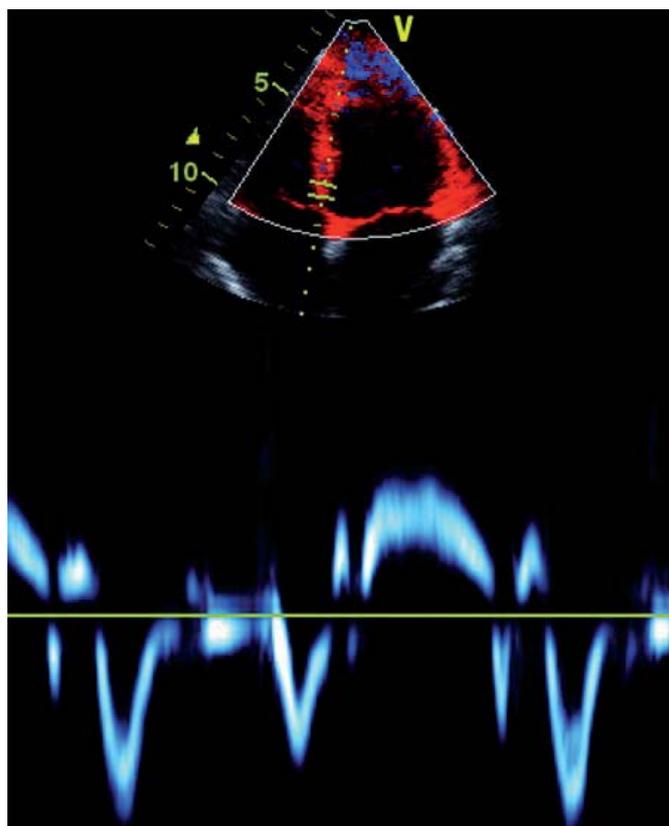


FIGURE 1: Pulsed Wave Tissue Velocity Imaging

Pulsed Doppler interrogation measures the instantaneous peak velocities from the myocardium which passes through the sample volume during the cardiac cycle. The sharp narrow positive spike represents myocardial velocity during the isovolumic contraction period. This is followed by a broad dominant positive waveform representing myocardial velocity during the ejection phase. There are two dominant negative waveforms (below the line) which represent myocardial velocity during rapid atrial filling (E-wave) and atrial contraction (A-wave), respectively.

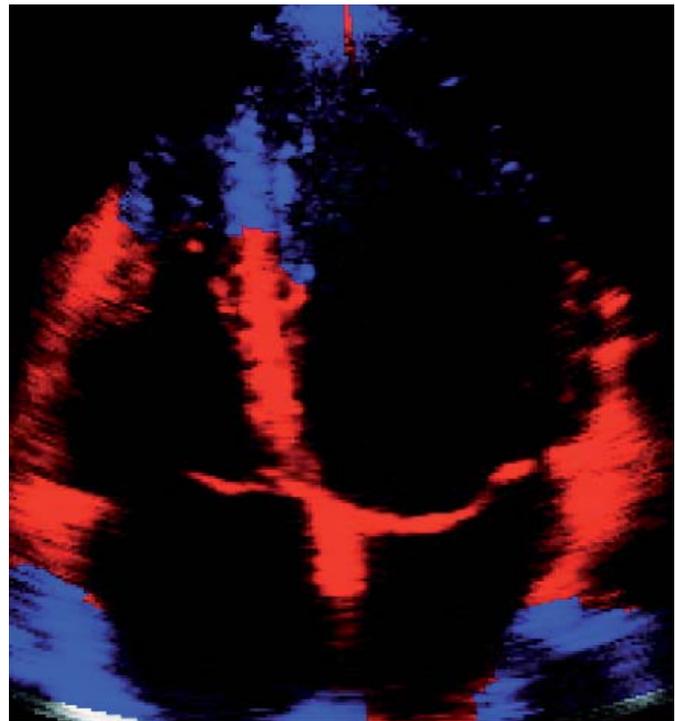


FIGURE 2: Colour Tissue Velocity Imaging

Red colour displays tissue motion towards the probe. Blue colour displays motion away from the probe.

proposed as a marker of intraventricular dyssynchrony and has been shown to be a powerful predictor of reverse remodeling. This index cannot be derived in patients with an akinetic septum or posterior wall and it is not always possible to get perpendicular M-mode sections through the LV.

Interventricular mechanical delay (IVMD) can also be determined using pulsed Doppler. The time difference between the onset of the pulmonary flow and the aortic flow > 40ms is considered indicative of interventricular dyssynchrony^(18,19). In the CARE-HF study, a prolonged aortic pre-ejection delay (>140ms) was an additional criterion reflecting interventricular delay in those with a QRS interval between 120ms -150ms⁽⁴⁾.

TISSUE DOPPLER IMAGING (TDI), TISSUE-TRACKING, STRAIN AND STRAIN RATE

With the limited role of conventional echocardiography in the assessment of cardiac dyssynchrony, several newer echocardiographic applications have emerged with potential application in CRT. These include the following:

Tissue Velocity Imaging

Tissue Velocity Imaging (TVI) uses myocardial Doppler frequency shifts to quantify regional myocardial function by measuring segmental peak systolic and diastolic tissue velocities. TVI can be displayed as pulsed Doppler (Figure 1), colour Doppler (Figure 2) and colour M-mode. The 2D colour TVI image can be converted to TVI waveforms to allow further off-line quantitative analysis (Figure 3).

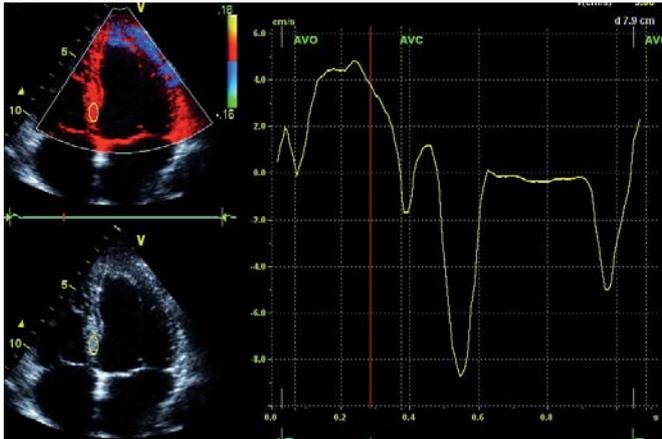


FIGURE 3: The regional velocity sampled from the basal septum in this normal subject is displayed in the diagram on the right. Conventionally, systolic motion of segments towards the apex (and hence the transducer) is ascribed a positive value while shortening of a segment is ascribed a negative value. Aortic valve opening and closure are displayed to enable accurate timing of mechanical events within the cardiac cycle.

Interventricular dyssynchrony has been defined by the difference in time-to-peak myocardial velocities between one RV segment and the mean of 6 LV myocardial segments in the apical 4-chamber, 2-chamber and long-axis views⁽²⁰⁾.

Intraventricular dyssynchrony is present when there is a delay of >60ms in the time to onset of peak systolic velocities from the QRS complex using a 2-sample model (basal septum and basal lateral wall)^(21,22). In a more complex and time-consuming 12-segment model, derived from the 6 basal and 6 mid-ventricular segments,⁽¹⁰⁾ Yu and colleagues defined intraventricular dyssynchrony as present when:

- a) there was a >100ms difference between the peak systolic velocities of any 2 of 12 LV segments or

- b) the SD (standard deviation) of all time intervals measuring time to peak systolic velocity in 12 LV segments was >33ms.

Tissue Tracking

Although TVI is used to identify areas of dyssynchrony, it is limited by the fact that it does not allow simultaneous comparison of regional timing in different segments within one cardiac cycle. Tissue Doppler measures the velocity at a single point and cannot discriminate between passive myocardial motion as a result of tethering and active myocardial contraction⁽²³⁾. TVI technology includes tissue tracking and strain rate imaging. Tissue tracking is performed in the apical view and allows the measurement and visualisation of longitudinal motion in each cardiac segment during the different phases of the cardiac cycle. This is done by integrating tissue velocities to yield tissue displacement, which measures the total distance that particular point travels. Tissue Tracking is displayed as a colour band representing motion during systole. Each point in the myocardium is colour coded, with displacement occurring from end-diastole to end-systole. The width of each colour bar is a measure of regional strain over the time period interrogated (Figure 4).

Tissue synchronisation imaging (TSI) is a parametric imaging tool derived from 2-dimensional (2D) TVI images. It automatically calculates and colour-codes the time-to-peak tissue velocity in every portion in the image, with reference to the QRS signal. The TSI algorithm detects positive velocity peaks within a specified time interval. The colour coding ranges from green (earliest), yellow, orange, to red (latest) within this interval. With TSI, the colour represents the amount of tissue motion delay rather than the absolute value of the tissue velocity. The variation in colour provides both a quantitative and qualitative

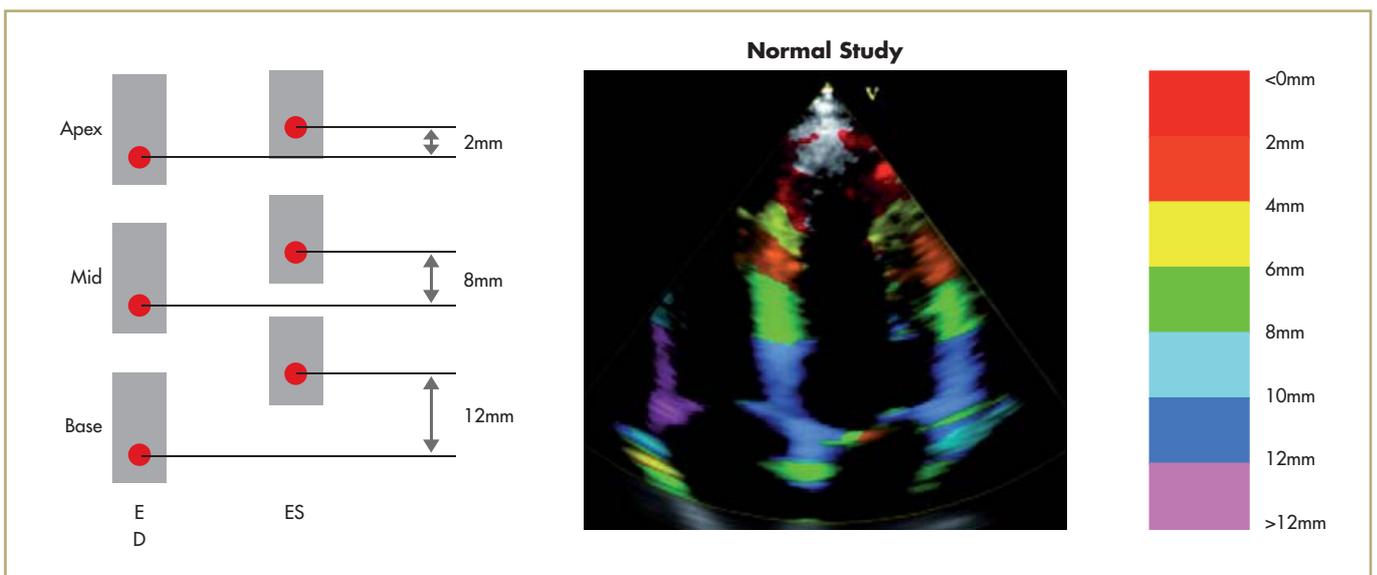


FIGURE 4: Tissue tracking displays systolic longitudinal displacement by integrating tissue velocity over time. Tissue Tracking is displayed as a colour band representing motion during systole. The system colour-codes each point in the myocardium with the displacement occurring from the end-diastole to end-systole. A normal left ventricle displays the lowest motion at the apex (shown as white in the diagram), while the mitral annulus will display the greatest motion. Systolic mitral annular displacement, determined by tissue tracking, correlates closely with left ventricular ejection fraction.

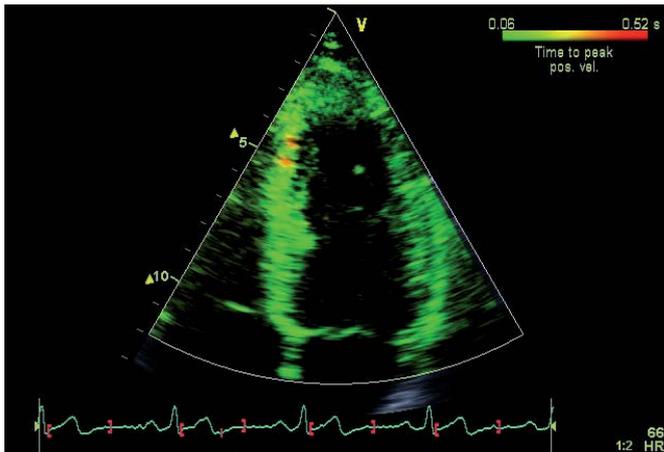


FIGURE 5: Tissue Synchronized Imaging is a parametric imaging tool based on Tissue Velocity Imaging that provides clinicians with additional image enhancement for assessing delayed cardiac motion. The TSI parametric image analyzes the tissue velocity signals within a specified portion of the cardiac cycle. Since these peaks will occur in relation to overall motion, delayed wall motion will produce a delayed peak velocity. The amount of delay within a defined area of the cardiac cycle, indicated by the markers on the ECG, is used to assign or map a colour to that location in the image. The colour represents the amount of tissue motion delay rather than the absolute value of the tissue velocity. The variation in colour provides both a qualitative and quantitative representation of wall motion delay, allowing easy and rapid identification and evaluation of asynchronous wall motion. The figure depicts a normal study with all regions shown in green, reaching peak velocity at the same time early in systole.

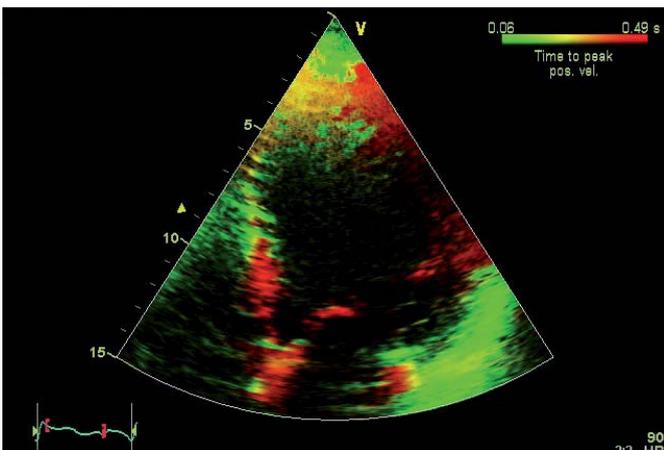


FIGURE 6: Utilizing Tissue Synchronized Imaging, it is easy to appreciate the dyssynchronous regions in the left ventricle. The regions which reach peak velocities at different times have different colours, with the red areas being most delayed.

representation of wall motion delay, allowing immediate identification of regional delay in systole by comparing the colour mapping of orthogonal walls (Figure 5 and 6)^(24,25).

Various TSI parameters have been used to predict an improvement in clinical outcome. Murphy, et al. used TSI to identify the area of latest peak systolic velocity before CRT. Pacing at this site resulted in the greatest clinical and hemodynamic improvement⁽²⁶⁾. Whilst Yu, et al, confirmed that the time-to-peak systolic velocity (Ts) measured in the ejection phase in 12 LV segments, derived in the apical view, was the best modality to predict reverse LV remodeling after CRT. When the lateral wall is delayed, the patient has a high likelihood of response to

CRT⁽²⁷⁾. In the absence of lateral wall delay, patients unlikely to respond to CRT were identified when the systolic synchronicity index, defined as the standard deviation of the peak tissue velocity in 12 LV segments in the ejection phase, was < 34.4ms.

Although this study did not find that post-systolic shortening (PSS), defined as contraction after aortic valve closure, was useful for the identification of responders, others have shown that, in non-ischemic heart failure, the presence of PSS in more than 20% of the basal segments on all three apical views was predictive of clinical improvement⁽²⁸⁾.

Strain and Strain Rate

The temporal analysis of myocardial motion by velocity imaging allows no definite conclusions about the timing of regional contraction. As already discussed, velocity imaging cannot differentiate passive myocardial motion related to tethering artefacts or cardiac translation from active myocardial contraction. To overcome the limitations of velocity imaging, strain and strain rate imaging have been developed to identify the regional deformation properties of the myocardium. The information is derived from tissue Doppler velocity data and measures the timing and extent of myocardial deformation. Strain measures the change in shape of myocardial segments and strain rate imaging measures how fast the change has occurred (Figures 7, 8). Strain is defined as the change in length normalized to the initial length of the myocardium and is therefore expressed as a percentage. Strain measures the activity of 2 points within the myocardium. Because the length at peak systole is shorter than the original length, strain (and strain rate) has a negative polarity when measured in the longitudinal axis⁽²⁹⁾. The opposite occurs in the short-axis plane (radial) when the myocardium thickens during systole so that strain and strain rate have a positive polarity.

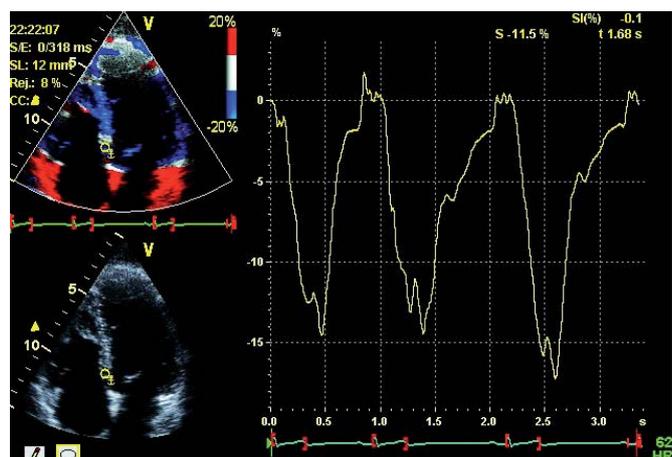


FIGURE 7: Strain Imaging provides regional detection of myocardial contraction. Strain measures the percent of regional deformation of the myocardium (percentage change in length). Systolic motion of the segments towards the apex (towards the transducer) is ascribed a positive value and shortening of the segment a negative strain value. The opposite will apply to regional lengthening. The diagram depicts a normal study with negative strain during systole in the basal septum. There is no lengthening of the myocardial segment during this time interval.

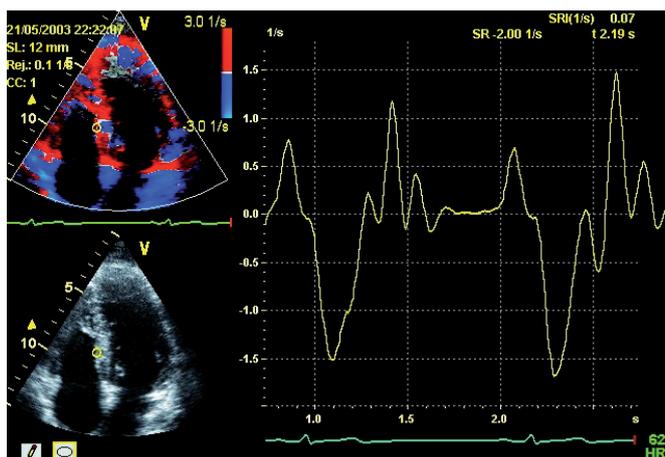


FIGURE 8: Strain rate measures the speed of deformation (change in shape) of the myocardium. As with Strain Imaging, systolic motion of the segments towards the apex (towards the transducer) is ascribed a positive value and shortening of the segment a negative strain rate value. Simultaneous ECG recordings allow correct timing of events. This normal study depicts a negative systolic Strain Rate in the basal septum.

Strain and strain rate imaging measure myocardial deformation in systole and are able to identify reliably the presence of delayed contractions and thus the presence of a recruitable contractile reserve that can be utilized by CRT, by transferring it from the pre or post-ejection period to the systolic ejection phase. Ischemic myocardial segments can also display PSS. These delayed segments would not be expected to respond to CRT.

REAL-TIME THREE-DIMENSIONAL ECHOCARDIOGRAPHY

This novel imaging modality allows functional assessment of all 16 individual segments of the LV. A cast of the LV is obtained and regional volume curves are obtained. A dyssynchrony index is obtained by calculating the time taken to each minimal volume for each segment as a percentage of the cardiac cycle. This is expressed as a percentage of the duration of the cardiac cycle to allow comparison between patients with different heart rates. Using this technique, it has been shown that mechanical dyssynchrony is increasingly prevalent with worsening LV function, independently of QRS duration⁽⁹⁾.

ECHOCARDIOGRAPHY AND LV LEAD PLACEMENT

One of the challenges for the echocardiographer is to identify the optimal LV segment for placement of the LV lead. Pacing in the “wrong” area may account for a failed response in appropriately selected patients. Moreover, incorrect lead placement may be detrimental and lead to further dyssynchrony⁽³⁰⁾.

Using tissue Doppler strain imaging, a recent study has confirmed that pacing at the site of maximal mechanical delay is associated with reverse remodeling,⁽²⁶⁾ a powerful predictor of a favourable clinical outcome^(28,31). Echocardiography could be helpful at the time of implantation to optimise lead position. Ongoing clinical trials seek to address this issue.

POST-IMPLANTATION USE OF ECHOCARDIOGRAPHY FOR FOLLOW-UP AND OPTIMISATION

The three primary aspects of programming or optimisation of resynchronisation therapy that have become salient to management have been the optimisation of atrio-ventricular (AV) delay, mechanical synchrony and interventricular timing. Although much attention has focused on the optimisation of the AV delay, it has become evident that optimisation of mechanical synchrony may be the most important parameter to target as an endpoint to ensure successful therapy.

Optimising Atrio-Ventricular Delay

Although AV-delay optimisation can clearly impact hemodynamics in patients undergoing CRT,^(32,33) it has less influence on LV function than the optimal pacing site⁽³⁴⁾. An optimal AV delay is that which allows completion of the end-diastolic filling flow prior to ventricular contraction, thereby providing the longest diastolic filling time. The AV interval can be optimised using 2 methods:

1. calculating the AV-delay interval from pulsed Doppler measurement of the timing of mitral valve closure at a short and long AV-delay setting (mitral inflow method)⁽³⁵⁾
2. determining the AV-delay that produces the greatest increase in the aortic velocity time integral (VTI) using continuous wave Doppler. A recent study has shown that the aortic VTI method may be superior to the mitral inflow method in patients with a QRS interval >150ms.⁽³⁶⁾

Optimisation of the Ventricular-to-Ventricular (VV)-Interval

In patients with heart failure and significant conduction delay undergoing CRT, simultaneous stimulation of the LV and right ventricle (RV) may not be appropriate. Therefore, altering LV-RV stimulation by varying durations may further optimise LV resynchronisation. The benefit of sequential versus simultaneous biventricular pacing (BVP) has been evaluated in a small study of 21 patients⁽³⁷⁾. This study used TDI with tissue tracking pre-operatively to identify regions displaying delayed longitudinal contraction. Post-implantation, it was confirmed that

individually tailored sequential rather than simultaneous BVP resulted in an additional increase in diastolic filling time, with a simultaneous significant increase in LV ejection fraction from 30+5% to 34+6%. It has been recommended that the VV-interval be optimised before the AV-interval, to prevent inappropriate AV-delay programming, which might reduce LV filling⁽³³⁾.

Assessment of Myocardial Remodeling

Myocardial remodeling is a complex process and not well understood. Positive remodeling is defined as a >15% reduction in LV end-systolic volume^(28,31). This has been observed in about 54% - 64% of patients at 3 months follow-up^(38,39). Echocardiography has also demonstrated a reduction in the severity of mitral regurgitation in CRT responders. This is related, in part, to resynchronisation of papillary muscle contraction that restores mitral subvalvular size and function towards normal and improved atrioventricular coupling⁽³¹⁾. The reduction in MR can be seen almost immediately after optimal CRT.

EVALUATING CRT “NON-RESPONDERS”

If CRT has not achieved its anticipated response, the following questions should be addressed:

1. Has the physiology of CRT been optimised for this patient? Has diastolic timing been optimally adjusted? Has systolic resynchronisation been fully enhanced? All of these issues can be addressed using echocardiography.
2. Is CRT being consistently delivered? Are the ventricles being consistently paced at all physiologic heart rates? Is the LV stimulus consistently suprathreshold? Is there consistent atrial and ventricular sensing? Answering these questions requires an understanding of how to use diagnostics from the CRT device.

FUTURE DIRECTIONS

Some potential issues that may be addressed include:

1. The role of echocardiography in the catheterisation laboratory to guide LV lead placement. It has been shown that, in patients with LBBB, RV apical pacing alters the activation wavefront of the LV compared with intrinsic rhythm⁽⁴⁰⁾. Perhaps echocardiography can be used in the catheterisation laboratory to ensure that RV pacing has not altered the LV segment with dyssynchrony. Also, the separate effects of RV, LV and BVP can be assessed.

2. The role of regional myocardial infarction on long-term clinical outcomes and whether echocardiography can address these issues.
3. The role of CRT in patients with heart failure and an EF<35% but with a QRS duration <120ms or a right bundle branch block pattern on ECG.
4. The role of CRT in those with dyssynchrony but with less severe symptoms of heart failure (NYHA functional class II) or with less severe LV dysfunction (EF 35% - 40%).

CONCLUSIONS

Current guidelines recommend CRT in patients with reduced LV ejection fraction, a prolonged QRS interval and severe heart failure symptoms despite optimal medical therapy. Based on these selection criteria, about one third of patients fail to respond. Echocardiography can be used to improve patient selection and should be included as part of the workup to identify potential candidates for CRT. In addition, echocardiography has an important role in the identification of the optimal site for LV lead placement and in the optimisation of CRT programming with regard to the AV- and VV- intervals. Echocardiography also allows assessment of resynchronisation and follow-up of patients after CRT.

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