REVIEW

Echocardiographic Criteria for CRT Patient Selection: Is There Still a Role?

Emmanouil Poulidakis, MD, Antonis S. Manolis, MD
Department of Cardiology, Evagelismos Hospital, Athens, Greece

Abstract

Cardiac resynchronization therapy (CRT) is a relatively new therapeutic option for patients with systolic heart failure (HF) and electrocardiographic evidence of dyssynchrony. However, with current selection guidelines, still a proportion of patients do not respond to this interventional therapy. Several echocardiographic criteria have been proposed to address this issue, but research so far has failed to provide a single and simple measurement with adequate accuracy for CRT candidate selection. While investigation for this subject is still under way, new possible roles of echocardiography in CRT implementation arise, such as assistance in selecting the site of left ventricular (LV) pacing lead and optimizing CRT device programming during follow up visits.

Key Words: cardiac resynchronization therapy; biventricular pacing; heart failure; echocardiography; optimization

List of Abbreviations
AV = atrioventricular; BiV = biventricular; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; HF = heart failure; LV = left ventricular; LVOT = Left ventricular outflow tract; RCTs = randomized clinical trials; STE = speckle tracking echo; TDI =Tissue Doppler imaging; VTI =velocity time integral

Introduction

Despite advances in medical therapy, prognosis of HF patients remains poor.[1,2] It is estimated that at least 20% of patients with systolic HF have evidence of conduction delay in their surface electrocardiogram (ECG), expressed by QRS prolongation.[2–4] For this subgroup of patients, which is reported to have higher mortality rates compared to those with normal QRS duration,[3] CRT is an established therapeutic option. CRT aims to restore the electrical dyssynchrony and its benefit has been proven in wide range of randomized clinical trials (RCTs).[5–18]

However, in the aforementioned RCTs, a significant proportion of patients, as much as 30%, did not respond to this interventional approach, despite fulfilling selection criteria. Taking into account the possible complications of biventricular (BiV) pacing, and the substantial cost, alternative selection tools have been sought. At the same time, it has been suggested that electrical dyssynchrony (QRS >120 ms)[19] is not sensitive enough to pinpoint the presence of mechanical dyssynchrony,[20–22] which in turn might be more important than electrical dyssynchrony.[23,24]

Mechanical dyssynchrony can be further divided into three main types. Atrioventricular dyssynchrony is the discordance between atrial and ventricular systole, which impacts ventricular filling and is important for CRT optimization.[25] Interventricular dyssynchrony refers to the delay between the onset of left and right ventricular contraction.[26–28] But even more important is the presence of intraventricular dyssynchrony, which reflects the delay in the contraction between LV segments.[29]

Echocardiographic Criteria

Echocardiography, has been deemed a suitable tool to detect the presence of mechanical dyssynchrony. Various measurements have been described based in almost all echo modalities.

Septal-to-posterior wall motion delay (SPWMD) is a simple index that measures the time from QRS onset to peak systolic movement of both the interventricular septum and the posterior wall, from the parasternal long axis view at mid ventricular level using m-mode.[30] The cut-off value has been set at 130 ms, but the technique can been further enhanced with the addition of color-coded tissue Doppler imaging (TDI), with a cut-off value of 252 ms.[31,32]

Lateral wall post-systolic displacement (LWPSD) is also based on M-mode. It compares maximal systolic movement of lateral wall with the onset of transmitral flow, and there is evidence of dyssynchrony when systolic wall movement exceeds mitral valve opening.[33] In any case, due to M-mode's limitations, the American Society of Echocardiography recommends to use M-mode based techniques only as an addition to another echo modality for dyssynchrony estimation.[31]

Left ventricular preejection interval (LPEI) is an index based on pulse-wave Doppler, and identifies dyssynchrony when >140 ms lapse between onset of QRS and aortic valve opening. In a more recent report, total isovolumic time – IVT (which is the sum of the time between aortic valve closure and mitral valve opening and vice versa) had at least equal predictive value with newer echo techniques.[32] Interventricular delay, defined by a difference >40 ms between the onset of aortic and pulmonary artery flow, is also based on pulse wave Doppler.[34]

TDI has been widely used for the detection of dyssynchrony. Pulse wave TDI can be used to measure the time between QRS and peak systole (time to Sm peak) or the onset of systole (time to Sm onset) in basal and mid LV segments. Opposing wall delay >65 ms has been estimated to predict CRT response with as much as 80% sensitivity and 92% specificity.[35] It is important to note that TDI is not suitable for application in the apical LV segments.[36] Yu and al, after measuring the time to peak systolic velocity in all 12 basal and mid segments, define as "Dyssynchrony Index" (DI) the standard deviation of these 12 measurements, which is reported to predict CRT response with high specificity and almost 100% sensitivity, in the studied population, when the cut-off is set at 32.6 ms.[37,38] Many investigators have published reports with numerous TDI indices, which differ in the timing of the measurements or the mathematical processing of the results, but their full presentation is beyond the scope of this review. However, it is important to note that TDI can be used to measure strain-rate and, subsequently, strain. Standard deviation of time-to-peak-strain (TPS-SD) in the 6 basal and 6 mid LV segments, can detect dyssynchrony, with a cut-off of 60 ms, at least in patients with dilated cardiomyopathy.[39]

Speckle tracking echo (STE) is a novel echocardiographic modality, which identifies and tracks the movement of echogenic speckles in LV wall across ensuing frames, order to measure primarily strain, and strain rate. Strain can be further divided in longitudinal, circumferential and radial, depending on the axis of LV wall deformation. Suffoletto and al measured time to peak systolic radial strain in the mid segments of LV wall, from parasternal short axis view. Difference > 130 ms between anteroseptal and posterior wall predicted CRT response with sensitivity of 89-91% and specificity of 75-83%.[40] There are also reports about measuring strain in another axis, but as far as dyssynchrony is concerned, most studies use the radial strain.[41] The Speckle Tracking and Resynchronization (STAR) prospective multi-center study tested whether STE can predict response to CRT. Baseline dyssynchrony was evaluated by 4 speckle tracking strain methods; radial, circumferential, transverse, and longitudinal ($\geq$130 ms opposing wall delay for each). Once again, radial strain had the highest sensitivity at 86% and specificity of 67% for predicting LV ejection fraction (LVEF) response. Serious long-term unfavorable events occurred after CRT, and happened 3 times more frequently in those who lacked baseline radial or transverse dyssynchrony than in patients with dyssynchrony. On the other hand, circumferential and longitudinal strains predicted response when dyssynchrony was detected, but failed to identify dyssynchrony in one-third of patients who responded to CRT.[42] Using STE again, this time to measure strain rate, Wang et al devised "LV discoordination index "(percent of stretch/shortening or thinning/thickening during ejection). A mid-ventricular radial discoordination index (RDI-M) >38% best predicted responders, especially in patients with ischemic cardiomyopathy.[43] With the use of STE, measurement of LV twist (and torsion) is also feasible, and connected to CRT response.[44–47]

Detection of inotropic contractile reserve, during stress echocardiography with low dose dobutamine, is a feasible method that could help identify possible CRT-responders with sensitivity of 76.9% and specificity of 85.7-86%, if an augmentation in LV ejection fraction of >5-7.5% is observed.[48,49] Viability of the LV wall, targeted for BiV pacing, should also be sought. Increase in strain (measures by STE) of at least 6% during low dose dobutamine infusion, is in favor of CRT response.[49]

Real time 3D echocardiography is the latest development in echo imaging, has the advantage of not being limited by geometric assumptions as 2D imaging, and could be used to screen for possible CRT responders. Kapetanakis et al after acquiring full volume LV loops from the apical window, divided this volume into pyramidal subvolumes based around a non-fixed central point, in order to gain an estimation of time-volume data corresponding to each of the 16 standard myocardial segments. They then calculated the time taken to reach minimum regional volume for each segment, and expressed it as a percentage of the cardiac cycle. The systolic dyssynchrony index (SDI) was defined as the standard deviation of these timings, and was later given a cut-off value of 5.6%.[50,51]

Despite the previous trend of using more and more complicated modalities, some recent reports concentrate on simple techniques to identify the characteristic movement of the interventricular septum, associated with left bundle branch block. Such an early inward motion, called the "septal flash"(SF) proved by Duckett et al to be associated with a specific left ventricular (LV) activation pattern predicting a favorable response to CRT, whether it was identified visually or by m-mode.[52] Szulik et al, in order to quantify a similar phenomenon, known as the "apical rocking", used an index called "apical transverse motion" from apical 4-chamber view and found it to be superior to conventional dyssynchrony indices. It is interesting that even the visual identification of apical rocking by experienced echocardiographers had high accuracy in predicting CRT response.[53]

PROSPECT and Other Negative Trials

Most of the encouraging data so far derive from small single center trials, where experienced echocardiographers measure a single index, in which they have particular expertise. However, data from multicenter trials (with the exception of the aforementioned STAR trial) are rather negative.

One of the most important reports, concerning the usefulness of echo indices in CRT candidate selection was the multi-center non-randomized PROSPECT trial, which examined 12 echo indices, based on M-mode, pulse wave Doppler and TDI. Patient population fulfilled the established by the guidelines (at the time of the study trial) criteria, with a QRS cut-off value of 130 ms, although, in some centers, patients with <130 ms were enrolled, if there were signs of mechanical dyssynchrony. Clinical response was defined by a composite score and echocardiographic response was defined by a reduction in LV end-systolic volume >15%. The ability of the 12 echocardiographic parameters to predict either clinical or echo response was poor; sensitivity ranged from 9% to 77% and specificity from 31% to 93%. All of the parameters tested had an area under the receiver-operating characteristics curve of <0.62. In addition, there appeared to be a great interobserver and intraoperator variability in analysis of dyssynchrony parameters, with coefficient of variation varying from 32% to 72% and from 16% to 24%, respectively.[54]

Several aspects of this trial have been heavily criticized. Results may just reflect the general difficulty of the TDI methodology. High interobserver variability for the measurement of end-systolic volume raises concerns about the quality of echocardiography in these centers. In addition, 20.2% of the subjects had a core laboratory measured LVEF >35% and should not, therefore, have been included in the study. Moreover, one-third of the images could not be analyzed even for LV end-systolic volume, due to suboptimal quality. There was also a problem with multiple echocardiographic machines from different vendors, while 40% were old machines incapable of acquiring good quality TDI images. Criticism has also been made about the site selection (according to volume of implantation and not according to echo expertise), the source of funding (device manufacturer) and the minimal training of 1 day, which clearly would be inadequate for TDI analysis. Despite the serious limitations of the PROSPECT trial, it should be noted that study design does not differ significantly from real life, which still warrants caution in echo indices implementation.[55]

On the other hand, the issue of implementing CRT in HF patients with narrow QRS, and echo criteria of dyssynchrony has been resolved. After the negative results of the RethinQ Study, which used M-mode techniques for patient selection,[56] it was suggested that newer indices may better detect CRT responders, even with narrow QRS. However, two recent trials, LESSER EARTH and Echo-CRT, found that BIV pacing in this population not only did not confer any clinical or echocardiographic benefit, but could also prove harmful.[57,58]

Pacing Site Selection

Despite the above results, which have caused skepticism over the adoption of echo criteria in CRT candidate selection, the field of CRT might still have room for echocardiography. It has been suggested that placement of the LV lead to the latest sites of contraction and away from the scar confers the best response to CRT. TARGET study tested this hypothesis, where unguided CRT implantation was compared to LV lead placement in the latest site of activation according to radial strain by STE. Sites with <10% amplitude in strain were dismissed due to possible scar presence. Patients with guided implantation were more frequently responders, both in echo (70% vs 55%) and clinical parameters (83% vs 65%).[59] STARTER trial tested the impact of similar strategy in survival rate free from appropriate defibrillation therapy for ventricular arrhythmias. Compared with the routine group, patients in the echo-guided group had improved CRT-D therapy-free survival rate (hazard ratio = 0.64) and were more likely to resynchronize their LV compared with the routine group (72% vs 48%).[60] It should be kept in mind that different echo modalities produce varying results. Faletra et al, in study comparing TDI, STE, 2D and 3D echo, reported that agreement among indices for the presence of dyssynchrony was generally low (kappa -0.02). Equally low was the agreement of each of these echocardiographic indexes in determining, in the same patient with heart failure, the latest LV mechanical contraction site.[36]

CRT Optimization

Perhaps, the most widely accepted use of echocardiography is the optimization of pacing settings in order to achieve the greatest hemodynamic benefit. In CLEAR trial, systematic CRT optimization was associated with reduced mortality and fewer hospitalizations.[61] However, optimization is not frequently performed, even in high-volume centers, with the exception of non-responders, mainly due to the fact that it is laborious, time-consuming, non-reproducible, and requires experienced personnel and patient cooperation.[62]

Several methods for atrioventricular (AV) optimization have been described that include pulsed-wave Doppler (PWD) measurements of mitral inflow velocities, continuous wave Doppler of the mitral regurgitant jet velocity envelope, or the systolic velocity time integral (VTI) by pulsed-wave Doppler in the LV outflow tract or continuous wave Doppler (CWD) recordings of peak aortic flow velocities.[63] Four of these methods, VTI of mitral inflow, VTI of LV outflow tract (LVOT), maximal EA duration and the Ritter formula, were compared with invasive hemodynamics in a previous trial. Maximal EA duration (which is more frequently used in real-life situations) is the longest diastolic filling time until the abbreviation of the A wave by mitral valve closure, while the Ritter formula measures the time from the ventricular paced deflection to closure of the mitral valve at a long AVD interval (i.e., 160–200 ms) and at a short AVD interval (i.e., 50–60 ms) and the onset of electrical activation until the end of the A wave (QA) and is provided by the following equation: AV optimal=+AV short + ([AV long +QA long] - [AV short +QA short]. The best correlation with invasive hemodynamics was demonstrated by transmitral flow VTI, followed by maximal EA duration and LVOT VTI. Ritter formula failed to show any correlation, possibly due to the fact that it was devised for patients with AV block, and may not be applicable to HF patients.[64]

Optimization of interventricular (VV) delay is less well established as it appears to marginally improve hemodynamics with no additional clinical benefit shown.[65–69] In a study by Boriani et al, the optimization of the V-V delay conferred no additional benefit compared with simultaneous biventricular stimulation.[70] In a more recent trial, compared with the best of the currently available device nominal AV and VV delays, 23-45% of CRT patients can yield additional acute hemodynamic effect by individual optimization of the delays, while a new nominal VV delay of 40 ms LV pre-activation was recommended.[71] In any case, VV optimization is performed by achieving the maximal LVOT VTI, measured from the apical 5 chamber view.[70]

However, the echo approach to optimizing the AV and VV intervals has recently been rivaled by the development of automated algorithms by the device manufacturers and the automatic programming of these intervals appears to be a close approximation of the more elaborate and tedious approach of using the echo method.[72-74]

Conclusion

The role of echocardiography in patient selection for CRT has yet to be defined. Recent data have conclusively demonstrated that BiV pacing in patients with narrow QRS, based on echocardiographic indices, is unarguably contraindicated. Nevertheless, the issue of minimizing CRT non-responders, among those with wide QRS, is still open. Furthermore, the role of echocardiography for CRT optimization is rivaled by automated algorithms incorporated into the CRT devices, however, echocardiography might still prove important for guiding LV lead placement.

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