Regression of left ventricular mass and wall thickness after cardiac resynchronization therapy: proof of pathophysiological concept

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This editorial refers to "Differential change in left ventricular mass and regional wall thickness after cardiac resynchronization therapy for heart failure" by Q. Zhang et al., on page 1423

Cardiac resynchronization therapy (CRT) has become an established therapy for patients with NYHA class 3 and 4 heart failure, with a left ventricular (LV) ejection fraction (EF) <35%, and a wide QRS complex of >120 ms, especially in patients with a complete left bundle branch block (CLBBB). A number of studies have shown that patients with these characteristics may benefit from this therapy in terms of quality-of-life (QoL), exercise capacity, LV function, LV dimensions/volumes, morbidity, and even mortality. The key to understanding these effects lies in the term asynchrony as the most important determinant for success of CRT. Asynchrony, which means that parts of the heart and particularly the LV are out of phase during LV contraction and relaxation, can occur at three levels within the heart: atrioventricular (timing of atrial contraction to LV and RV contraction and relaxation, interventricular (between LV and RV), and intraventricular (between different segments of the LV). Asynchrony leads to several deleterious pathophysiological effects: abnormal interventricular septal wall motion, increased regional/global wall stress, reduced dP/dt, reduced pulse pressure, reduced EF and cardiac output, increased LV dimensions/volumes, LV regional hypertrophy, reduced diastolic filling time, increased mitral regurgitation, increased myocardial oxygen consumption, and decreased cardiac energetic efficiency. The final common pathway of all these effects is overt clinical heart failure with its inherent loss of QoL, hospital readmissions, and mortality. CRT may abolish and even reverse several, and sometimes all of these effects. If the effects of CRT are to be evaluated it is important to discriminate clinical responders from patients with so-called reverse remodelling. In the former, the clinical improvement may be due to a placebo effect (estimated to occur in 40% of cases after CRT), whereas in the latter improvement is a reflection of favourable pathophysiological changes after CRT, which usually, but not invariably, are also accompanied by clinical improvement. In the next section, the focus will be on the pathophysiological changes after CRT. For the understanding of these changes there are three factors, which are of paramount importance in determining whether a patient will be a responder to CRT in terms of reverse remodelling. These are the magnitude and extent of mechanical asynchrony, the amount and localization of myocardial viability, and the position and timing of pre-excitation (and therefore pacemaker lead positioning, programming, and venous anatomy). It is obvious that QRS width, and morphology (which mainly reflect interventricular asynchrony) are poor indicators of mechanical asynchrony. Despite prolonged QRS duration, 20–30% of patients are non-responders to CRT. Therefore, assessment of asynchrony by ultrasound or other imaging techniques should be the goal. Although there is no doubt on the importance of optimizing the AV interval, there is still an ongoing debate and research about the predictive value of inter- vs. intraventricular mechanical asynchrony. To further complicate this matter, there are several ultrasound techniques for evaluating interventricular asynchrony (pulsed-wave Doppler vs. tissue Doppler), and intraventricular asynchrony (M-Mode echocardiography, 2D- and real-time 3D echocardiography, tissue Doppler imaging (TDI), and strain-, and strain rate imaging). All of these techniques have their relative strengths and weaknesses, and a detailed description and discussion is beyond the scope of this editorial.

After CRT, in patients with LV volumetric reverse remodelling, there is a reduction of LV dimensions/volumes, mitral regurgitation, and an improvement in LVEF. The time-course of these events may vary from acute to up to 18 months. LV reverse remodelling defined as a 10% reduction of LV end-systolic volume (LVESV) after 3–6 months of CRT was observed to be associated with a significantly lower all-cause mortality and heart failure events. From experimental work and retrospective patient data it was already known that the early-activated region of the myocardium (i.e. the septum in CLBBB patients) is thinner than the...
late activated part (i.e. compensatory hypertrophy of the posterolateral wall).\(^3\) This fits in with the finding that the lateral wall strain (rate) in patients with heart failure and CLBBB is higher (with a higher wall stress) than in the septal wall before CRT, whereas after CRT this relationship is reversed.\(^1\)

The article by Zhang et al.\(^5\) in this issue of the journal is important from a pathophysiological point of view, as it is unique in that it describes significant regression of LV mass (assessed by 2D echocardiography) after 3 months of CRT in patients with volumetric reverse remodelling (i.e. the volumetric responders with a 10% reduction in LVESV), whereas in patients who were non-responders, there was a significant increase in LV mass. Furthermore, in responders LV wall thickness in the septal, lateral, anterior, and inferior wall was significantly decreased, and EF, myocardial performance index, LV sphericity index (both end-diastolic and end-systolic) all improved. This was in contrast with performance index, L V sphericity index (both end-diastolic and end-systolic) all improved. This was in contrast with the non-responders, in whom the septal- and lateral wall thickness increased, and the sphericity index worsened. Importantly, there was no significant difference in the extent of improvement in LV mass or other parameters of reverse remodelling between ischaemic and non-ischaemic patients after CRT. Also St John Sutton et al.\(^6\) have observed decreases in LV mass (assessed by 2D echocardiography) in the CRT group after 3–6 months in the MIRACLE trial compared with a control group without CRT. That study, however, was not designed to observe the close correlation between change in LVESV and change in LV mass in volumetric responders to CRT as in the present study by Zhang et al. An earlier study of Saxon et al.\(^7\) did neither observe a decrease in LV mass, nor a change in sphericity index 3 months after CRT. Therefore, the present study is the first, which describes in detail structural reverse remodelling after 3 months of CRT as a late sequel of volumetric reverse remodelling (which was observed already a day after CRT) both in patients with and without ischaemic cardiomyopathy. This decrease in LV mass in responders occurred in all four basal wall segments as regression of LV wall thickness, being a reflection of a lower global and regional wall stress. The 40% non-responders in the present study constitute a remarkably high number. Also puzzling is the finding that in these patients, although there is an unfavourable volumetric and structural remodelling, after 3 months of CRT, mitral regurgitation improves, as well as positive dP/dt. Clinical parameters like NYHA class, 6-min walk test, and QoL also improved in the non-responder group, but these might be attributed to a placebo effect, as mentioned earlier.

One may speculate if real-time 3D echocardiography, as a more accurate technique for LV volumes, -mass, and 3D LV sphericity index\(^8\) was used, instead of 2D echocardiography, the percentage of non-responders may be less. Asynchrony assessment by 3D techniques, derived from regional volume-time curves, would probably have yielded different results and responder rates.\(^9\) Before CRT implantation an assessment of potential recruitable stroke volume with CRT can be made and the best stimulation side can be targeted on a polar map display.\(^10\) Furthermore, acute changes (improvement) in LV volumes, function, and mitral regurgitation, can be readily assessed with this technique in the catheterization laboratory during the testing of different stimulation sites, and also at the bedside, during AV- and VV interval optimization. These questions remain to be answered by future studies. Nevertheless, the study by Zhang et al. provides proof of the pathophysiological concept that structural reverse remodelling after CRT is a late sequel of (early) volumetric reverse remodelling.

Conflict of interest: none declared.

References