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Echocardiography and Other Noninvasive Imaging Techniques in the Selection and Management of Patients with Cardiac Resynchronization Therapy

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Additional information is available at the end of the chapter

Abstract

Cardiac resynchronization therapy has become a widely used procedure for the treatment of patients with heart failure and severely impaired systolic function who associate left bundle branch block and remain symptomatic, in New York Heart Association II to IV functional class, despite maximum tolerated medical therapy. Imaging evaluation of these patients is complex, aiming to provide an accurate and extensive assessment before and after implantation, although a standardized protocol is yet to be implemented. Extensive research has been conducted to assess the ability of different imaging techniques and parameters to identify and quantify mechanical dyssynchrony, assess myocardial remodeling, provide prognostic information, or help guide lead placement and pacing parameters optimization in this category of patients. For these purposes, ultrasound-based imaging techniques, as well as cardiac magnetic resonance imaging, multislice cardiac computed tomography and nuclear ventriculography have been and are currently used, for research, as well as for clinical purposes. The aim of the current paper was to provide some insights into the imaging assessment of candidates and patients who have undergone cardiac resynchronization therapy.

Keywords: cardiac resynchronization therapy, mechanical dyssynchrony, echocardiography, cardiac magnetic resonance imaging

1. The role of imaging techniques in assessing patients with cardiac resynchronization therapy: general considerations

During the last two decades, cardiac resynchronization therapy (CRT) has become a valuable therapeutic procedure for patients with heart failure (HF) due to dilated cardiomyopathy (DCM),

improving prognosis, symptoms, quality of life, and ventricular function [1–6]. Current ESC guidelines on cardiac pacing and CRT recommend the procedure as a class I indication in HF patients with left bundle branch block (LBBB), QRS width ≥120 ms, and left ventricle ejection fraction (LVEF) ≤35%, who remain in New York Heart Association (NYHA) functional class II, III, and ambulatory IV despite optimal medical therapy [7].

According to these guidelines, patient selection mainly relies on clinical and electrocardiogram (ECG) characteristics, while the role of echocardiography is limited to determining LVEF. Despite this rather frugal approach, extensive research involving echocardiography and other imaging techniques has been conducted over the last few years, with the purpose of improving the selection and management of CRT candidates. Since CRT is still a rather expensive procedure [8–10], and not entirely risk-free [11], even if performed by experienced electro-physiologists, efforts were made to establish sound patient selection criteria, as well as to find accurate methods, techniques, algorithms, and tools for prognosis assessment and pacing optimization. As a consequence, a plethora of ultrasound imaging parameters for cardiac mechanics and dyssynchrony evaluation have been developed, and expert consensus state-ments were released [12, 13] in order to help clinicians choose the best therapeutic strategy.

Early studies on mechanical dyssynchrony parameters seemed somewhat promising. For instance, Yu et al. attempted to prove that CRT was beneficial in patients who had echocar-diographic evidence of mechanical dyssynchrony, even if they had narrow QRS complexes. In their research, results were quite spectacular, raising hope that CRT indications might extend beyond the recommendations of the guidelines [14]. Regrettably, the results of the much larger Echocardiography Guided Cardiac Resynchronization Therapy (Echo-CRT) trial contradicted these findings, highlighting the deleterious effects of CRT in patients with evidence of mechanical dyssynchrony at echocardiography and narrow QRS complexes (QRS complex duration <130 ms) [15].

In addition to that, the Predictors of Response to CRT (PROSPECT) trial tested the sensitivity and specificity of 12 different echocardiography mechanical dyssynchrony parameters, yielding disappointing results. The sensitivity and specificity of the studied parameters were either too low or discordant, and, as consequence, none of them was acknowledged as being clinically useful [16]. Sanderson JE challenged the results of the PROSPECT trial, stating that this trial was rather a study of error and did not provide an accurate assessment of the reproducibility and clinical value of mechanical dyssynchrony parameters; according to this author, the results of the PROSPECT trial were justified by the fact that participating centers were more focused on electrophysiology and lacked the technical possibilities and/or the expertise for an appropriate echocardiographic assessment [17]. Bax and Gorcsan also found flaws in the PROSPECT study, pointing out that among selected patients, 20.2% had an LVEF >35% while 37.8% had end-diastolic dimensions <65 mm, and were therefore unlikely to develop spectacular reverse remodeling since there was little remodeling and systolic function impairment to begin with; in addition to that, they brought up technical issues, such as the fact that ultrasound machines that have been used for the study came from three different vendors, while also suggesting that the high interobserver variability in some parameters might have been justified by the lack of a systematic examination protocol [18].

As a consequence, there is currently not enough proof to either fully embrace or dismiss myocardial dyssynchrony parameters. In fact, some studies have suggested that the evaluation of cardiac mechanics by echocardiography may have quite an important role in optimizing pacing parameters [19], choosing the most appropriate site for lead placement [20], and assessing patient prognosis [21], particularly if advanced ultrasound imaging techniques, such as speckle tracking, are used.

Data on the preferences of clinical practitioners are currently scarce. In a relatively recent European survey, 68% of physicians in the responding centers declared that they only relied on guideline criteria for selecting CRT patients, but 66% acknowledged using echocardiography for pacing parameters optimization. Among these, 37% stated they used tissue Doppler imaging, 20% used speckle tracking-based techniques, and only 10% used three-dimensional echocardiography [22], with the latter two being less used, probably due to limited availability.

Besides that, it is important to remember that echocardiography examination of patients with CRT is not limited to mechanical dyssynchrony assessment and must include a thorough study of left ventricular (LV) systolic and diastolic dysfunction, mitral regurgitation, right chamber structure and function, or the possibility of pulmonary hypertension. All these topics will be further discussed in this chapter.

Beyond echocardiography, other imaging techniques, such as multislice detector computer tomography (MDCT) or cardiac magnetic resonance imaging (CMRI), can be very useful in the management of patients who are candidates for CRT. Evaluation by MDCT, for instance, can safely exclude significant coronary artery disease [23] and accurately describe coronary veins anatomy [24], which can facilitate lead placement. CMRI provides the advantages of very accurate LVEF determination, the ability to identify the extent and location of fibrosis by late gadolinium enhancement, and an extensive study of myocardial deformation and dyssynchrony by tagging techniques [25].

2. Echocardiography parameters for the assessment of patients with CRT

2.1. Examination of the left chambers. LV size, systolic function and diastolic function. Left atrial size and function

Echocardiographic assessment of left chamber dimensions and function in patients who are candidates for CRT or have already been submitted to the procedure is essential.

Conventional bidimensional echocardiography can be used for measuring LV end-diastolic (EDD) and end-systolic (ESD) diameters and, preferably, LV volumes, assessed by the biplane Simpson's modified method and indexed to body surface area [26]. To enhance the quality of endocardial delineation, contrast agents can also be used, particularly if an extremely accurate evaluation of regional myocardial motion is also desired [27, 28], while three-dimensional echocardiography increases the accuracy of volumetric measurements by reducing errors due to the foreshortening of the LV [26].

LV dimensions were previously shown to predict the response to CRT. In the Multicenter Automatic Defibrillator Trial-CRT (MADIT-CRT) for instance, an LV end-diastolic volume (LVEDV) indexed to body surface area (BSA) ≥125 mL/m^2 was associated with a favorable response to CRT [29].

In a substudy of the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial, EDD and EDS were shown to decrease 3 months after CRT (7.3 ± 0.8–6.8 ± 0.8 cm, p < 0.001, and 6.2 ± 0.8–5.9 ± 0.8 cm, p < 0.05, respectively), with further reduction after 12 months since device implantation (by 8.4 ± 7.8 and 8.8 ± 7.8 mm, respectively, both p < 0.001), with better results in patients with idiopathic DCM vs. patients with ischemic cardiomyopathy (8.9 and 9.8 mm, p < 0.01) [30]. The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study also yielded significant reductions in EDD and ESD, as well as in LV mass at 6-month follow-up [31]. By contrast, in the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) trial, no significant changes were recorded in neither LV dimensions, nor in LVEF, despite improved quality of life scores and NYHA functional class [32]. However, most of the patients in this trial had ischemic cardiomyopathy (64% vs. 36% with idiopathic DCM in the CRT-D group and 75.8% vs. 26.4% in the implanted cardioverter-defibrillator group) [32], which is very likely to have confounded results, since ischemic etiology [29, 33, 34] and the presence of scar tissue [35] and non-viable myocardium [36] are known predictors of limited response to CRT and reverse remodeling.

As previously mentioned, LVEF is the single echocardiographic parameter that has been accepted as a CRT patients' selection criterion in current guidelines [7], and the cutoff value has been established at 35%. LVEF has proved to be one of the most important parameters for assessing the success of CRT in all major clinical trials, as well as smaller studies that addressed this issue [37–44]. In MADIT-CRT despite more reduction in LV dimensions in the LVEF >30% group, clinical outcomes were similar in patients with lower LVEF [45]. A subanalysis of data from the REVERSE trial revealed similar extents of reverse remodeling and clinical benefits in patients who had LVEF <30% vs. LVEF >30%, which may be justified by the fact that, unlike patients included in the MADIT-CRT trial, patients in REVERSE only had mild HF [38].

Interestingly, responders to CRT [38] and particularly super-responders in whom the LVEF becomes >50% [46] have an excellent prognosis, with a reduced number of ventricular tachyarrhythmias and good clinical progression at 2.2 years; the authors concluded that, in such patients, switching off the ICD function to prevent inadequate therapies from the device might be considered.

Highlighting regional kinetic abnormalities by echocardiography could also be an important issue, considering the fact that it may help identify patients with ischemic DCM, which is associated with poorer outcomes after CRT and less reverse remodeling [29–36, 47].

Moreover, diastolic function assessment is not less important in this category of patients, since it was shown to improve after CRT, in parallel with the LVEF [47] and particularly in responders [48]. Diastolic dysfunction has been previously assessed by either conventional echocardiography, including parameters such as transmitral flow waves velocities and E-wave deceleration time, diastolic myocardial velocities, the E/e' ratio, diastolic filling duration, or

isovolumic relaxation time, evaluated by pulsed wave and tissue Doppler imaging [48, 49], or advanced techniques, such as speckle tracking [50, 51].

During the last decade, left atrium (LA) dimensions, particularly LA indexed volume (LAVI) [52] and LA function, have become an important part of LV diastolic function assessment and studies exploring the use of these parameters in CRT patients have recently been published [53–59]. For instance, the MADIT-CRT trial showed significant reductions in LAVI in CRT-D vs. ICD-only patients [53]. Major improvements in LAVI 3–6 months after CRT have also been reported by Yu [54], Aksoy [55], and D'Andrea et al., the latter also showing better results in patients with idiopathic DCM, by comparison with ischemic DCM patients [56]. In addition to that, MADIT-CRT results highlighted the value of LAVI <40 ml/m² as a predictor of clinical response [29], which is also endorsed by Yu et al. who reported lower LAVI in responders [54]. In both the MADIT-CRT trial [53] and in the research by Kloosterman et al., increased preimplantation LAVI was associated with increased risk of HF progression and death, independently of LV volumes [57]. Other studies approached LA myocardial strain assessment in patients with CRT, suggesting its prognostic value in assessing the risk for atrial fibrillation development [58] or the response to CRT [59].

2.2. Right ventricular size and function evaluation: pulmonary hypertension assessment by echocardiography

Although the assessment of left chambers is essential in patients who are candidates for CRT or have undergone the procedure already, right chamber evaluation should not be overlooked. Echocardiography-based studies on the topic are scarce, since bidimensional ultrasound imaging has to overcome the obstacles posed by the complex anatomy of the right ventricle (RV). Volumetric measurements can be flawed due to gross geometrical assumptions, since the anatomic shape of the RV hardly resembles any geometric figure, and trabeculations of the RV free wall can hinder adequate tracings of myocardial borders. Also, normal values have not been firmly established for some right chamber parameters, such as the right atrium (RA) volume, which currently remains, however, the preferred parameter for assessing RA size [60], replacing RA area [26].

Despite these caveats, right chamber evaluation by echocardiography, as well as pulmonary artery pressure estimation following current guidelines [61], can and should be performed in CRT patients, as evidence regarding these parameters has started to accumulate, and right chamber dilatation has been shown to associate with higher mortality in HF patients [62].

Data from radionuclide ventriculography studies suggest that impaired RV systolic function, with RV ejection fraction ≤20%, is an independent predictor of mortality and hospitalization due to HF [63], and that poorer systolic function is associated with a lower response rate after CRT [65], accordingly, the evaluation of right chambers may have a certain role in selecting patients for CRT. Moreover, increased RA area and impaired myocardial deformation of the AD were proven to be negative predictors of response to CRT, as were ischemic DCM and low intraventricular asynchrony [65].

In the MADIT-CRT trial, RV ejection fraction was considerably improved, and patients with the highest values had the lowest rate of adverse events at one year [66].

2.3. Mitral regurgitation assessment

Mitral regurgitation is another target for echocardiographic assessment in chronic HF patients, since it has been shown to alter prognosis [67, 68]. In DCM, mitral regurgitation is usually functional, developing as a consequence of mitral annulus dilatation, but mostly due to the change of balance between tethering forces, pulling the leaflets towards the LV, and the forces that favor normal closure of the mitral valve. Tethering forces are amplified by LV remodeling and dilatation which result in an increased sphericity index and papillary muscle displacement. In addition to that, the normal closure of the mitral valve is impaired by the reduction of myocardial contractility and by ventricular contraction dyssynchrony [69], particularly in the presence of LBBB [70].

Quantifying mitral regurgitation in these patients can be challenging, since the regurgitation jet is often eccentric and should include measurements of vena contracta, the tenting area, as well as of the area of regurgitant orifice and the regurgitation volume by the proximal isovelocity surface area (PISA) method, when it is feasible. The extensive evaluation of mitral regurgitation should be completed by a thorough evaluation of the ventricular function and the asynchrony of contraction [71].

One study by Kanzaki et al. revealed the significant reduction of mitral regurgitation immediately after CRT [70], which was most likely caused by contraction synchrony recovery. Similar results have been reported by Breithardt et al. [72]. Moreover, LV reverse remodeling and diminished tethering forces were shown to contribute to reducing mitral regurgitation on the long term [73]. As far as short-term evolution is concerned, more data emerged supporting mitral regurgitation dependency on ventricular dyssynchrony, as one study proved its reduction after CRT, but also highlighted the fact that switching off the CRT device aggravates the regurgitation even if the event occurs six months after implantation [74]. A similar, although smaller study, also reported the reversal of mitral regurgitation, suggesting that CRT should be continued indefinitely [75]. For these reasons, it is reasonable to take into account mitral regurgitation reduction as a criterion for procedure success, particularly since it is associated with clinical response [76–77].

Mitral regurgitation assessment should be done carefully and accurately in non-responders, since some of these might benefit from further interventional treatment by MitraClip, which was shown to reduce symptoms and promote LV reverse remodeling [78], or by surgical mitral annuloplasty [79].

2.4. Dyssynchrony parameters evaluation

2.4.1. Clinical utility

Cardiac mechanics assessment by echocardiography is currently considered a challenge, and research in the field has been extensive and endorsed by newly emerging techniques. However,

despite all research efforts, none of the explored dyssynchrony parameters had proved to be solid and reproducible enough for predicting the response to CRT, and, thus, for helping in patients' selection. Data from the CARE-HF study supported the use of echocardiographic dyssynchrony parameters, showing that patients who had altered values responded better to CRT [80], and had more reverse remodeling [81, 82]. In addition to that, Penicka et al., for instance, proved that both the parameters for interventricular and intraventricular dyssynchrony, assessed by tissue Doppler, were predictors of reverse remodeling and functional recovery of the LV [83].

As previously mentioned, the PROSPECT trial challenged the accuracy of echocardiographic dyssynchrony parameters [16] and was challenged in its turn by some authors [17, 18].

More recent and elaborate techniques motivated researchers to go further in the attempt to find the optimal parameters for dyssynchrony quantification. Suffoletto et al. explored the advantages of the speckle tracking technique, showing that radial dyssynchrony assessed by this method predicted the response to CRT on long and short term [84]. The evaluation of global strain [85], as well as the evaluation of longitudinal, circumferential, and radial strain by tissue Doppler, also provided encouraging results [86]. However, these methods are costly, not available in many clinical centers and time-consuming, requiring strenuous offline analysis.

More available methods, such as tissue Doppler, are, unfortunately, hindered by lower reproducibility in DCM patients, by comparison with normal individuals, probably due to the complex contraction movements of the dilated heart and the method's lack of standardization [87].

The controversy regarding the echocardiographic evaluation of ventricular dyssynchrony extends over their use for optimizing pacing parameters in CRT patients. Some electrophysiologists prefer out-of-the-box settings and only adjust delays if the patients are non-responders. This attitude is endorsed by the quite large SMART-AV (The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy) trial in which 1014 patients were enrolled; in this study, the ECG-based SmartDelay optimization algorithm, as well as echocardiography, did not show any benefit for optimization by comparison with the out-of-the box approach in which a standard atrio-ventricular delay of 120 msec was established [88]. Similar results emerged from smaller studies, such as the one by Sawhney et al. who compared the effects of pacing with out-of-the-box delays with those chosen after Doppler echocardiography, revealing quality of life and functional NYHA class improvement, without significant changes in LVEF and 6-minute walk test distance [89]. In a larger study, on 215 patients, delay adjustments only provided additional benefit in a low number of patients [90]. Vidal et al. also approached this issue, reporting minimal benefits in patients with optimized parameters [91]. A retrospective analysis of multicentric trials endorses the use of adaptive CRT, based on ambulatory measurements of intrinsic conduction, in addition to conventional echocardiographic assessment, for optimization [92].

Although there is no consensus regarding the correct approach on the necessity and benefit of optimization, or the appropriate means to perform it, American guidelines for the echocar-

diographic assessment of CRT patients released by the American Society of Echocardiography, endorsed by the Heart Rhythm Society, recommends considering echocardiography for pacing parameters adjustment [12]. Accordingly, for adjustment of atrio-ventricular delays, the guidelines suggest the evaluation of the transmitral flow by pulsed wave Doppler, based on the premises that a long delay can lead to E and A wave fusion, diastolic mitral regurgitation, and exposes the patient to the risk of native conduction that may lead to loss of resynchronization. On the other hand, an abnormally short atrio-ventricular delay can result in a truncated A wave, as a consequence of premature closure of the mitral valve [12]. The Ritter method and the iterative method are suggested as optimization algorithms [12, 92, 93]. For ventriculo-ventricular delay adjustment, the guidelines recommend measurements of the aortic velocity time integral after modifying the delay by 20 ms, starting with the maximal pre-excitation of the LV [12].

For adjusting both delays, a fast algorithm was suggested—QuickOpt—available on St Jude Medical devices, that was proved inferior to echocardiographic evaluation [94].

2.4.2. Cardiac mechanics evaluation parameters

Echocardiographic dyssynchrony evaluation protocols may differ from center to center according to logistics, the available ultrasound machines and softwares, as well as the experience of the examiners and the number of hospitalized CRT patients. Since dyssynchrony evaluation methods are not perfectly standardized, the choice of assessment parameters can be influenced by the examiner's opinion or the particularities of the case.

Figure 1. Transmitral flow assessment. Measurements of diastole and cardiac cycle duration.

Atrio-ventricular dyssynchrony criteria [12, 13]:

- duration of diastole—duration of diastolic filling measured on the pulsed wave Doppler transmitral flow, from the onset of the E wave until the end of the A wave, at a sweep speed of 100 cm/s;

- duration of the cardiac cycle—measured using identical tags on successive QRS complexes;

- duration of diastole to cardiac cycle ratio; values <40% suggest atrio-ventricular dyssynchrony (**Figure 1**);

- assessment of fusion of the E and A waves on the transmitral flow or the truncated A wave [12, 13].
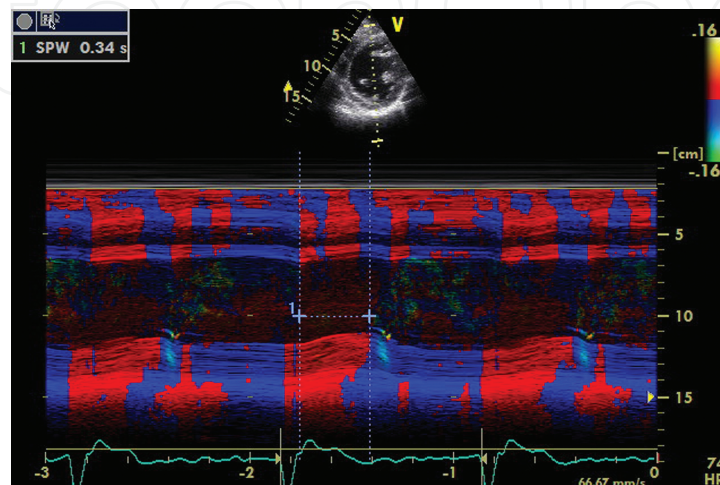

Figure 2. Septal-to-posterior wall motion delay measurement, using color M-mode imaging, from the parasternal short-axis view at papillary muscle level.

Intraventricular dyssynchrony criteria

- SPWMD (septal-to-posterior wall motion delay)—the delay between the maximal contraction of the posterior wall and the maximal contraction of the septum or anterior wall (**Figure 2**); SPWMD can be measured using either M-mode, or, preferably, color M-mode, from the parasternal short-axis view; values ≥130 msec suggest intraventricular dyssynchrony [12, 13]; Pitzalis et al. demonstrated the utility of this parameter as a predictor of remodeling after CRT [95].

- Q-MI: the time interval from the onset of the QRS complex to the onset on the transmitral flow, assessed by pulsed wave Doppler at a sweep speed of 100 cm/s [12, 96];

- Q-PW: the time interval from QRS onset until the maximum contraction of the LV posterior wall, evaluated by color M-mode, at a sweep speed of 100 cm/s [12, 96];

- The (Q-PW)—(Q-Mi) difference—negative values are considered normal (in the absence of intraventricular dyssynchrony, the maximum contraction of the LV posterior wall occurs before mitral valve opening) (**Figure 3**) [96];

- Aortic pre-ejection time (A-PEP)—measured from the onset of the QRS complex until the onset of the aortic flow, evaluated by pulsed wave Doppler from the apical five-chamber view at a sweep speed of 100 cm/s; values above 140 ms suggest intraventricular dyssynchrony [96];

- Measurements of delayed mechanical activity by tissue Doppler analysis of opposing walls motion (interventricular septum, lateral wall; anterior wall, inferior wall) using the apical two- and four-chamber views (**Figure 4**); measurements should be performed on minimum 3–5 cardiac cycles and in post-expiratory apnea; differences ≥65 ms predict the acute hemodynamic response post-CRT [83, 97, 98];

- Spectral tissue Doppler assessment of contraction delay between opposing LV walls; images are acquired from the apical two- and four-chamber views; the sample volume is placed 1 cm below the mitral annular plane, guided by color tissue Doppler, with narrow sector; the time interval from the onset of the QRS complex until maximal systolic myocardial motion (peak of the S-wave) is measured, at a sweep speed of 100 cm/s; maximum differences ≥65 ms and the septum to lateral wall difference ≥65 ms suggest intraventricular dyssynchrony [98, 99]. Although the method is widely available, it is hindered by the fact that analysis of the delays is performed in different cardiac cycles and is strictly limited to the basal area of LV walls; moreover, the method is time-consuming and measurements are performed online, being, thus, dependant, on translational movements of the heart. All these obstacles may result in low accuracy measurements.

- Tissue synchronization imaging

  Tissue synchronization imaging is performed by the offline analysis of bidimensional images from the apical four-, three- and two-chambers views with overlaid color tissue Doppler, using specialized software. To acquire appropriate images, pulse repetition frequencies, color gain, and sector depth and width should be optimized, to ensure the highest frame rate frequency [100].

  Tissue synchronization imaging allows the automatic and color-coded calculus of the time interval from QRS onset until maximum myocardial velocity in different points. The algorithm uses as reference points the onset of the QRS complex, either automatically identified by the echocardiograph, or manually adjusted by the examiner, as well as the onset and end point of the pulsed wave Doppler recording of the aortic flow, as surrogates of systole beginning and ending. The objective of the analysis is to assess post-systolic myocardial shortening in 2, 6, or 12 segments [101, 102]. The method requires a high degree of training, dedicated acquisition and analysis software, which is seldom available in many centers and is time-consuming. Yu et al. reported low interobserver and intra-observer variability of 5.9% and 4.2%, respectively [100]; however, in their study, measurements were most likely performed by highly skilled echocardiographers and might not be reproducible by less experienced examiners.

- Septal flash

  In the presence of LBBB, the interventricular septum has a particular two-phase active contraction pattern, with a leftward motion occurring in the pre-ejection phase, followed by a second excursion later in ventricular systole [103]. This particular inward/outward movement called septal flash (**Figure 5**) is visible by conventional bidimensional imaging, but is better assessed by M-mode or, preferably, by color M-mode, from the parasternal long-axis view [104].

Although apparently simplistic, as it does not require elaborate measurements or advanced technology, septal flash assessment is reliable, reproducible, and a proven good predictor of response to CRT [104], even in patients with atrial fibrillation [105] in which other imaging mechanical dyssynchrony parameters may sometimes be difficult to assess.

- Apical rocking

Apical rocking refers to the transverse movement of the apex, due to LV enlargement and asynchronous contraction of the interventricular septum and LV lateral wall. It can be visually assessed from the apical four-chamber view or can be quantified using specialized software and imaging techniques. The latter has proven superior to classical parameters of dyssynchrony quantification in terms of identifying dyssynchrony and predicting the response to CRT [106, 107].
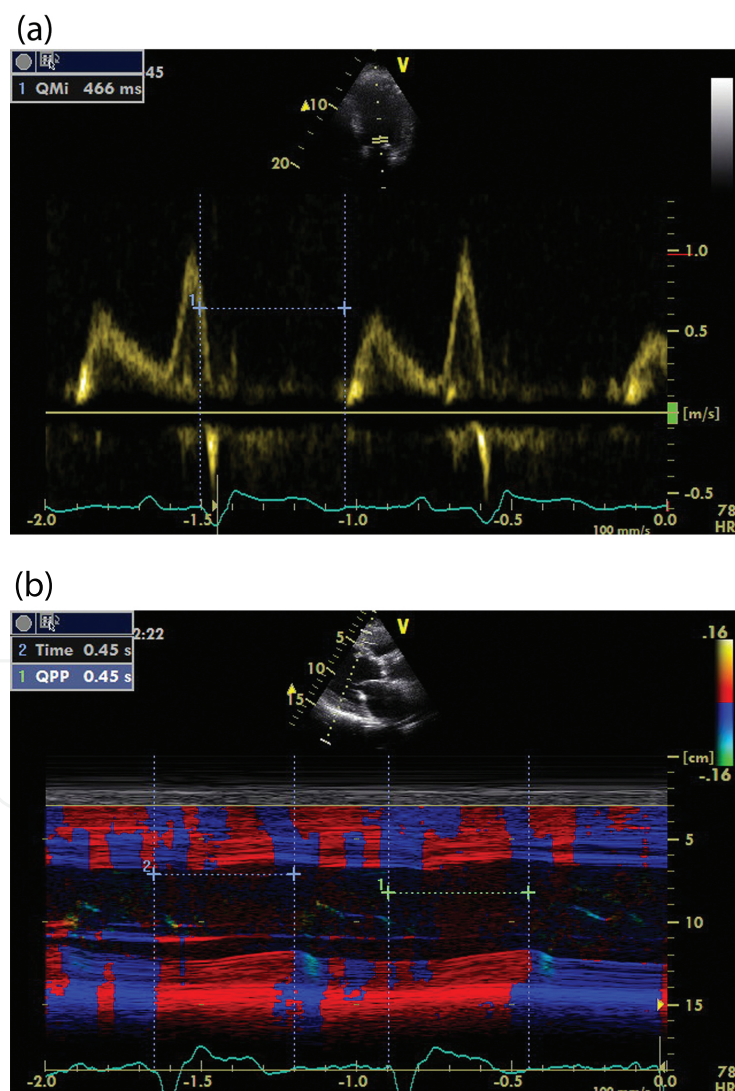

Figure 3. Assessment of left intraventricular dyssynchrony. (a) Q-Mi measurement, on the pulsed wave Doppler transmitral flow. Q-PW measurement, using M-mode, from the parasternal long-axis view.
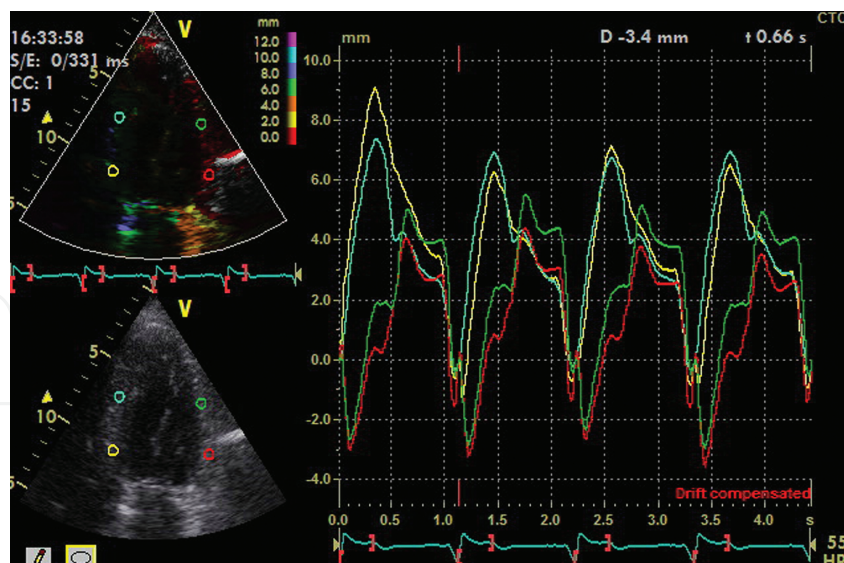
Figure 4. Assessment of left intraventricular dyssynchrony by color tissue Doppler, from the apical four-chamber view. Maximum contraction of the left ventricle lateral wall is significantly delayed by comparison with septal contraction.
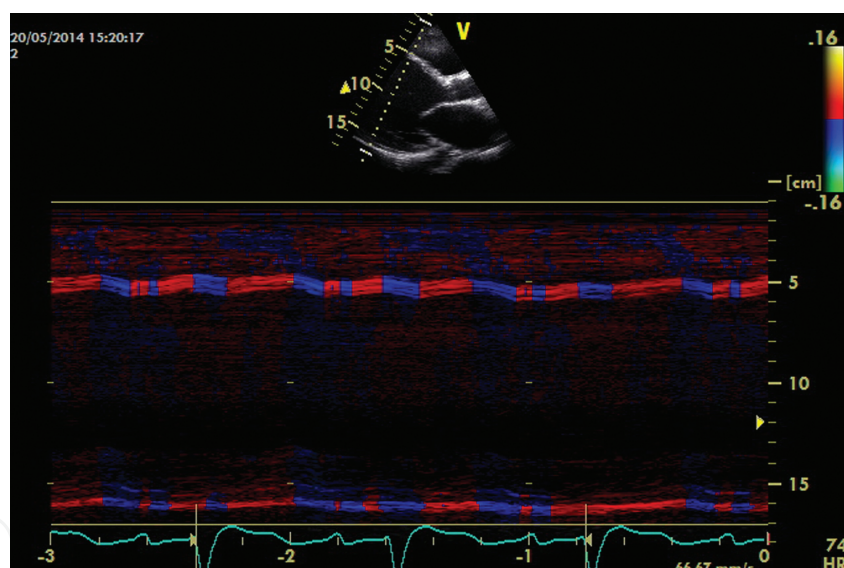

Figure 5. Septal flash evaluation by color M-mode from the parasternal long-axis view.

Interventricular dyssynchrony criteria

- A-PEP—aortic pre-ejection time, measured from QRS onset until the onset of the aortic flow analyzed by pulsed wave Doppler, with the sample volume placed in the LV outflow tract in the apical five-chamber view; values ≥140 ms are considered a criterion of intraventricular dyssynchrony [96].

- P-PEP—pulmonary pre-ejection time, measured from the onset of the QRS complex to the onset on the pulmonary artery flow measured from the RV outflow tract, in the parasternal

short-axis view; for measuring both parameters, as well as all other time-related measurements, a sweep-speed of 100 cm/s should be used;

- Interventricular motion delay—the delay between the contraction of the RV and the LV, assessed by the difference in the two pre-ejection times; values ≥40 msec suggest interventricular dyssynchrony (**Figure 6**); Ghio et al. suggested an association between IVMD and ventricular remodeling after CRT [81].
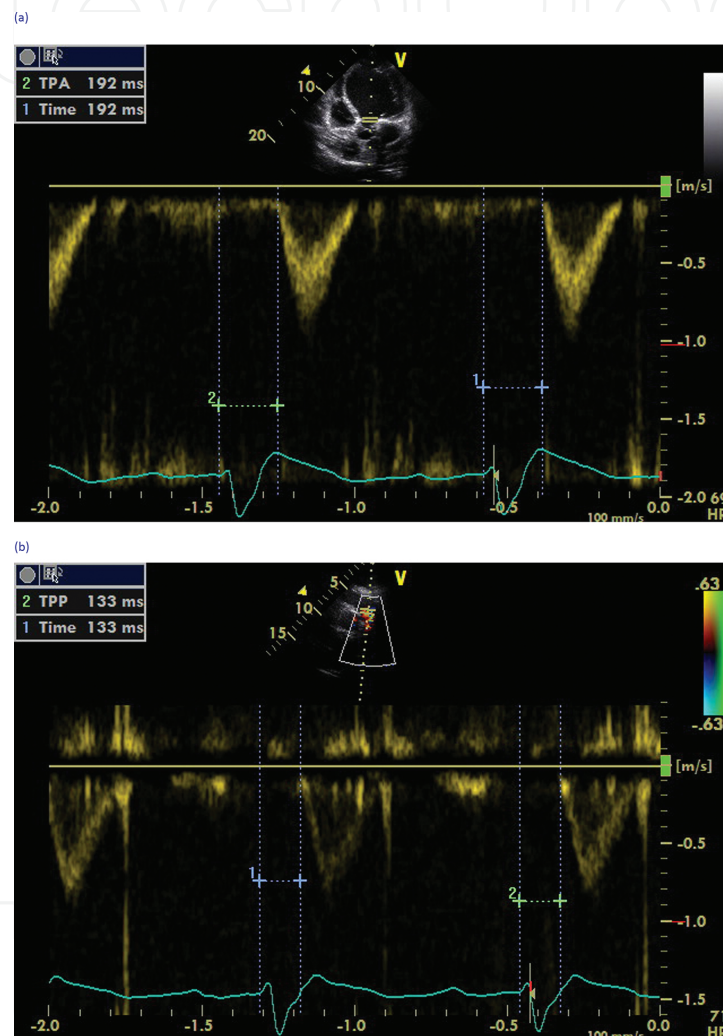

Figure 6. Interventricular dyssynchrony evaluation. (a) A-PEP measurement by pulsed wave Doppler from the parasternal short-axis-view. (b) P-PEP measurement by pulsed wave Doppler from the apical five-chamber view.

3. Multimodality imaging in the assessment of CRT patients

In CRT, procedural success depends on optimal lead placement, with reasonable stimulation thresholds and impedances in the absence of complications such as lead displacement, infection, coronary sinus dissection, or phrenic nerve stimulation.

The Resynchronization Reverse Remodeling in Systolic Left Ventricular Dysfunction (RE-VERSE) [108, 109] and SEPTAL-CRT [110] trials provided evidence that RV lead placement is not essential for procedure success, as similar results have been reported for both apical and mid-septal positions. However, when placing the coronary sinus lead, the optimal site for stimulation should be chosen, provided that venous anatomy is favorable. The importance of coronary sinus lead placement has been highlighted by several major trials. In the MADIT-CRT study, apical placement of the LV lead was associated with poorer outcomes [111], while in REVERSE, lead placement in the basal area of the LV posterolateral wall was associated with more LV reverse remodeling and longer intervals until either death or first hospitalization for HF [108].

Initially, the exact placement of the coronary sinus lead did not seem to be utterly important, as shown by the MADIT-CRT trial [111]. However, the Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy (TARGET) study presented evidence that survival was increased if LV pacing occurred in the area of maximum contraction delay, provided there was no scar tissue on site [112]. Similar results have been reported in a smaller study [113].

Considering the results of these large trials, imaging techniques for identifying the area of maximal delay, the presence and location of scar tissue, and for describing venous anatomy could be helpful. In both the TARGET trial and another smaller study, speckle tracking was used to identify the area of maximum mechanical delay [112, 113].

Beyond cardiac ultrasonography, other imaging techniques have proved their use for targeting the areas for optimal lead placement. CMRI, for instance, can help identify the area of maximum mechanical delay by myocardial tagging techniques [114, 115], while also providing data on scar location [116, 117] and scar burden [118] by late gadolinium enhancement imaging, as well as an accurate quantification of LV and RV dimensions and systolic function [119, 120]. Also, although MDCT is more widely used for this purpose, CMRI scans with ECG-triggered respiratory-navigated three-dimensional SSFP after the injection of dimeglumine gadobenate and ECG-triggered inversion recovery assessment can be used for venous sinus anatomy visualization [117] (**Figure 7**).

Cardiac magnetic resonance imaging has been compared against speckle tracking echocardiography, yielding reasonable limits of agreement [121]. Some authors suggest the additive value of echocardiographic assessment of myocardial delays by speckle tracking and CMRI for identifying scarred areas in order to identify the best area for lead placement [122].

Although the efficiency of CMRI in assessing the response to CRT has been proved in some studies [114, 118], its routine clinical use in patients who have already undergone the implant procedure is somewhat hindered by the fact that, in most cases, CMRI-safe leads and devices are not available. Also, patients with CRT-D are exposed to the risk of inappropriate shocks.

MDCT is also a reliable method in the assessment of candidates for CRT, by being able to safely exclude significant coronary artery lesions [123], and, implicitly, the ischemic etiology of the DCM, as well as by offering a detailed and accurate description of venus anatomy that can help electrophysiologists in preparing the implant procedure [124, 125]; a keen study of venous

anatomy (**Figure 8**), combined with the identification of the area of maximum contraction delay by either echocardiography or CMRI, contributes to choosing the appropriate strategy before starting the implant procedure. As a consequence, during the intervention, the electrophysi-ologist can concentrate on the operation itself, rather than worrying over choosing the appropriate site for stimulation.
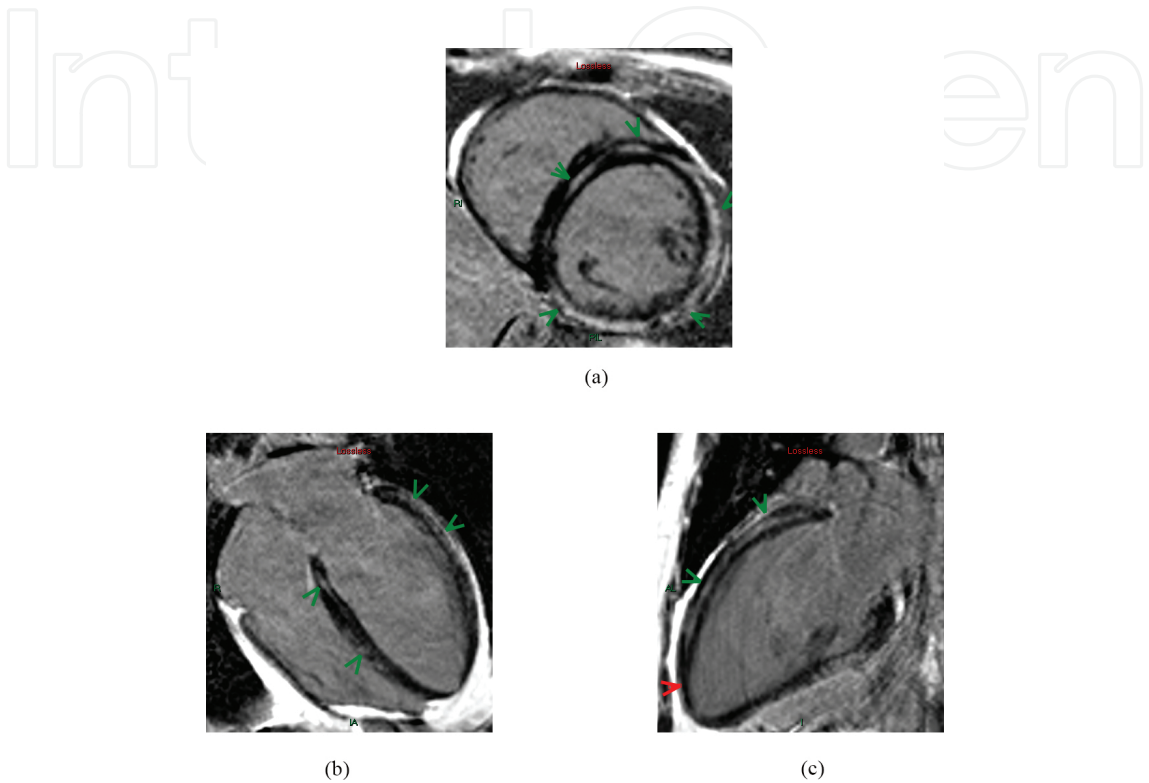

(a)

(b)   (c)

Figure 7. Late enhancement image in a patient with clinical presentation of myocarditis; midwall late gadolinium en-hancement is present in the interventricular septum and diffuse subepicardial enhancement is visible on the lateral wall (arrows) in short-axis CMR views (a), four-chamber CMRI views (b) and two-chamber CMRI views (c).
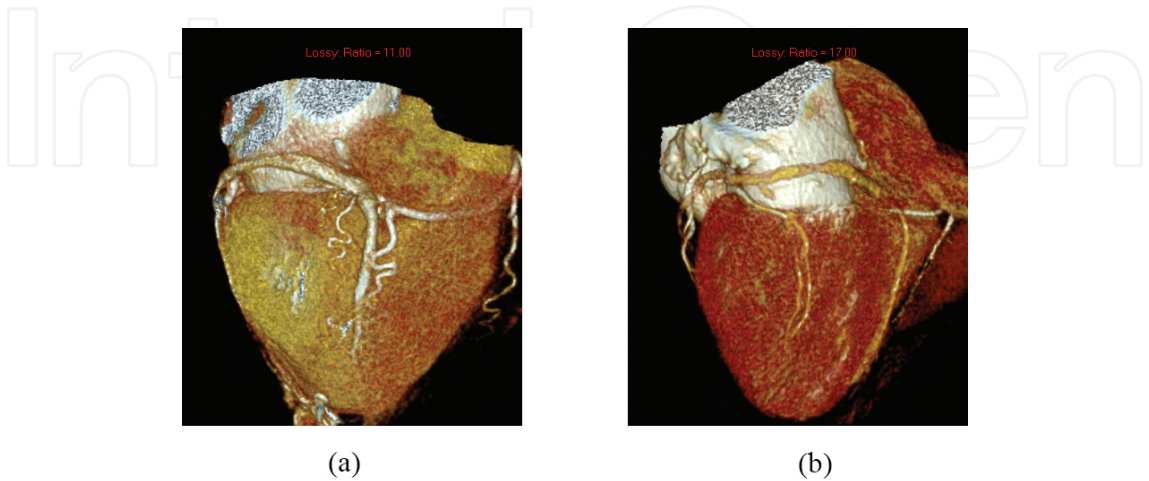

(a)   (b)

Figure 8. Coronary venous anatomy using 3D volume rendered reconstructions.

The ongoing Imaging CRT trial aims to evaluate the benefits of multimodality imaging by speckle tracking echocardiography, single-photon emission computed tomography, and cardiac computed tomography in identifying the optimal positions for lead placement [126].

The extensive research conducted in this field proves the interest and necessity for developing evidence-based protocols in order to get optimum CRT results.

4. Conclusion

Despite the fact that areas of controversy still exist regarding the imaging assessment of patients with CRT, it is undisputed that it will always have an essential role in this type of patients. The extensive research on the topic, the fast progress and development of new imaging techniques, as well as the possibility of skill improvement in interested examiners, are likely to contribute to a more and more accurate assessment of the patients, thus improving management.

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