

Role of Cardiac Ultrasound in Selecting Patients Who Respond to Cardiac Resynchronization Therapy in the Light of the PROSPECT Study

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Cardiac resynchronization therapy (CRT) is an established therapy in patients with advanced systolic heart failure and electrical conduction delays; in such patients CRT can improve symptoms, exercise tolerance, left ventricular function and prognosis.¹ The 2008 update of the European Guidelines CRT recommends CRT as class I therapy for heart failure (HF) patients in New York Heart Association (NYHA) functional class III or IV despite maximal medical therapy who have left ventricular dilatation and systolic dysfunction, wide QRS complex at surface ECG and who are in sinus rhythm.² Guidelines recommendations reflect the broad enrolment criteria used in the trials which demonstrated the benefits of CRT.¹⁻⁵ However, in a proportion of patients receiving CRT the clinical conditions remain unchanged and there is no reverse remodelling of the left ventricle.⁴ Identifying a priori the patients who will not improve after CRT would give the possibility to avoid implants and avoid unnecessary risks in patients who are unlikely to benefit; additionally, this would strongly increase cost-effectiveness of the therapy. Therefore, refinement of selection criteria for CRT is a worthwhile objective of research. After single-center studies proposed measurements of mechanical dyssynchrony at echocardiography as useful tools to identify potential responders to CRT, the Predictors of Response to CRT (PROSPECT) trial was designed to test prospectively, in a multicenter setting, the ability of such parameters to predict CRT response.⁶ The trial concluded that although many echocardiographic measures of dyssynchrony are significantly related to the outcome, none is able per se to distinguish responders from non responders to a degree that should affect clinical decision making.

The question is therefore the following: which is the current role of cardiac ultrasound in the selection of responders to CRT? The answer is not difficult, but first of all it is of paramount importance to recognize that there are several definitions of responsiveness to CRT in the literature and that the same dyssynchrony index may be associated or not with the outcome after CRT depending on which definition of responsiveness is used. Second, we need an unbiased interpretation of the results of PROSPECT to understand the limits of this study prior to any attempt to move forward. Finally, no real step forward can be accomplished if we forget to consider the many characteristics which influence the response to CRT.

How to Define the Response to CRT

Two different approaches have been used in the literature to define responsiveness to CRT. Focusing on the clinical conditions of the patients, responders have been defined as those patients in whom NYHA class is reduced after CRT or functional capacity at the exercise test is increased, or as those who had no hospitalisations due to heart failure and/or those who survived long-term. All cause mortality is an objective and hard end-point that is often considered the primary outcome for assessing the benefits of treatments in HF patients; however, short term studies which may not take into account survival necessarily rely on changes in NYHA class or in exercise capacity.⁷ The other approach to define the response to CRT is to look at variables which have been used in clinical trials on HF patients as surrogate end-points for mortality and to define responders those patients in whom such variables improve. Reverse remodelling of the left ventricle is an example. The concordance observed in HF trials between the effects of drugs on clinical outcomes and on reverse remodelling has justified the use of left ventricular ejection fraction or of end-systolic volume measured with echocardiography as surrogates for mortality.⁸ However, the role of surrogate end-points in HF trials is challenging and there is always the possibility of a discrepancy between such end-

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points and mortality, as highlighted by the Cardiac Resynchronization in Heart Failure (CARE-HF) trial. In this trial no association was found between the aetiology of HF (ischemic or non ischemic aetiology) and the primary clinical end-point of the study (death or cardiovascular hospitalisation).¹ On the contrary, the echocardiographic data of the trial demonstrate in the same patients a significant and strong interaction between aetiology and the extent of reverse remodelling after CRT: the extent of reverse remodelling was in fact significantly higher at 18 months in patients with non ischemic aetiology than in patients with ischemic heart disease.⁹ The paradox of discrepant effects of CRT on left ventricular function and outcome in patients with ischemic heart disease suggests that only some of the benefit of CRT is mediated by reverse remodelling. We do not yet have an explanation for this observation but it is tempting to speculate that CRT may reduce mortality regardless of an improvement in cardiac function because electrical resynchronization reduces sudden arrhythmic death. In any case, these observations demonstrate how difficult it is to obtain answers outside the context of randomised trials with a long term follow-up, in which the control population is necessary to obtain information on the natural history of the disease. We have in fact to consider that patients surviving may not be considered responders if patients in the control group survive as well during the same follow-up period; at the same time, a patient who dies is not necessarily a patient who has received no benefit by the treatment (if a similar patient in the control group dies in a shorter period of time).

The take-home message is that the search for indices which might improve the prediction of CRT response beyond that obtained by QRS width is important but we have to keep in mind that although “reverse remodelling” and “improved survival” may overlap, these are not synonymous.

PROSPECT: Results and Limits of the Study

Superficially, the conclusion of PROSPECT could be that echocardiographic measures of dyssynchrony are useless as predictors of response. However, this conclusion is completely wrong. PROSPECT is not a “negative study”: in fact several echocardiographic parameters of dyssynchrony turned out to be significantly associated with improvement in clinical and reverse remodelling outcomes at 6 months. Furthermore, from a pathophysiological point of view it is extremely interesting to notice that the parameters which were statistically significant included: *a*) the left ventricular filling time, an index of atrio-ventricular dyssynchrony; *b*) the interventricular

mechanical delay, an index of inter-ventricular dyssynchrony; and *c*) the lateral to septal delay at tissue Doppler imaging (TDI), an index of intra-ventricular dyssynchrony. These data strongly support the hypothesis that the greater the overall mechanical dyssynchrony at baseline the higher the likelihood of responsiveness to CRT. That none of these parameters was able to distinguish responders from non responders with high sensitivity and specificity may be explained in many ways.

As discussed in the paper, variability of TDI measures is an issue and may have been exaggerated in the study by the decision to use different echocardiographic platforms and equipments to collect and analyse images; nonetheless, rather than considering this decision as a limitation, we should consider it as a strength of the study. PROSPECT has been designed to be a picture of the real world because it is obvious that if we want to give worldwide suggestions on how to use echocardiography to select candidates to CRT, then the suggestion must be worldwide applicable. Following PROSPECT, further information has been gained on variability of TDI measures.¹⁰ It is now clear that variability of TDI only partly depends on difficulties in recognizing peaks and nadir of the velocity profiles; this may be true when the velocity profile is domed or when bimodal velocity curves are present, given that there is no possibility to identify the physiologically “correct” peak. Unfortunately, variability is inherent in TDI methodology: it is impossible to standardize the position of a sample volume of few millimetres in length within left ventricular segments which are a couple of centimetres long, knowing that even subtle changes of the sample volume position may result in substantial changes in peak velocities and in timing and numbers of peaks. Can we reduce variability using greater sample volumes at TDI? Can we reduce variability using different techniques such as speckle tracking which do not require the use of small sample volumes? These questions may deserve precise answers.

When PROSPECT was designed, in 2003, the Steering Committee identified from the literature 12 echocardiographic dyssynchrony measures to be tested in the study as potential predictors of response to CRT. Since then, technology has improved giving us the possibility to dramatically improve our understanding of regional left ventricular mechanics. It is overly simplistic to assume that velocity profiles are the best way to assess regional mechanics and therefore to assess mechanical dyssynchrony. After all, velocity simply tracks motion, which may be either passive movement or active contraction, but when we compare two segments of the left ventricle (eg, the septum and the lateral wall) trying to identify delays in regional left ventricular mechanics, we obviously want to compare the contraction (not the

passive movements) of the segments. Strain might therefore be a better way to study left ventricular mechanics and it might be superior to velocities to identify dyssynchrony. Additionally, the left ventricle undergoes a 3-D motion which can be fully described defining its longitudinal, radial and circumferential vectors. Although TDI allows a precise assessment of velocities in the longitudinal direction, there is no theoretical reason to disregard movement/contraction in the radial and circumferential directions. Speckle tracking strain can be used to evaluate myocardial deformation in the longitudinal, radial, and circumferential directions; in a recent study radial dyssynchrony was found to be the only type of dyssynchrony which differed between responders and non responders.¹¹ In a similar study, a combined assessment of longitudinal dyssynchrony at TDI and of radial dyssynchrony at speckle tracking strain allowed a marked increase in sensitivity and specificity of prediction as compared to the use of each type of dyssynchrony alone.¹²

The take-home message is that we cannot be blind to the positive results of PROSPECT and we cannot blame echocardiography as being unable to select responders if we are still unable to understand which is the best echocardiographic technique to specifically identify and selectively quantify the mechanical substrate amenable to CRT in the failing left ventricle.

Moving Forward From PROSPECT

To summarize again, PROSPECT has shown that no magic number is yet available to predict response to CRT; at the same time, PROSPECT has also clearly demonstrated that cardiac dyssynchrony is related to the outcome after CRT. Research continues on new methods to assess dyssynchrony but in the meantime we have to use echocardiography not as a crystal ball to predict the future but more as a pathophysiological tool. Which means, in our opinion, defining the precise role of all relevant parameters involved in the response to CRT.

Dyssynchrony should be studied at all levels, since not only intra-ventricular dyssynchrony but also inter-ventricular and atrio-ventricular dyssynchrony are related to the outcome, as demonstrated in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE), CARE-HF and PROSPECT studies.^{1,4,9} Additionally, we have to acknowledge that dyssynchrony is not the only issue which determines the response to CRT, since the presence of viable myocardium is a prerequisite for response. Viability may be assessed with stress echo or transmural myocardial fibrosis may be identified

with cardiac magnetic resonance but even aetiology of heart failure is a rough indicator of the response to CRT.^{9,13,14} End-stage disease is also likely to respond less to CRT in terms of left ventricular function.⁹ From a statistical point of view, it would be correct to include these different parameters into a multivariable equation with the aim to improve prediction; however, it is likely that even such an equation could not perform well since we still lack relevant information on all the processes which regulate the response to CRT. Preliminary, we should therefore acknowledge the heterogeneity in response to CRT and better understand the factors associated with such a heterogeneous response. Categorizing patients as either responders or non-responders is simplistic, given that, although most patients benefit from CRT, in some patients cardiac function after CRT returns to near normal, a situation which appears to deserve the title of cardiac remission, and others may actually continue to deteriorate despite CRT. In a recently published paper, patients were classified as super-responders, responders, non-responders, and negative responders on the basis of the direction and extent of changes in left ventricular function 6 months after CRT.¹⁵ Of interest, the study showed that super-responders less frequently had severe mitral regurgitation and more frequently had non-ischemic aetiology of HF, longer QRS duration, left bundle branch block (LBBB) configuration; more extensive left ventricular dyssynchrony was also present in super-responders.¹⁵ This approach could be further explored in a larger database of patients including a greater number of clinical and echocardiographic variables.

Conclusions

Acknowledging the complexity of factors influencing the response to CRT, from dyssynchrony to the myocardial substrate of the functional response, is necessary to plan future research. The paradox of discrepant effects of CRT on left ventricular function and outcome in patients with ischemic heart disease suggests that only some of the benefit of CRT is likely to be mediated by reverse remodelling and this is an issue which should be better explored in the future. Taking in mind these considerations is, since now, important to avoid the risk that inaccurate selection may ultimately lead to deny to some patients the potential clinical benefits of CRT.

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