Review Article

Techniques for identification of left ventricular asynchrony for cardiac resynchronization therapy in heart failure

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Abstract

The most recent treatment option of medically refractory heart failure includes cardiac resynchronization therapy (CRT) by biventricular pacing in selected patients in NYHA functional class III or IV heart failure. The widely used marker to indicate left ventricular (LV) asynchrony has been the surface ECG, but seems not to be a sufficient marker of the mechanical events within the LV and prediction of clinical response. This review presents an overview of techniques for identification of left ventricular intra- and interventricular asynchrony. Both manuscripts for electrical and mechanical asynchrony are reviewed, partly predicting response to CRT. In summary there is still no gold standard for assessment of LV asynchrony for CRT, but both traditional and new echocardiographic methods have shown asynchronous LV contraction in heart failure patients, and resynchronized LV contraction during CRT and should be implemented as additional methods for selecting patients to CRT.

Keywords: cardiac resynchronization pacemaker therapy; electrical and mechanical asynchrony; echocardiography

Introduction

Cardiac Resynchronization Therapy

The most recent treatment option of medically refractory heart failure includes cardiac resynchronization therapy (CRT) by biventricular pacing in selected patients in NYHA functional class III or IV heart failure (HF) caused by idiopathic dilated (DCM) or ischemic cardiomyopathy, with QRS duration ≥ 130 milliseconds, left ventricular (LV) end-diastolic diameter ≥ 55 mm, and ejection fraction ≤ 35%[1]. Pacemaker treatment for severe HF started at the beginning of the 1980's, when beneficial effects of dual chamber pacing with short atrioventricular-delay were claimed[2]. However, a later study did not confirm these results[3]. Modification of ventricular mechanical activation sequence by pacing from the right ventricular outflow tract also demonstrated various hemodynamic results[4-6]. Due to the fact that LBBB can cause asynchronous electrical activation and deterioration of LV pump function which can be corrected for by CRT, a new era of CRT by biventricular pacing of both right and left ventricle has rapidly developed in recent years[7-9]. There are a large number of HF patients suffering from intra- and interventricular asynchronous contraction and relaxation assumed by the surface ECG further deteriorating an already hemodynamically compromised left ventricle[10]. Biventricular pacing is assumed to provide a more coordinated pattern of ventricular contraction, and reduce intraventricular and interventricular asynchrony.

The acute improvement of LV performance by CRT was demonstrated by reduction of capillary wedge pressure and an improvement in peak dp/dt without increase in myocardial oxygen consumption[11-14]. Long-term clinical benefits by CRT in terms of improvements in the 6-minutes hall walk distance, NYHA functional class and quality of life indices and increasing maximal and submaximal exercise capacity measured by oxygen consumption were demonstrated in several studies, even at diminished myocardial energy cost[15]. Even if CRT has proven to improve several hemodynamic and clinical indices in almost 70% of the patients, it is still difficult to define responders to CRT treatment, and most commonly composite clinical endpoints have been used. Of major interest is of course to decrease the number of clinical non responders, which is described to be at approximately 30 %[16,17].

The main focus of this manuscript is to review LV asynchrony, and to present an overview of techniques for identification of left ventricular intraventricular and interventricular asynchrony.

Assessment of left ventricular asynchrony

Electrical asynchrony

Surface ECG: The widely used marker to indicate LV asynchrony has been the surface ECG. The rational for that, is that the electrical delayed stimulation may lead to a mechanical delay of the respective LV areas. In LBBB the lateral free wall is activated later than the interventricular septum and thus leads to a delayed contraction of LV free wall. This surrogate marker represented by LBBB is one of the criteria indicating implantation of CRT[1]. It is shown that LBBB leads to impaired pump function which can be improved by CRT [7-9]. LBBB is also a predictor of sudden cardiac death in DCM[18] .

In 29 patients Alonso et al showed that reducing the QRS duration by CRT correlated to a positive clinical response suggesting a hemodynamic improvement associated with narrowing of QRS indicating reduction of the mechanical asynchrony of LV contraction. The study concluded even that the optimal placement for hemodynamic LV improvement of the right and LV leads would be those sites that could induce the greatest shortening of QRS duration[19]. However, still there is no evidence for prediction of clinical response based on baseline QRS width or by the reduction of the QRS width effected by CRT in the individual patient.

Electrophysiological mapping: An additional method to elucidate the intraventricular activation pattern in HF patients eligible for CRT is electroanatomical activation mapping. In 26 patients Peichl et al. showed that the surface ECG is of limited value to describe the complex conduction disturbance of the LV[20] . They found differences in electroanatomical LV activation between ischemic cardiomyopathy and DCM with similar QRS morphology on the surface ECG.

Also Yu et al. showed that endocardial electrical LV activation sequences was variable among 7 HF patients with LBBB[21]. Lambiase et al. showed hemodynamic improvements in 10 HF patients by CRT in terms of increased cardiac output and dP/dt(max) when the LV was paced by placing the pacing lead away from areas with demonstrated slow conduction[22]. They concluded that clinical non response may reflect LV lead placement in regions with slow conduction which can be avoided by pacing in more normally activated LV regions.

Mechanical asynchrony

3D-tagged magnetic resonance imaging (MRI): Asynchronous contraction of LV was demonstrated in patients with DCM with intraventricular conduction delay by Curry et al. , who used MRI[23]. MRI is a time consuming method and can so far not be employed in patients with implanted pacemakers.

Scintigraphic blood pool and phase image analysis: By using gated equilibrium radionuclide angiography and Fourier phase analyses Fauchier et al. demonstrated in 103 patients with DCM that QRS duration was related to both interventricular and intraventricular asynchrony[24]. Further, intraventricular asynchrony was an independent predictor of cardiac event (cardiac death, worsening of HF and heart transplantation) in DCM and the prognosis was related to intraventricular rather than to interventricular asynchrony.

Another radionuclide angioscintigraphy study by Toussaint JF et al. in 21 patients showed that resynchronization by CRT between LV apex and base which persisted up to 12 months was also associated with a persisting improvement in LV systolic function[25]. The same group showed in 34 patients that basal asynchrony and early resynchronization demonstrated by radionuclide angioscintigraphy might predict long-term evolution of ventricular function after CRT in patients with very broad QRS (179 ± 18)[26].

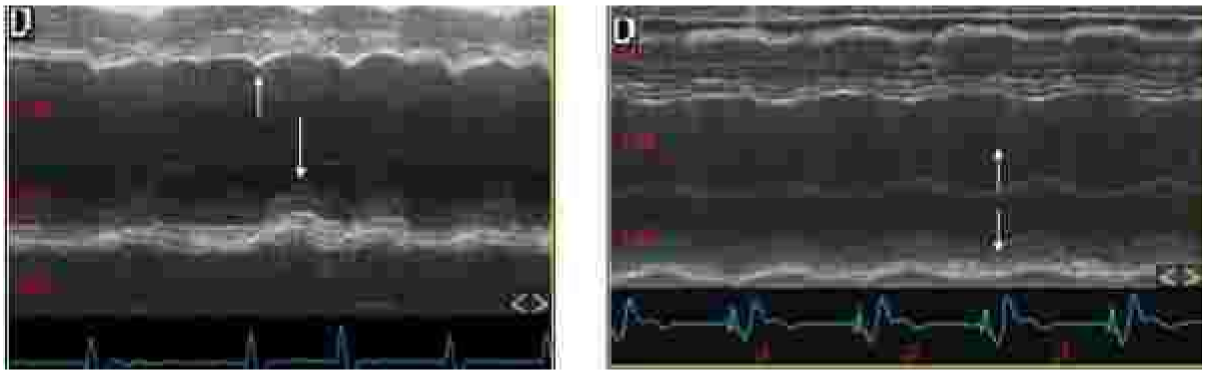
Kerwin et al. used gated blood pool scintigraphy in 13 patients to demonstrate asynchronous contraction of LV and to show the resynchronizing effect of CRT[27]. DCM with intraventricular conduction delay was also associated with significant interventricular asynchrony. Improvements in interventricular synchrony during CRT correlated with acute improvements in LV ejection fraction. One limitation of the scintigraphic methods is the relatively poor time resolution of 30 fps.

Echocardiographic methods: Echocardiography is an essential method to diagnose HF and is also used to evaluate the effect of treatment to improve cardiac performance. The echocardiographic measurement of LV fractional shortening by M-mode and EF measured from two-dimensional images by using Simpsons method in accordance with the recommendations of the American Society of Echocardiography Committee, are widely used parameters for cardiac evaluation[28]. An additional method is the use of the Doppler principle to measure and quantify blood flow velocity. The method is based on the fact that the frequency of reflected ultrasound from a moving target towards the transducer is higher than the transmitted frequency. When the reflecting target is moving away from the transducer, the frequency is lower than the original transmitted ultrasound frequency. The Doppler signals from the moving red blood cells have low amplitude and high velocity, and the echocardiographic methods used are continuous wave Doppler, pulsed Doppler and color flow imaging. A recently developed ultrasonographic method is tissue velocity imaging (TVI). This method uses frequency shifts of ultrasound waves to calculate myocardial tissue velocity at lower velocities, but higher intensity compared to blood flow velocity measurement. TVI can be used to measure movements of cardiac structures and to assess regional LV contractility, which has been shown in both animal experiments and human studies[29,30]. The TVI method is used in a wide range of cardiac diseases to characterize systolic ejection velocities. Recent research showed the usefulness of TVI for assessing the severity of LV and interventricular asynchrony in patients with HF receiving CRT because of the excellent time resolution which can be achieved by TVI providing frame rates of 100 frames per second (fps) or more, i.e. a time resolution of 10 ms. Another assessment of regional LV function is the calculation of the myocardial velocity gradient or strain rate imaging, reflecting deformation and thereby a more direct measurement of contraction and relaxation using data set from color-coded TVI[31-33]. Postprocessing the color coded TVI (c-TVI) data set can as well be used to evaluate the time related contraction pattern of the LV, which is less angle dependent than strain itself. Major interest of the regional time aspect of LV contraction measured bt TVI has increased because of the promising results of CRT in HF patients.

Conventional echocardiography

M-Mode: Using the septal-to-posterior wall motion delay in M-mode recordings from the parasternal short axis view Pitzalis et al. demonstrated in 20 patients that a septal-to-posterior wall motion delay of ≥ 130 ms and QRS duration ≥ 150 ms predicted response to CRT in terms of > 15 % reduction of left ventricular end-systolic volume index in 79% of the patients. The authors demonstrated the prediction of reverse remodelling by septal-to-posterior wall motion delay to be more precise than the QRS duration (accuracy 85% vs. 65%)[34]. The same group demonstrated using this method in 60 patients that ischemic cardiomyopathy, changes in the QRS duration after implantation, and SPWMD significantly correlated with progression toward HF (defined as a worsening clinical condition leading to a sustained increase in conventional therapies, hospitalization, cardiac transplantation, and death). A long SPWMD remained significantly associated with a reduced risk of HF progression. An improvement in LVEF was observed in 79% of the patients with a baseline SPWMD of ≥ 130 ms and in 9% of those with an SPWMD of <130 ms (p <0.0001).[35]

The septal-to-posterior wall motion delay in M-mode recordings can also be examined in the parastrenal long axis view and a decrease of the posterior delay during CRT can be shown (**Figure 1**).



Prior to CRT **3 Months of CRT**

Figure 1: The septal-to-posterior wall motion delay in M-mode recordings can be examined in the parastrenal long axis view and a decrease of the posterior delay during CRT can be shown

Doppler echocardiography: The measurement of interventricular electromechanical delay using pulsed Doppler imaging was examined by Rouleau et al in 35 patients with DCM[36]. A QRS width of more than 150 ms was correlated with a delayed aortic flow compared to the pulmonary flow as well as a delayed mitral annulus systolic wave compared to tricuspid annulus systolic wave. The authors concluded that QRS of more than 150 ms is a good marker of interventricular mechanical asynchrony.

Various echocardiographic parameters of ventricular asynchrony were examined by Bordachar et. al in 41 patients undergoing CRT. Changes in interventricular asynchrony, defined as the difference between the aortic and pulmonary pre-ejection delays and determined as the time from the onset of the QRS complex to the beginning of each respective systolic ejection by pulsed wave Doppler imaging were not correlated with changes in cardiac output, whereas several TVI modalities could confirm high correlation with hemodynamic changes[37].

The use of pulsed tissue velocity Doppler imaging by Ansalone et al in 21 non ischemic patients receiving CRT demonstrated a reduction of asynchronous contraction of LV basal segments. After CRT, LV performance improved significantly in patients with better LV resynchronization evaluated by TVI, whereas the QRS narrowing was not predictive of this functional improvement[38].

The effect of inflow based AV optimization adopted from use in DDD pacing[39] showed in CRT responders, that changes in preload only partly could explain the improved LV performance in terms of pulse pressure. The authors emphasize the importance of LV resynchronization for improved LV performance[40].

Functional mitral regurgitation is reduced by CRT in patients with HF and LBBB shown in 24 patients by Breithardt et al, explained by a more coordinated LV contraction and due to the increased closing force (left ventricular systolic pressure rise)[41] .

Newer echocardiographic methods

Contrast echocardiography: A new echocardiographic method based on contrast variability imaging was used in 10 patients by Kawaguchi et al. to quantify asynchrony and magnitude of resynchronization achieved by CRT[42]. The method showed that lateral wall motion occurred earlier during CRT and that both spatial and temporal asynchrony in the LV contraction declined with LV pacing and CRT correlated with increasing ejection fraction.

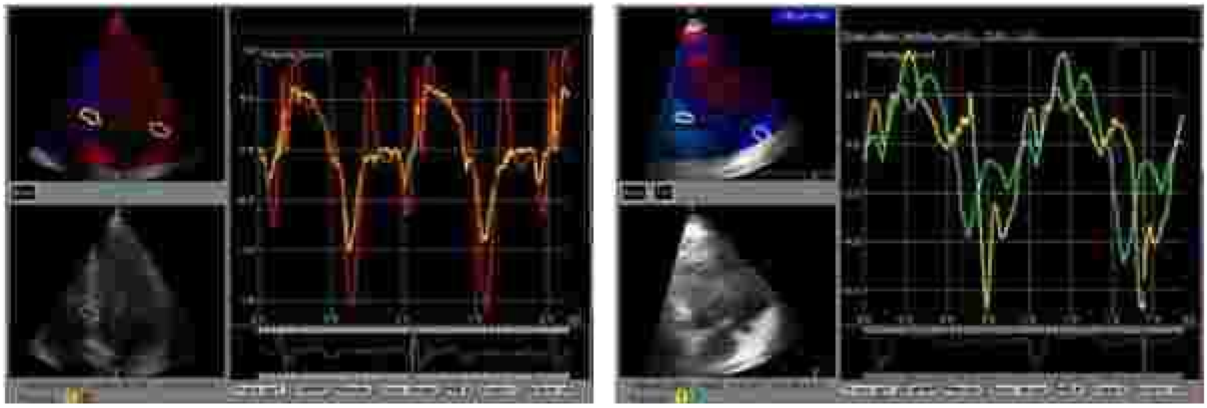
Borderline detection: A semiautomatic border detection method based on the fact that each region of the ventricular endocardial wall undergoes a periodic cycle of inward and outward displacement was performed in 34 patients by Breithardt et al. The authors showed a septal-lateral resynchronization during CRT by using this echocardiographic phase analysis of radial endocardial wall motion predicting an acute hemodynamic response (dp/dt)[43] .

Three dimensional echocardiography: Three dimensional (3 D) echocardiography has been used by Kim et al. to document hemodynamic improvement by CRT and additionally to identify LV segments with asynchrony[44]. The latter 3D echocardiographic method uses semi-automated contour analysis by a fast-rotating second harmonic transducer and was used in 16 patients by Krenning et al. to demonstrate a reduction of the LV contraction delay during CRT. The authors claim that this new 3D echocardiographic method might also be used to select the optimal pacing site during CRT [45].

Tissue Color Doppler Velocity Imaging (c-TVI): The excellent time resolution of c-TVI by using a postprocessing procedure is used in several studies to demonstrate the regional time aspect of LV contraction. In addition to the high time resolution another main advantage of c-TVI method is the possibility of comparing the contraction pattern of different LV regions simultaneously from the recording. Synchronicity of LV contraction pattern in the structurally normal heart is demonstrated and compared to HF patients with bundle brunch block showing a significant asynchrony within the LV in the HF patients[46,47]. (**Figure 2**)

Comparing surface ECG with the mechanical contraction pattern in HF patients showed that neither QRS duration nor QRS pattern predicts the mechanical asynchrony. Even HF patients with normal QRS width can have significant LV asynchronous contraction[48,49]. The reduction of post systolic LV contraction was demonstrated during CRT by Soegard et al. and is assumed to be an indirect marker of LV resynchronization[50]. Based on data from 25 patients receiving CRT the same group did also show by tissue Doppler imaging that occurrence of postsystolic contraction prior to CRT may predicts improved systolic performance and reversed LV remodelling during CRT whereas QRS duration failed to predict resynchronization efficacy[51] .

Using c-TVI has shown resynchronization during CRT, both as measurement of regional contraction timed to the QRS complex by Yu et al. and measured as an absolute resynchronization of the contraction of LV septum and the lateral free wall by Schuster et al. and by Bax et al.[52-53,54]. One study by Bax et al in 25 patients showed a possible predictive value of c-TVI asynchrony prior to implantation which points in the same direction as Yu et al in 30 patients[55,56].



A B

Figure 2: c-TVI curves at basal sites of interventricular septum (IS) and lateral free wall (LFW). **A** Control person: normal peak velocity and synchronous peaks at IS (yellow line) and LFW (red line). **B** Heart failure patient with LBBB: reduced peak velocities and asynchronous peaks at IS (yellow line) and LFW (green line).

Strain and strain rate imaging: The measurement of LV segment shortening or lengthening (strain) is also used to demonstrate resynchronization during CRT, but the more angle dependency of strain compared to TVI allows only the measurement of relative resynchronization because of the fact that the different regions have to be examined in separate recordings. However a resynchronization effect by CRT is shown using the strain method by Breithardt et al.[57]

Summary

The above mentioned manuscripts deal partly with concordance or disconcordance of electrical and mechanical markers of asynchrony. Despite the findings of angioscintigraphic asynchrony related to the QRS complex[58], in summary surface ECG seems not to be a sufficient marker of the mechanical events within the LV. However, the invasive endocardial activation mapping correlated well with tissue Doppler imaging to locate the latest segment of activation in the 7 patients with HF and LBBB published by Yu et al.[21]. The possibility of improving the LV function deteriorated by asynchrony using CRT, calls for a method of selecting patients with mechanical LV asynchrony prior to implantation of CRT. The published material so far demands in our opinion at least one additional method to surface ECG to reveal LV asynchrony. Several non invasive methods have been used and in small studies even predicted clinical or hemodynamic improvement by CRT. There is still no gold standard for assessment of LV asynchrony for CRT, but both traditional and new echocardiographic methods have shown both asynchronous LV contraction in HF patients, and resynchronized LV contraction during CRT and should be implemented as additional methods for selecting patients to CRT.

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