Review Article

Noninvasive Cardiovascular Imaging as a Guide to Cardiac Resynchronization Therapy

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Cardiac resynchronization therapy (CRT) is an established therapeutic option with proven efficacy in patients with symptomatic HF. Large, prospective, clinical trials have demonstrated the important role of biventricular pacing in improving symptoms and reducing both hospitalization and mortality in HF patients.[1-5] However, a significant proportion of patients (~30%) do not respond to CRT, partly because of inappropriate selection before pacemaker implantation.[1,6]

A prolonged QRS duration, i.e. >120 ms and ideally >150 ms, as a selection criterion[7] for CRT in patients with chronic HF and a left ventricular ejection fraction (LVEF) ≤35%, who remain in NYHA functional class II or III and ambulatory IV despite adequate medical treatment, is not accurate for predicting a favorable CRT response. About 70% of HF patients with a wide QRS complex present mechanical asynchrony, while on the other hand, approximately 30% of patients with a normal QRS complex (<120 ms) have mechanical asynchrony[8] and could benefit from CRT.

Recent advances in echocardiography, as well as emerging imaging modalities such as cardiac magnetic resonance imaging (CMRI), cardiac computed tomography (CCT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), have attracted increasing interest for the guiding of CRT in HF patients. The aim of this review is to discuss the role of noninvasive cardiovascular imaging in the selection and follow up of patients who are candidates for CRT.

Echocardiography

Conventional echocardiography has a central role in the evaluation of CRT candidates.[7,9] An echocardiographically estimated LVEF≤35% constitutes one of the criteria for biventricular pacing, while Doppler indices are used for optimization of the pacemaker after the implantation, adjusting the delay between pacing of the left atrium and ventricle (AV delay), and the delay between pacing the left and right ventricle (VV delay). In addition, a reduction of LV end-systolic volume by >15% and an increase in LVEF by >5% 3-6 months after device implantation are reliable parameters for characterizing the responders to CRT.

Echocardiography in the evaluation of mechanical asynchrony

Echocardiography, and novel echocardiographic techniques in particular, may also be beneficial for evaluating the pattern and severity of cardiac mechanical asynchrony, regardless of the duration of the

QRS complex on the electrocardiogram, as well as for guiding the LV lead of the biventricular pacemaker to the site of latest mechanical activation.

The term "mechanical asynchrony" reflects the time differences in contraction (systolic asynchrony) or relaxation (diastolic asynchrony) between different myocardial segments of the LV (intraventricular asynchrony) or between the LV and right ventricle (RV) (interventricular asynchrony).[10] Intraventricular asynchrony is commonly seen in patients with HF, where alterations in cardiac structure and function may lead to electromechanical disturbances in some regions of the failing myocardium. In most cases, there is an early activation and contraction of the interventricular septum and late activation-contraction of the inferolateral LV wall, resulting in heterogeneously increased wall stress, contractile impairment, and delayed relaxation.[11] Among all types of mechanical asynchrony, intraventricular is considered as the main factor associated with systolic dysfunction in patients with HF and could play an important role in the selection of CRT candidates.[12]

The echocardiographic methods currently used for the evaluation of asynchrony are M-mode and Doppler echocardiography, tissue Doppler imaging, speckle tracking imaging, and three-dimensional echocardiography.

M-mode and Doppler echocardiography

M-mode echocardiography is a simple, conventional method for the evaluation of LV intraventricular asynchrony that estimates the septal-to-posterior wall radial motion delay, using the long- and mainly the short-axis parasternal view (Figure 1). The evaluation of intraventricular asynchrony using M-mode echocardiography is feasible in 50-60% of patients and may be enhanced using the color-coded M-mode technique. According to Pitzalis et al,[13] a cutoff value of >130 ms for the time delay between the septum and the posterior wall before CRT predicts a better outcome after biventricular pacing in patients with non-ischemic heart failure. However, this finding is not in agreement with the results of another study, which failed to correlate the septal-to-posterior wall motion delay with reverse remodeling or clinical improvement in patients undergoing CRT.[14] Despite its high temporal resolution, M-mode evaluates cardiac asynchrony in only one dimension and is usually limited by poor acoustic windows. Besides, it presents difficulties in differentiating the abnormal septal motion due to right ventricular pressure or volume overload from that due to passive or active movement of myocardial segments in patients with wall motion abnormalities, such as prior myocardial infarction or scar. For these reasons, M-mode is not ideal for the evaluation of asynchrony and it should be used only as a complementary method, in combination with other echocardiographic techniques.

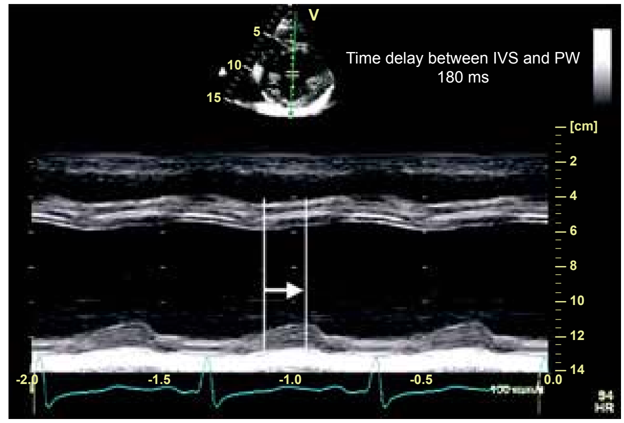

Figure 1. M-mode short-axis view of the left ventricle. The time delay between the maximum contraction in the intraventricular septum (IVS) and posterior wall (PW) is 180 ms, suggesting mechanical asynchrony.

Doppler echocardiography contributes mainly to the evaluation of LV-RV interventricular asynchrony, by measuring LV and RV pre-ejection intervals from the onset of the QRS on the ECG to the initiation of aortic and pulmonary outflow on pulsed-wave Doppler. A time difference of ≥50 ms in the pre-ejection period constitutes a marker of interventricular asynchrony, with additional prognostic value concerning the response to CRT.[15] However, interventricular asynchrony is considered, according to other studies,[16,17] as a nonspecific marker for the evaluation of cardiac asynchrony, which is less valuable than intraventricular asynchrony in the prediction of the response to biventricular pacing.

Tissue Doppler imaging

Tissue Doppler imaging (TDI) is used to estimate the longitudinal systolic velocity or strain/strain rate of any LV segment. The time to peak systolic velocity or strain of any opposing LV wall is then compared to evaluate the potential presence of intraventricular asynchrony. TDI has been the most investigated echocardiographic modality for evaluating mechanical asynchrony and can be carried out either during the echocardiographic examination of the patient, or offline.

Several models have been constructed, based on this modality, to evaluate intra-ventricular asynchrony. According to the 2-segment model,[16] the asynchrony index is derived from the time difference between the peak systolic velocities of the basal septal and lateral wall, using the apical four-chamber view. A time delay >65 ms is characterized as intraventricular asynchrony and is predictive of the clinical response (improvement in NYHA class and six-minute walking test) and reverse ventricular remodeling (reduction of LV end-systolic volume by >15%) post CRT (Figure 2).[16,18] A 6- or 12-segment model, acquired using multiple views (4-, 2-, and 3-chamber views), is used for the estimation of the time to the peak velocity in the basal 6, or basal and mid 12 myocardial segments, respectively. Asynchrony index in the 6-segment model is defined as a peak velocity difference >110 ms and predicts CRT response and reverse remodeling.[19] A standard deviation >33 ms in the 12-segment model indicates to severe intraventricular asynchrony and predicts reverse remodeling post CRT with sensitivity and specificity 100% and 78%, respectively, when the QRS complex is >150 ms, and 83% and 86%, respectively, when the QRS complex duration is 120-150 ms.[20-22]

Tissue synchronization imaging (TSI) is a parametric TDI-based technique, used additionally for the qualitative evaluation of synchronicity. The early and late activated segments are displayed in green and yellow/orange/red, respectively, depending on the severity of the delay. The TSI algorithm automatically calculates and color-codes the time to peak tissue velocity in every depicted myocardial segment within a specified time interval, with reference to the QRS signal (Figure 3). It has been demonstrated that TSI accurately measures LV asynchrony and predicts the

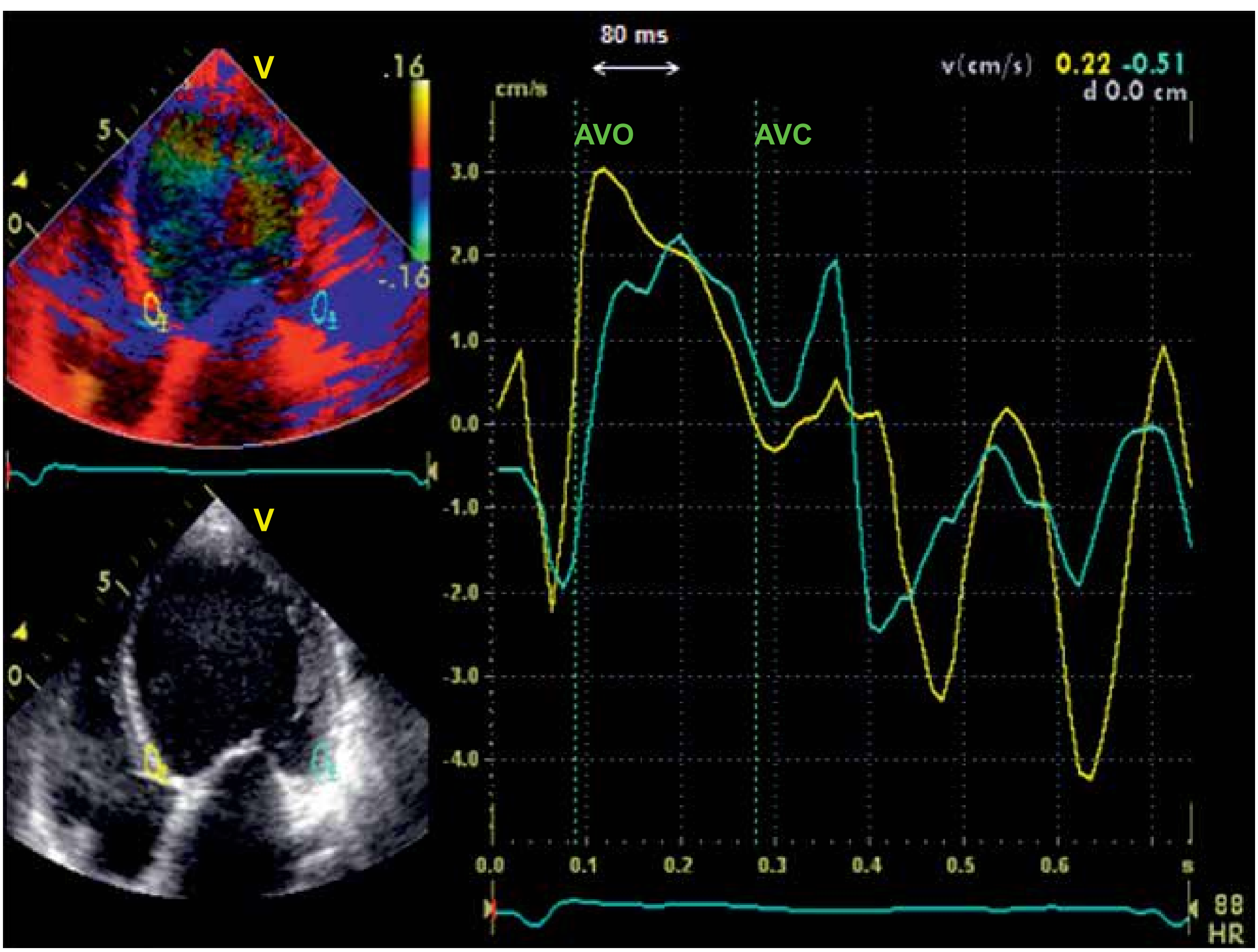

Figure 2. Four-chamber apical view. The time difference of 80 ms between the peak systolic velocities of the basal septal (yellow curve) and lateral wall (light blue curve) suggests intraventricular asynchrony.

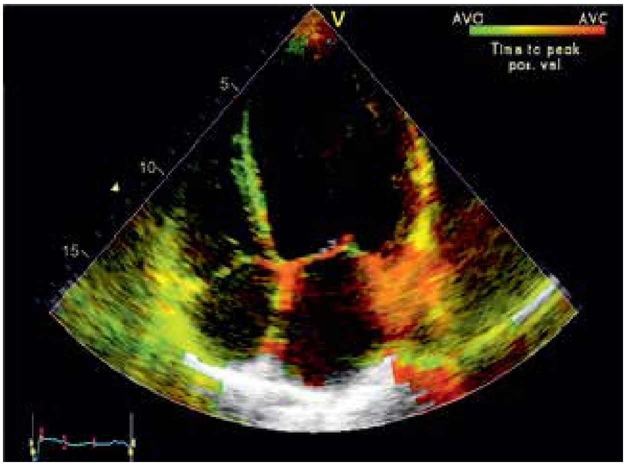

Figure 3. Four-chamber apical view. Tissue synchronization imaging in a heart failure patient with mechanical asynchrony. The early activated segment is displayed in green and the late segment in yellow/orange.

acute[23] and long-term[24] response to CRT with a cut-off value of 65 ms for the time to peak systolic velocity delay. In addition, lead placement at the site of the latest systolic velocity, as evaluated by TSI time-to-peak velocities, is associated with the greatest clinical and hemodynamic benefit of CRT.[25] However, other studies have demonstrated a lower predictive value and poor reproducibility of TSI compared to TDI for the evaluation of timing of contraction.[26]

Another parameter of cardiac asynchrony, based on TDI indices, is the "apical rocking motion" of the LV, which is the mechanical consequence of asynchronous contraction induced by left bundle branch block (LBBB).[27] It comprises a short initial septal contraction during the isovolumic contraction period, followed by lateral movement of the apex and stretching of the septum during the ejection time, and can be easily visualized in the apical 4-chamber view and quantified by measuring apical transverse motion from the integration of velocity and displacement traces. In a recent study,[28] apical rocking was used as a surrogate asynchrony parameter in patients undergoing dobutamine stress echocardiography (DSE). Apical rocking during DSE predicted the CRT response and was associated with improved long-term survival after biventricular pacing.

As regards strain and strain-rate indices derived from TDI data, they are theoretically superior in the evaluation of "true" myocardial contraction, discriminating this from movements due to a tethering effect from adjacent myocardial segments. Nonetheless, it has been reported in previous studies that they are inferior to TDI velocities in predicting the LV reverse remodeling response after biventricular pacing,[29,30] mainly because of the higher variability in measurements.

TDI, in general, is a simple method for the evaluation of cardiac asynchrony and presents high temporal resolution, similar to that of M-mode echocardiography. On the other hand, the analysis is time-consuming and it is not possible to assess more than two LV segments simultaneously. Furthermore, the results depend on the angle of the ultrasound beam, and there is high intra- and interobserver variability due to the fact that a slight change in the position of the sample volume may lead to a significant change in the velocities or strain.[31]

Speckle tracking imaging

Speckle tracking imaging (STI) is a relatively novel echocardiographic technique, whereby specific acoustic markers of the myocardium, called "speckles," are tracked, frame by frame, during the cardiac cycle, to estimate regional myocardial strain (Figure 4). STI allows the assessment of deformation and asynchrony in longitudinal, radial, circumferential and rotational axes, having a very good correlation with CMRI.[32] It is an angle-independent method and can efficiently differentiate myocardial active wall thickening from passive wall motion due to tethering effects. However, STI has low temporal resolution—particularly in dilated hearts, which require a large sector size for imaging—and it is a time-consuming method, though less so than TDI. A previous study showed that a time difference of >130 ms in peak radial strain between the anterior-septal and posterior wall predicts the response to CRT with sensitivity and specificity 83% and 80%, respectively.[33] In another study,[34] the concurrent evaluation of longitudinal velocity and radial strain was able to predict effectively the response post CRT. The combination of a time difference of >130 ms in peak radial strain between the septal and posterior wall and a time difference of >60 ms in peak longitudinal velocity between the septal and lateral wall was correlated with the greatest improvement in NYHA and LVEF post CRT. According to a recent, multicenter trial[35] that included 130 patients undergoing CRT, both radial and longitudinal strain were associated with a favorable LVEF response and a long-term reduction in mortality, LV assist device implantation, and transplantation, over 3.5 years of follow up.

STI may have also offer a potential benefit in terms

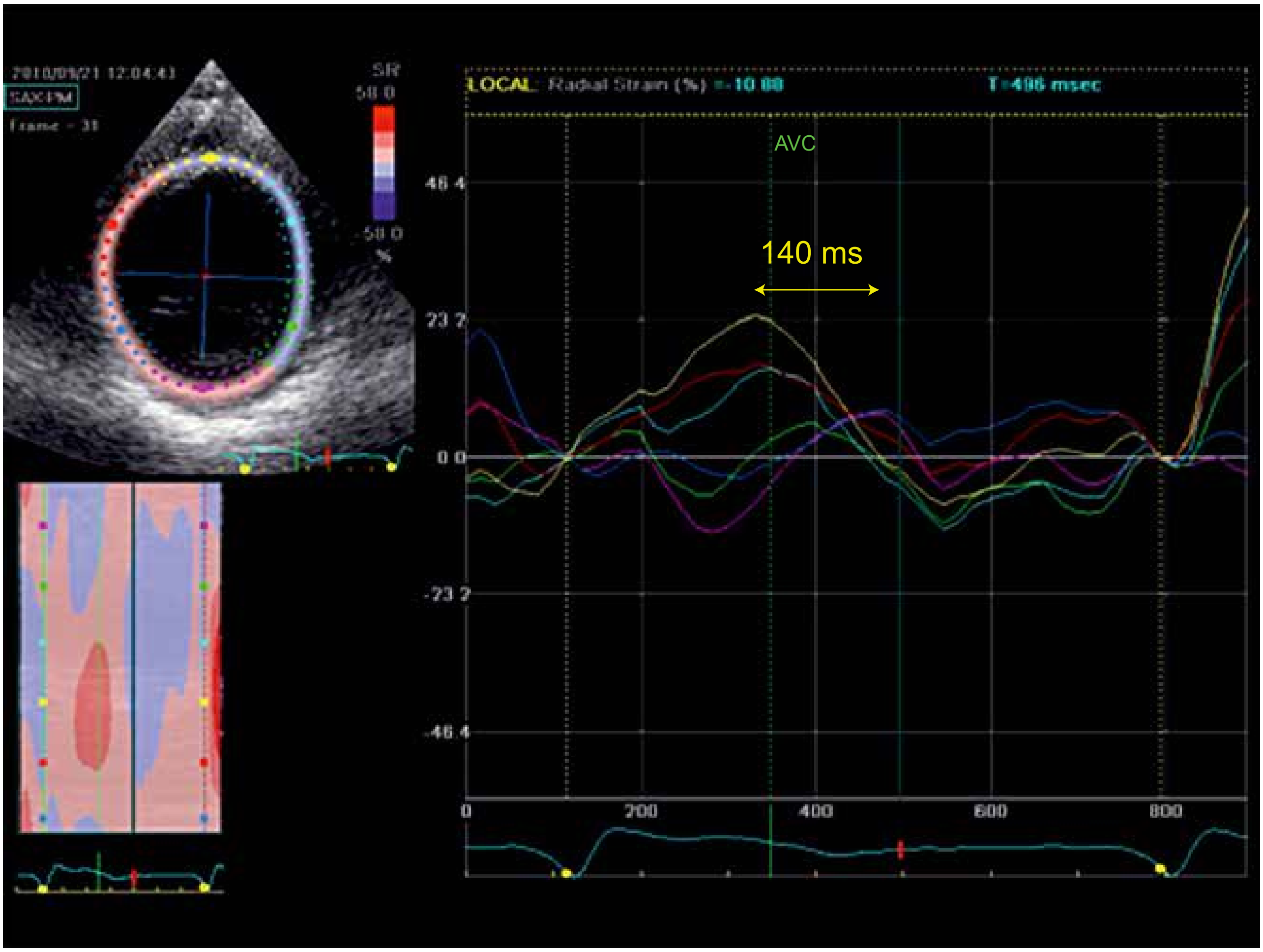

Figure 4. Short-axis view. Radial strain in six myocardial segments, estimated using speckle tracking imaging. The time difference between the peak radial strain in the anterior-septal and posterior wall is 140 ms.

of echocardiographically guided LV lead positioning. In a sub-study of the STARTER trial,[36] patients with a QRS duration <150 ms and/or non-LBBB, who had the LV lead in the exact concordant or adjacent segment to the site of latest activation according to STI radial strain, exhibited a lower event rate of HF hospitalization or death within two years of follow up. In another study,[33] patients with LV lead placement concordant to the latest activated myocardial segments, as measured by STI radial strain, presented more favorable reverse remodeling compared to those with a discordant lead position.

Three-dimensional echocardiography

Three-dimensional echocardiography (3DE) is a promising technique for the global assessment of LV synchronicity. It can simultaneously evaluate global and regional ventricular volumes and contraction during the cardiac cycle. Asynchrony indexes may be acquired by three methods: triplane tissue Doppler (TTD), regional volume-time curves (RVTC) and three-dimensional speckle tracking (3DST).

TTD imaging allows the simultaneous acquisition of TDI and TSI from all LV segments (apical 4-, 3-, and 2-chamber views) during a single heartbeat. The software automatically calculates the time from the beginning of the QRS to peak systolic velocity in 12 segments.

In the RVTC technique, a full 3D volume of the LV is first acquired, the endocardial borders are traced, and a virtual model of the LV cavity and bullseye are then obtained. Regional volume-time curves for each of the 16 or 17 LV segments are displayed and intraventricular asynchrony is finally assessed by comparing the times to the minimal regional volume for each segment (Figure 5). The systolic asynchrony index is the standard deviation of time to minimal regional volume expressed as a percentage of the cardiac cycle. A value >6.4% predicts the response to CRT with 88% sensitivity and 85% specificity, according to a previous study.[37] Marsan et al, in another study,[38] suggest that an LV asynchrony index from 16 segments >5.6% predicts a reduction in LV end-systolic volume by >15% post biventricular pacing.

Finally, 3DST is a novel application that analyses regional 3D wall motion using regional curves of displacement. 3-D datasets are displayed in 5-6 different cross-sections; the endocardium is traced, and the epicardium is then automatically generated and manually adjusted. The software automatically divides the LV into 17 color-coded standard segments and generates corresponding time-strain curves from which the potential asynchrony in contraction can be evaluated (Figure 6). It has been shown[39] that a strain asynchrony index ≥3.8%, using area tracking, was predictive of the response to CRT with 78% sensitivity and 100% specificity. Recently,[40] the role of rotational asynchrony in the long-term effects of CRT was also investigated using 3DST, and it was shown that global peak twist does not present significant differences between the responders and non-responders to CRT.

Three-dimensional echocardiography allows the global assessment of LV synchronicity within a few minutes, with excellent spatial resolution. In addition, it differentiates myocardial active wall thickening from passive wall motion (3DST). On the other hand it has low temporal resolution and is difficult to perform in patients who have an irregular heart rhythm and very large ventricles. There are no optimal cutoff

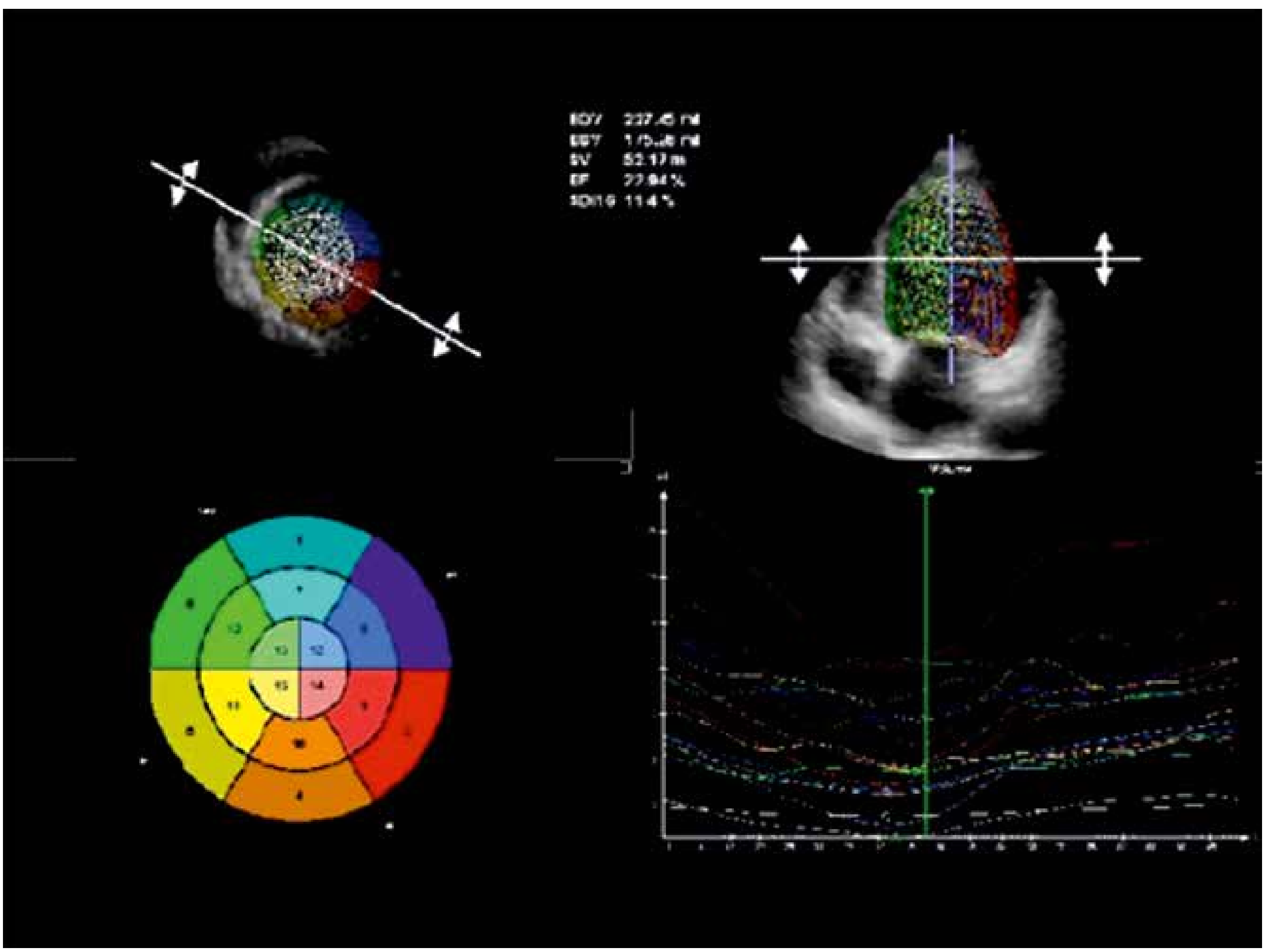

Figure 5. Regional Volume-Time Curves technique. RVTC for each of the 16 LV segments are displayed and intraventricular synchronicity is assessed by comparing the times to minimal regional volume for each segment. An asynchronized myocardial contraction is demonstrated as the 16 myocardial segments reach their minimal volumes in various time and standard deviation of time to minimal regional volumes is 11.4%.

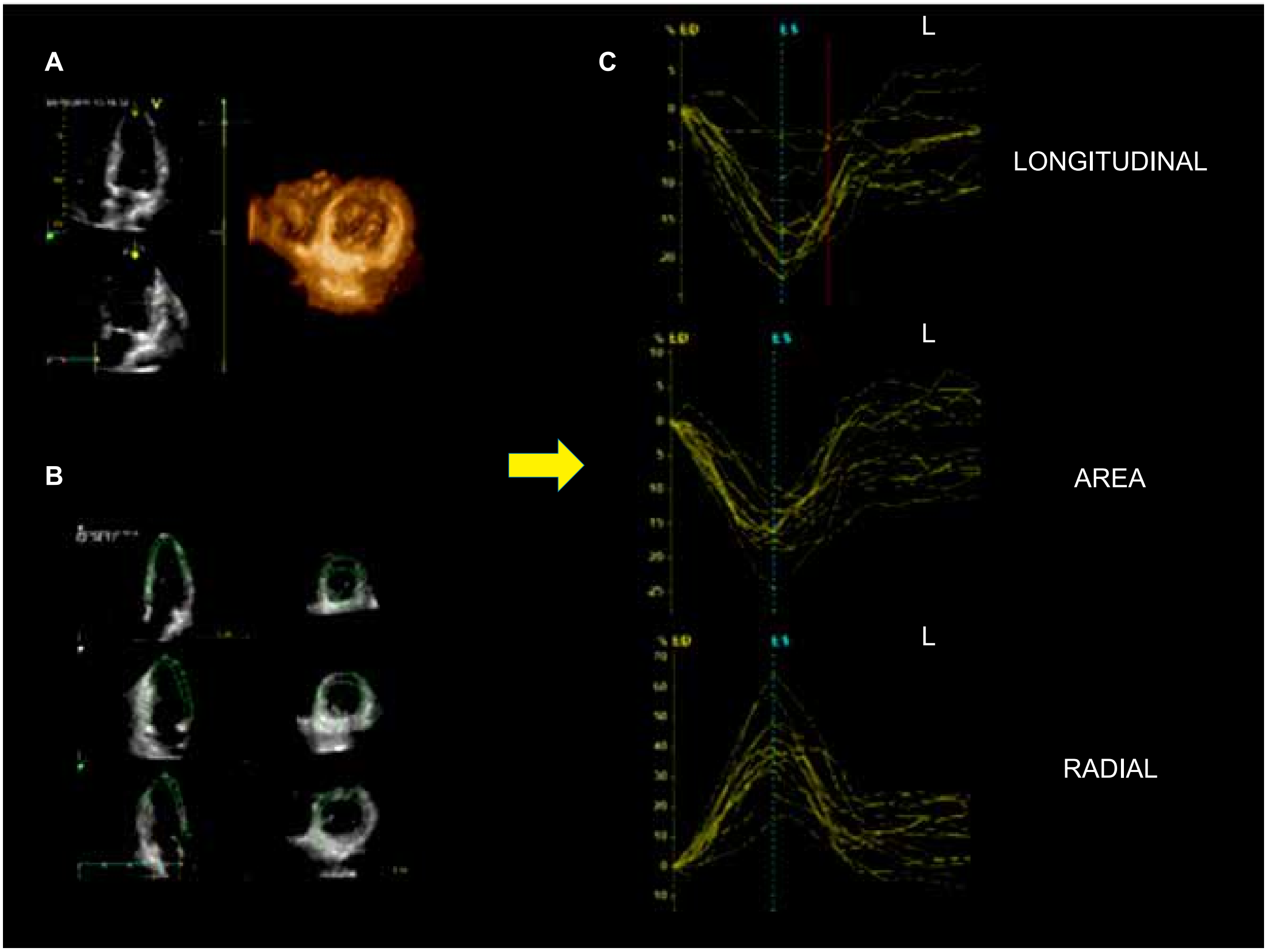

Figure 6. Three-dimensional speckle tracking. 3-D datasets (A) are displayed in three apical and three short-axis views, where the endocardium is traced and the epicardium is then automatically generated and manually adjusted. (B) The longitudinal, area (which is coupled with factors from both longitudinal and circumferential strain), and radial strain curves and corresponding time-strain curves are then automatically taken from the 17 left ventricular segments. (C) The time to peak strain is then estimated for each of the 17 strain curves and, finally, the asynchrony index is measured from the standard deviation of the curves. In this case longitudinal, area, and radial strain curves reach their peak values almost simultaneously, demonstrating synchronized contraction.

values so far, and the method still requires expertise and further study.

In conclusion, the echocardiographic evaluation of mechanical asynchrony is difficult, owing to the complex and three-dimensional cardiac shape and movement. Although echocardiography has a considerable role in the evaluation of patients with HF, none of the current echo indices is, so far, considered ideal for the estimation of asynchrony. The ranges of normal values have been evaluated in a limited number of patients, while in 10% of healthy subjects more than one echo-parameter of intraventricular asynchrony can be outside the normal range of values.[41] A relatively recent, large, multicenter, nonrandomized study,[42] despite its design problems and the lack of expertise of many centers in the evaluation of the novel echo indices, demonstrated a failure of the conventional and TDI echo parameters to improve patient selection for CRT, mainly as a result of the number of factors inherent in the determination of these values, including operator dependence, angle of interrogation, and acoustic windows.[9,42] Besides, the novel techniques of speckle tracking and 3DE need further evaluation. The combination of conventional and novel echo techniques in clinical practice is currently, according to the authors of this review, the best approach in order to evaluate mechanical asynchrony and reach the appropriate decision for CRT.

Stress echocardiography in CRT

Stress, dobutamine, or exercise echocardiography provides additional help in the identification of CRT candidates, mainly by evaluating myocardial viability and the dynamic behavior of LV asynchrony.[43] Myocardial viability is assessed as both global and regional contractile reserve in the target myocardial segments for the LV lead (latest activated segments). Global LV contractile reserve is an independent predictor of event-free survival after CRT and its presence helps in predicting the clinical and echocardiographic response to CRT.[43,44] Recent studies have shown that assessment of LV contractile reserve concomitantly with other echo indices is more effective in identifying the CRT responders. Thus, in patients with a >20% increase in LVEF during low-dose dobutamine stress echo (LDDSE) and LV lead positioning in the most delayed mechanical segment, the response rates to CRT and HF hospitalization-free survival are improved,[45] while LDDSE contractile reserve along with interventricular asynchrony together result in better differentiation between responders and non-responders.[46] Regional contractile reserve in the segments of latest activation is estimated mainly using TDI and speckle tracking velocity and strain indices. It has been shown that an increase of 2% in regional strain, in combination with an improvement in LVEF, has predictive value in the evaluation of CRT responders,[47] whereas an absence of regional contractile reserve is associated with a non-significant improvement in mechanical asynchrony.[43]

As regards the latter, LDDSE intraventricular asynchrony, demonstrated by TDI indices or apical rocking motion, is associated with an improvement in LV systolic function post biventricular pacing and is considered as an independent predictor of CRT response.[28,48] Furthermore, according to a previous study,[49] the detection of a characteristic instantaneous septal motion during isovolumic contraction (so-called septal flash) seen on LDDSE may be considered as a marker of LBBB-induced asynchrony and could identify patients who will benefit from CRT.

Cardiac magnetic resonance imaging

CMRI is a modality that accurately evaluates myocardial structure and function.[36] In terms of CRT, CMRI seems to have an important, alternative role. Not only does it provide a reliable and accurate assessment of LV volumes and EF, but it also estimates the degree of mechanical asynchrony. It is also useful in the detection and quantification of scar tissue in myocardium and its spatial relation to the site of LV pacing. Finally, CMRI can successfully evaluate the venous coronary anatomy, allowing the optimal guidance of LV lead deployment.[50]

Evaluation of asynchrony

Interventricular and intraventricular asynchrony can be assessed qualitatively or quantitatively by a cine MRI technique as well as by more sophisticated techniques such as myocardial tagging, and strain-encoded imaging (SENC).[9,51]

Cine MRI allows the accurate evaluation of LV volumes and regional myocardial thickening using numerous short-axis slices from the apex to the base of the LV. It provides a relatively reliable estimation of inter- and intraventricular asynchrony using software that estimates the regional time from the beginning of contraction to minimum volume or to maximal radial wall thickening.[52,53] The CMR tissue synchronization index (CMR-TSI) is then calculated as the standard deviation from the respective time differences in end-systolic timing.[51]

CMRI-derived measurements of radial asynchrony, using feature tracking following the processing of routine CMRI cine acquisitions (FT-CMR), have been shown to be comparable with those from STI.[54] In a recent study,[55] the time delay of the radial displacement curves was estimated in a 17-segment LV model, creating a regional asynchrony map. There was a significant difference between the delay times in normal subjects and in patients with asynchrony, and a 70% agreement in identifying the latest contracting segment.

Finally, in another cine MRI study,[56] the LV asynchrony indices, evaluated by longitudinal strain analysis using a 4-chamber view, were significantly prolonged in patients with late gadolinium myocardial enhancement (LGE) and in CRT responders. According to the investigators, longitudinal strain analysis with 4-chamber cine MRI could also be useful in the evaluation of cardiac mechanical asynchrony.

Myocardial tagging (MT) is, in general, based on tissue markers called tags, which are produced by induced perturbations of the magnetization with selective radiofrequency saturation and form an orthogonal grid that is applied to the imaging plane. It can be used for myocardial motion and deformation analysis in two, and recently in three dimensions. The analysis of dark tagged lines allows the evaluation of myocardial deformation along longitudinal, radial, and circumferential axes and is analogous to STI, but with higher spatial resolution and reproducibility.[57,58] The evaluation of the time difference in intra-myocardial motion and deformation provides the assessment of myocardial asynchrony.[9]

SENC MRI is a technique that directly evaluates strain, using a standard tagging sequence, without the need for post-processing. It has a higher spatial resolution than standard tagging and provides the measurement of both circumferential and longitudinal myocardial strain data.[59]

The aforementioned CMRI techniques provide a useful approach for the evaluation and follow up of patients who are likely to have a biventricular pacemaker implanted, but a simplified and standardized asynchrony index that may be used to efficiently screen and follow up patients with CRT has not yet been established.

Evaluation of scar tissue

There has been accumulating evidence that the quantity and location of scar tissue in patients with HF play an important role in the results of CRT. CMRI, with the use of LGE, has become the gold-standard for the assessment of myocardial scarring.[60-62]

With respect to the quantity of scar, a significant direct relationship has been demonstrated between scar burden and response to CRT and an inverse relationship between scar burden and the reduction in LV end-diastolic volume post-CRT.[63] A cutoff value of <15% for scar burden in patients with ischemic and non-ischemic cardiomyopathy was associated with clinical responders to CRT, with a sensitivity and specificity of 85% and 90%, respectively.[60]

As regards the transmurality of the scar, a previous study[61] showed that, in patients with ischemic cardiomyopathy, scar transmurality ≥50% is associated with a suboptimal response to CRT, in terms of a composite clinical score (survival for 1 year with no heart failure hospitalizations, and improvement by ≥1 NYHA class or ≥25% in six-minute walking distance).

Regarding the location of the scar, it has been shown[62] that in patients with ischemic cardiomyopathy the posterolateral scar was associated with no change in asynchrony (14% vs. 81%, p: 0.05) and lower response rates to CRT. Furthermore, the combination of an absence of lateral wall transmural scar and the presence of asynchrony, characterized by a time delay >65 ms between septal and lateral wall, predict favorable effects post CRT with a sensitivity and specificity of 90% and 60%, respectively.[64]

Optimal lead location

The rate of responders post CRT is lower and LV remodeling is non-significant when the lead is not located in the latest contracting segment.[65] In addition, the myocardial scar occupying the LV pacing region is associated with a non-response to CRT.[66] CMRI seems to contribute to optimal lead placement, not only by the evaluation of the site and extension of the scar, but also by imaging the respective coronary vein.[66,67] Using a very simple adaptation of the routine 3D magnetic resonance coronary angiography sequence, CMRI can reliably depict coronary venous anatomy. The combination of scar assessment with LGE and the anatomy of the coronary veins allows the placement of the pacing leads in an area with the greatest electrical and mechanical activation delay, while the area of extensive scarring can be avoided.

Compared to echocardiography, CMRI has potential advantages with respect to mechanical asynchrony evaluation, such as less operator dependency and higher reproducibility of measurements. On the other hand, there are several limitations.[68] The analysis of CMR images is time-consuming regarding the acquisition and analysis of the data, while MT and SENCE are complex post-processing techniques that are mainly confined to research facilities. Moreover, CMRI cannot be used for bedside assessment, and is contraindicated in patients with implanted cardiac devices.

To sum up, CMRI allows the evaluation of the major factors that affect the response to CRT. However, despite its potential advantages in the assessment of asynchrony and in estimating the scar burden, there is no CMRI index currently used in clinical practice for the evaluation of patients undergoing CRT. Large, prospective trials are needed to address the role of CMRI in terms of hard clinical endpoints in CRT patients before this method can be adopted in clinical practice.

Other modalities

Cardiac computed tomography

CCT is an evolving technique for the evaluation of patients with HF. The recent developments of this method have led to improvements in both temporal and spatial resolution that have expanded the potential role of the technique in assessing patients who are to undergo biventricular implantation. CCT can contribute to the evaluation of mechanical asynchrony and the assessment of venous anatomy, assisting LV lead placement. The scar in the myocardium can also be identified and quantified by dual-source multidetector CCT.

The role of CCT in the assessment of asynchrony has been investigated in a previous study.[69] CCT was compared with echocardiography in patients with HF and normal controls and the index of asynchrony was estimated, using the standard deviation of the time from the R-wave of the electrocardiogram to maximal wall thickness as assessed by CCT. The asynchrony index was highly reproducible and statistically different between the two groups, presenting a good correlation with 2-dimensional ($r=0.65$, $p=0.012$) and 3-dimensional ($r=0.68$, $p=0.008$) echocardiographic asynchrony. Compared to CMRI, CCT overestimates the LV volumes and EF in patients with LV dysfunction and shows lower interobserver agreement, according to another study.[70]

The incremental value of CCT, in combination with the novel echo technique of STI, in guiding optimal left ventricular lead placement during CRT has also been demonstrated.[71] LV segments with the latest mechanical activation were estimated using STI radial strain and CCT was used for anatomical evaluation of the coronary sinus and its branches. According to the results, the combination of echocardiography and CCT is a feasible method of indicating the most appropriate LV site and coronary sinus branch for lead placement, and is thus effective in increasing the number of responders after CRT.

In conclusion, CCT could be a useful technique, in combination with echocardiography and CMRI, for the assessment of asynchrony, quantification of scar, and evaluation of venous anatomy, assisting in determining the optimal LV lead placement in HF patients undergoing CRT. The two major disadvantages of the method, radiation exposure and the prolonged time of the procedure, limit its use in clinical practice.

18F-fluorodeoxyglucose positron emission tomography/computed tomography

This is a hybrid method, during which patients undergo positron emission tomography/computed tomography (PET/CT) imaging after intravenous injection of 18F-fluorodeoxyglucose (18F-FDG). In theory, this method improves the detection of nonviable myocardial areas and provides an alternative means of evaluating asynchrony. In a previous study,[72] 18F-FDG PET/CT with 3D image fusion showed that CRT nonresponders had a greater global scar burden, a higher incidence of LV lead placement within scar tissue, and a higher rate of intraventricular asynchrony than did responders. In another study,[73] Gated F-18 FDG PET/CT was moderately correlated with gated Tc-99m sestamibi SPECT in assessing LV asynchrony. FDG PET/CT is not currently used in clinical practice for the evaluation of CRT candidates.

Single-photon emission computed tomography

SPECT represents a promising tool for the investigation of patients with HF and is useful for the selection and optimization of CRT. It evaluates LV systolic function and provides information about the amount of scar and the degree of mechanical asynchrony. SPECT myocardial perfusion imaging (SPECT-MPI) has been compared to LV mechanical asynchrony parameters obtained by echocardiography. In a study of 75 patients undergoing CRT,[74] SPECT-MPI demonstrated an excellent correlation with 2D echocardiography and a fairly good correlation with 3D echocardiography in assessing LV mechanical asynchrony.[75] Furthermore, in a study of 42 HF patients treated with CRT, the LV mechanical asynchrony parameters measured by SPECT were shown to predict the response to CRT.[76] The cutoff values from SPECT showed sensitivity and specificity values of 70% and 74%, respectively, in predicting the clinical response to CRT. Finally, regarding the relationship between baseline resting perfusion pattern and hemodynamic response to CRT, it has been shown that, despite clinical improvement, patients with severe resting perfusion defects on SPECT-MPI do not show significant improvement in LVEF or a reduction in LV volumes post CRT.[77]

The use of SPECT for the evaluation of CRT has several limitations, as the method has low spatial resolution, is time-consuming, and entails relatively high radiation exposure. Furthermore, the technique has not been tested and validated in randomized prospective studies. For these reasons SPECT is not yet indicated for patients undergoing CRT.

Conclusions

Although CRT has been proved to be an effective method of reducing morbidity and mortality in HF patients, there is still a high proportion of non-responders to biventricular pacing. Conventional echocardiography has an important role in the selection and follow up of patients undergoing CRT, and advanced techniques such as TDI, STI, and 3D imaging have extended its role in the evaluation of asynchrony. However, none of the current echo indices is considered as a gold standard for the guidance of CRT and, for the time being, the combination of conventional and novel echo parameters seems to be more effective in clinical practice. CMRI is a more sophisticated method, which not only evaluates mechanical asynchrony but also estimates the scar burden and the optimal placement of pacemaker leads, providing a more complete study for CRT. However, it is time-consuming and no large clinical trials have yet addressed its effects on hard clinical endpoints in CRT patients. Other modalities, such as CCT, PET, and SPECT, have been proposed as alternative methods for CRT evaluation, but have not yet been validated. Fusion techniques of more than one imaging modality are also under investigation and present a promising approach. Ultimately, future randomized control studies will be needed to further clarify the utility of noninvasive cardiovascular imaging as a guide to CRT.

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