European Heart Journal (2017) **38**, 739–741
doi:10.1093/eurheartj/ehw595

**EDITORIAL**

# How to RESPOND to the quest to increase the effectiveness of cardiac resynchronization therapy?

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*Online publish-ahead-of-print 20 December 2016*

**This editorial refers to 'Contractility sensor-guided optimization of cardiac resynchronization therapy: results from the RESPOND-CRT trial'†, by J. Brugada *et al.*, on page 730.**

Cardiac resynchronization therapy (CRT) is an electrical treatment based on biventricular or left ventricular (LV)-only pacing that was initially applied as a last-resort therapeutic solution for patients with severe heart failure (HF) associated with left bundle branch block. Despite the technical limitations of devices and leads in the first phases of clinical use, the clinical use of CRT rapidly moved from uncontrolled evaluations to randomized controlled trials (RCTs) that definitively validated its role in appropriately selected patients with NYHA II–IV heart failure.[1–3] Moreover, the favourable outcome of appropriately selected patients implanted with a CRT device has been confirmed in 'real-world' studies and in evaluations focused on cost-effectiveness.[4–6]

As with any treatment, assessment of patient outcomes after CRT differs from assessment of the percentage of patients who can be classified as 'responders' on the basis of individual responses. A series of investigations reported that the proportion of responders to CRT is in the range of 57–67% among patients with moderate to severe HF.[3,7] The attempts to improve the response to CRT, evaluated in terms of LV reverse remodelling, an endpoint used as a surrogate of outcome, has prompted a series of studies aimed at identifying the clinical, echocardiographic, and electrocardiographic profile of responders, identifying and quantifying LV dyssynchrony (by echo, magnetic resonance imaging, nuclear cardiology, etc.) and quantifying scar tissue (as a marker of 'non-correctable' dyssynchrony and for appropriate LV lead positioning), assessing the relationship between acute haemodynamic response and long-term response or outcome and assessing the impact of tailoring of atrioventricular (AV) and interventricular (VV) interval programming on indices of LV function, response to CRT, and patient outcome.[1–3,7]

A series of data from clinical studies support the concept that in acute evaluations AV delay optimization improves LV performance and stroke volume by allowing adequate diastolic filling of the left ventricle as well as reduction of diastolic mitral regurgitation.[8] Similarly, acute evaluations with Doppler echocardiography showed that VV delay optimization may reduce or eliminate dyssynchrony and maximize cardiac output, with significant reduction of mitral regurgitation.[3,8] On the basis of this background, optimization of suboptimal programming of AV and VV intervals could constitute the most common and most correctable variable that may lead to improvement of response to CRT. Optimization and tailoring of AV and VV programming has been traditionally done with use of echocardiographic techniques, but this requires exhaustive, iterative sampling that cannot be proposed for daily practice and does not constitute the standard of most of the centres implanting CRT devices.[3]

The influence of echocardiographic optimization of patients implanted with CRT has been the subject of controlled studies[9] and one meta-analysis including data from 12 studies and 4356 patients with evidence of no significant differences in clinical or echocardiographic outcomes between patients who underwent AV and/or VV delay optimization and patients who underwent empiric device programming.[8] This neutral effect was confirmed even when the meta-analysis was done only on randomized studies, or on isolated AV delay or VV delay optimizations.[8] The changes in optimal setting with regard to VV intervals between rest and exercise,[10] as well as during follow-up,[11] might explain the limitation of optimization performed at rest, at a single time point, before discharge.

In the present issue of the journal, Brugada and colleagues present the results of RESPOND-CRT, a prospective, randomized, double-blinded, multicentre, non-inferiority trial evaluating the effect of

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

† doi:10.1093/eurheartj/ehw526.

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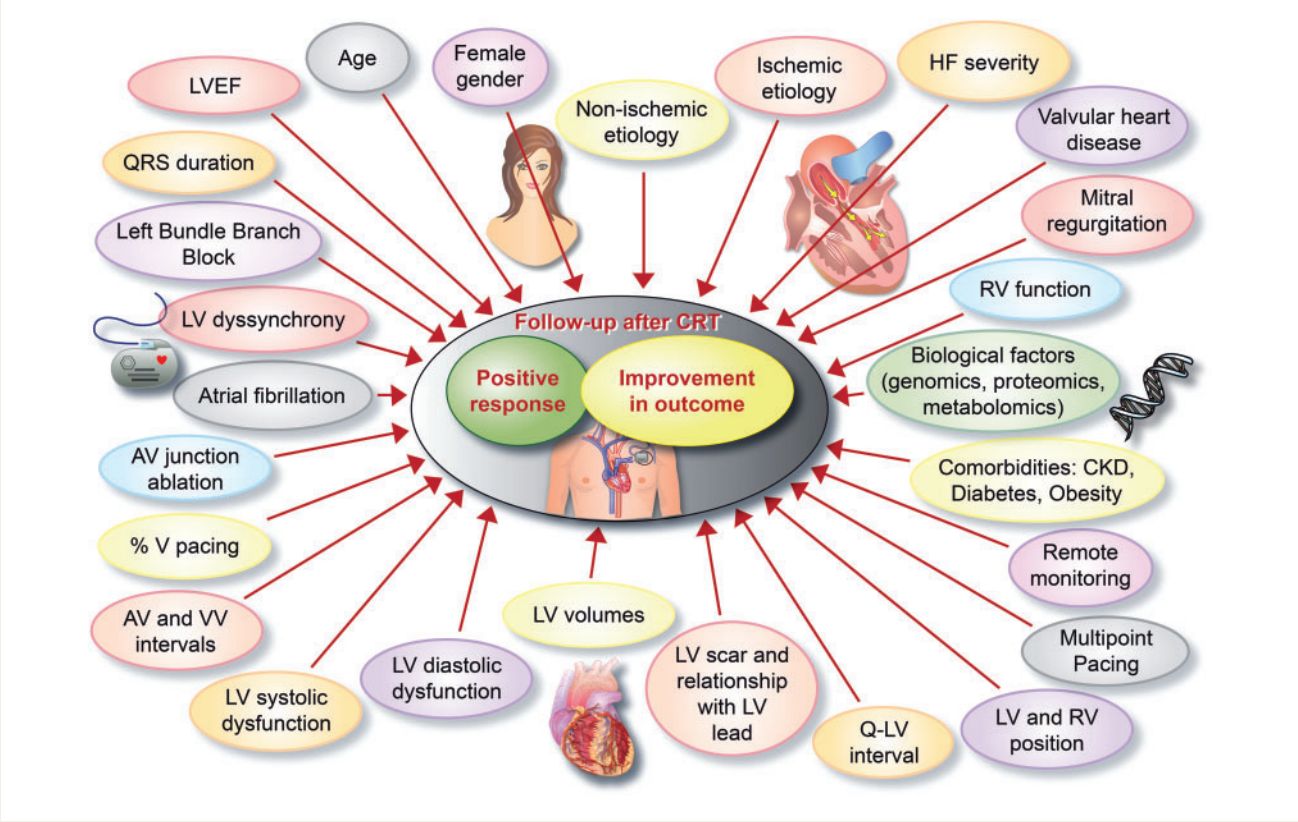


**Figure 1** The complex network of inter-related factors that that may condition and modulate a positive response to cardiac resynchronization therapy (CRT) and/or an improvement in outcome after implant of a CRT device. AV, atrioventricular; CKD, chronic kidney disease; HF, heart failure; LV, left ventricular; RV, right ventricular; VV, interventricular.

weekly, automatic CRT optimization based on a SonR contractility sensor vs. an echo-guided optimization of AV and VV timings.[12] The SonR system uses an accelerometer sealed in the atrial lead to measure mechanical vibrations generated in the heart during isovolumetric contractions which are correlated with LV $dP/dt_{max}$. The device processes these signals through a specific algorithm, with the result of automatic optimization of AV and VV intervals, that in this study was performed every week.

The primary efficacy endpoint of RESPOND-CRT was the 12-month rate of clinical responders (patient alive, without HF-related events, with improvement in functional class or quality of life). In a population sample of 998 patients, the rate of response was high (75.0% in the SonR group vs. 70.4% within the echo group). The non-inferiority of SonR vs. echo-guided optimization was demonstrated, but not its superiority. In the long term, no significant differences were found in the composite of death or HF hospitalizations, while the risk of first HF hospitalization was significantly reduced in the SonR group.[12] Other ancillary analyses were done and showed no significant differences in reverse LV remodelling at 12 months, but a significantly higher rate of responders in SonR patients with a history of atrial fibrillation at baseline or with renal dysfunction.[12] These observations have all the limitations of subgroup analysis but deserve interest for more focused prospective evaluations. As is known, atrial fibrillation in CRT may interfere with clinical response by decreasing the percentage of biventricular pacing,[6] requiring AV junction ablation in order to achieve the same effects and outcome of patients with sinus rhythm,[13] but the impact of history of atrial fibrillation on changes in optimal programming of AV and VV intervals is not defined. In this regard, the study protocol of RESPOND-CRT, not including repeated echocardiographic optimization, may have helped to highlight a benefit in some patient subgroups, in relation to the more frequent automatic optimization of AV and VV intervals performed weekly in the SonR group.[12] Chronic kidney disease (CKD) is an important co-morbidity in HF patients, with a reported prevalence of up to 55%[14] with maintained CRT-related benefits in the case of mild to moderate CKD, but with a higher risk of adverse outcomes.[5,14] Advanced CKD is a well-recognized independent predictor of cardiac mortality and HF hospitalization.[14] In view of the expected increase of patients affected by CKD that will occur in western countries in parallel with progressive population ageing, it is clinically necessary to investigate responses and outcomes of CRT in the very complex setting of patients with advanced CKD, where multiple co-morbidities may co-exist.[5,14]

The role of CRT optimization with regard to outcomes is not clear and probably involves complex assessment, since it has been reported that baseline LV $dP/dt_{max}$ rather than acute haemodynamic effects of biventricular pacing are predictive of the most relevant clinical outcomes at 1 year.[15] In the approach to these complex

evaluations, we should stress that clinical outcome and clinical response are different endpoints in the assessment of CRT recipients and, moreover, may differ according to the setting where CRT has been applied (moderate to severe HF, mild HF, pacing for bradycardia in a patients with LV dysfunction, pacing following AV juction ablation in permanent atrial fibrillation with LV dysfunction).[2,16] The article by Brugada and colleagues[12] tried to answer the research question of whether response can be improved by means of an RCT, and the authors have to be congratulated for their efforts. However, the multitude of inter-related factors that may condition and modulate either a positive response to CRT and/or an improvement in outcome after implant of a CRT device with defibrillation capabilities (*Figure 1*) suggest the need for multiparametric analyses performed on large data sets, corresponding to so-called 'big data', taking into account the enormous amount of patient data that can nowadays be collected, processed, and interpreted.

'How to RESPOND to the quest to increase the effectiveness of cardiac resynchronization therapy?' More than 20 years after the pioneering experiences that started the clinical use of CRT, the answer to this burning question appears really challenging and will require the synergetic convergence of efforts from different fields, ranging from molecular biology and basic sciences to bioengineering, medical informatics, imaging, electrophysiology, experimental cardiology, HF pathophysiology, and, last but not least, clinical cardiology.

**Conflict of interest:** G.B. received speaker's fees (small amounts) from Boston Scientific and Medtronic.

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