

# Reversing heart failure by CRT: how long do the effects last?

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**This editorial refers to ‘Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study’<sup>†</sup>, by C. Linde et al., on page 2592**

Device-based treatment of advanced systolic heart failure by cardiac resynchronization therapy (CRT) is a fairly invasive procedure when compared with conservative pharmacological therapy. Despite all efforts to improve the safety, feasibility, and clinical efficacy of the implantation procedure, a small, but not negligible, perioperative risk and the possibility for long-term complications such as device infection and lead dislocation remain. Furthermore, the upfront costs at the time of implantation are comparatively high. However, the large amount of available evidence which has been accumulated over the last two decades from many well-controlled and randomized trials has proven that the procedure is highly cost-effective and efficient in well selected patients.

The stimulus to place an additional pacing lead on the delayed activated left ventricular free wall in patients with left bundle branch block (LBBB) to improve cardiac haemodynamics was based on pathophysiological principles, well-performed animal experiments, and thoughtful clinical observations. However, what initially was meant to be a rescue therapy for end-stage heart failure patients,<sup>1,2</sup> has, over time, transformed into a life-saving routine treatment which is now indicated as soon as a patient with depressed systolic function and LBBB develops symptoms of heart failure [e.g. New York Heart Association (NYHA) class  $\geq$  II].<sup>3</sup> Part of the evidence to support this aggressive therapeutic approach in patients with mild symptoms of heart failure comes from the 12-month results of the REVERSE trial,<sup>4</sup> which was the first prospective, randomized trial to include patients with less than NYHA class III–IV. Although the primary endpoint—a composite score of the clinical response of heart failure—failed to reach statistical significance in the 12-month results, the REVERSE study did fulfil the expectations according to its study acronym and showed significant reverse remodelling effects on left ventricular (LV) dimensions with

improved functional parameters at the 12-month follow-up. More recently, the MADIT-CRT study confirmed and further substantiated the beneficial effects of CRT in NYHA I–II patients.<sup>5</sup>

Most of the available study data from controlled trials so far are limited to a follow-up duration of between 12 and 24 months. But what happens thereafter? Will the beneficial effects of CRT last for a longer period, will it dissipate, or will it be necessary to adapt the pacing parameters during treatment? Small trials have demonstrated that the optimal pacing settings such as the atrioventricular (AV) and interventricular (VV) delay settings may change over time and that reoptimization should be considered after 6–12 months.<sup>6</sup> This effect has been attributed to the reverse remodelling process and the associated improvement in electromechanical coupling. The presence of reverse remodelling—typically defined as a reduction in LV end-systolic volume  $> 15\%$ —has been identified as a powerful predictor for a decrease in mortality.<sup>7</sup> However, a responding patient who experiences significant reverse remodelling and (maybe) improved electrical conduction over time, i.e. a decrease in QRS by reverse remodelling, may no longer need biventricular stimulation. Furthermore, it has been well demonstrated that CRT causes a redistribution of regional wall stress which unloads the delayed activated myocardial segments and allows for recuperation of the most affected, overloaded myocardial regions (Figure 1, panel A).<sup>8</sup> When this new contraction pattern during CRT is not perfectly synchronous (which is rarely the case), it is conceivable that during active CRT with a dominance of pacing from the LV electrode, a previously early activated region might be transformed into a late activated region and may thus be exposed to the higher end-systolic wall stress.<sup>9</sup> This reversed (i.e. in the opposite direction) dyssynchrony may over time promote a new remodelling process (Figure 1, panel C). Such a patient would probably show an initial period of temporary improvement, before he/she may develop new signs of heart failure.

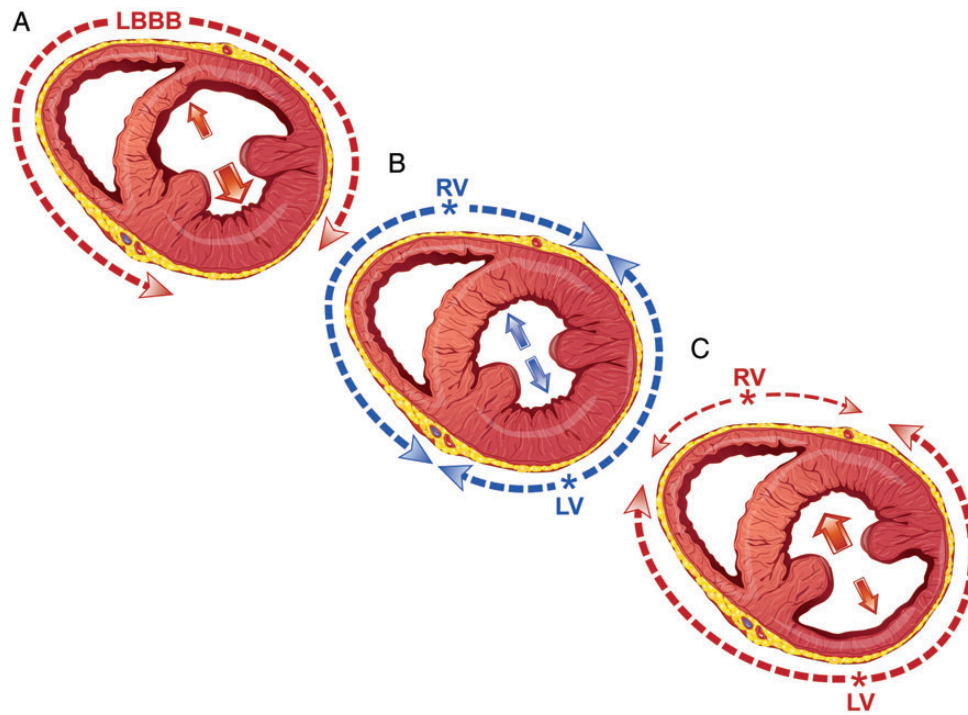
Is there any clinical evidence to support these rather provocative theoretical considerations? Probably not much. The REVERSE investigators have now reported results from a pre-specified long-term follow-up for the patient group which was initially randomized to

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**Figure 1** Long-term impact of different ventricular activation patterns on regional load and hypertrophy. A, delayed LV activation in LBBB unloads the septum and increases the regional load in the delayed activated postero-lateral wall resulting in compensatory hypertrophy.<sup>8</sup> B, Optimized CRT may normalize these pathologic relationships by simultaneous and more rapid ventricular activation. C, Hypothetical (and probably exaggerated) result of suboptimal CRT with early LV activation (reverse dyssynchrony). The early activated posterolateral wall is exposed to a lower regional load and the late activated opposing wall (i.e. the septum) responds with regional hypertrophy.

active CRT, representing two-thirds of the total study population.<sup>10</sup> With an average follow-up duration of  $54.8 \pm 13$  months, this report represents one of the longest experiences from a well-defined study population of a controlled, randomized trial. Only the CARE-HF investigators reported a comparable follow-up duration, with a median duration of between 50 (control group) and 56 months (CRT group) in the long-term follow-up analysis.<sup>7</sup> In REVERSE, a significant reverse remodelling effect was observed within the first 12 months of follow-up, with an additional small reduction in LV volumes during the second year of CRT. Beyond this period, there was remarkably little change in LV morphology and function, with a stable ejection fraction well above 30% on average. These data are important and by no means self-evident. At first sight, it reassures us that there is no evidence for an attenuation or even loss of CRT efficacy over time as speculated above.

However, a closer look at the data reveals that this conclusion only holds true for the overall study population and might not apply to the individual patient: the REVERSE study was performed without a dedicated protocol for optimization of the pacing parameters; however, the study design allowed AV and VV optimization to be performed before discharge.<sup>11</sup> In the present long-term analysis, no information is provided regarding how many patients underwent such an optimization procedure and it is unclear whether and, if yes, in how many patients reoptimization was performed later during follow-up. Also, it should be noted that in REVERSE, the observed reverse

remodelling effect after 12 months was significantly (roughly three times) larger in patients with a non-ischæmic cardiomyopathy (NCM) and that the time to first hospitalization was shorter in patients with an ischæmic origin (ICM) of heart failure.<sup>12</sup> Thus, a subgroup analysis which addresses these questions would be important and of clinical relevance, in particular for the treatment of ICM patients.

We have learned over the years that ICM patients do benefit from CRT, but to a lesser degree than NCM patients, and that the individual requirements for optimization as well as for lead placement are more variable. A recently published single-centre experience with an average follow-up of  $\sim 3.5$  years showed a progressive remodelling effect with increasing LV volumes in the patient cohort with adverse clinical events.<sup>13</sup> The presence of an ICM, male sex, and a narrow QRS width ( $< 140$  ms) were predictors for non-response. Thus, a close look at the morphological changes in each individual patient and in particular in the ICM patients and in those who experience adverse clinical events such as rehospitalization seems warranted. If a certain degree of reverse remodelling can be documented after 6–12 months, i.e.  $> 15\%$  reduction in LV end-systolic volume, and this effect persists over the following visits, then there is probably no need for further ‘fine-tuning’ (e.g. AV and VV optimization) of the device. However, if such an effect cannot be documented and/or if the remodelling continues with a progressive enlargement of the LV cavity, then a detailed individual assessment is clearly

warranted and the different possible reasons for non-response must be checked.<sup>14</sup>

Another, somewhat confusing finding of the REVERSE long-term analysis is the fact that the initial beneficial effects on exercise tolerance as measured by the 6 min hall walk distance and on the perceived heart failure symptomatic (NYHA class) seem to vanish over time despite the generally positive effects on structural parameters and hospitalization. Again a more detailed analysis with a focus on the relationship between morphological changes and clinical parameters might help to clarify these apparently conflicting findings.

In summary, the reported long-term data from REVERSE confirm previous observations and reassure us that CRT is—in carefully selected patients—a very powerful therapy with long-lasting beneficial effects on structural remodelling in systolic heart failure. However, in the individual patient, the effects can by no means be taken for granted, and a close supervision is always indicated. The documented structural changes in LV volumes and ejection fraction may be taken as a guide for the routine clinical follow-up visit and for identification of non-responders, which require a more detailed individual assessment.

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