Cardiac Resynchronization Therapy:

Prospect for Long Lasting Heart Failure Remission

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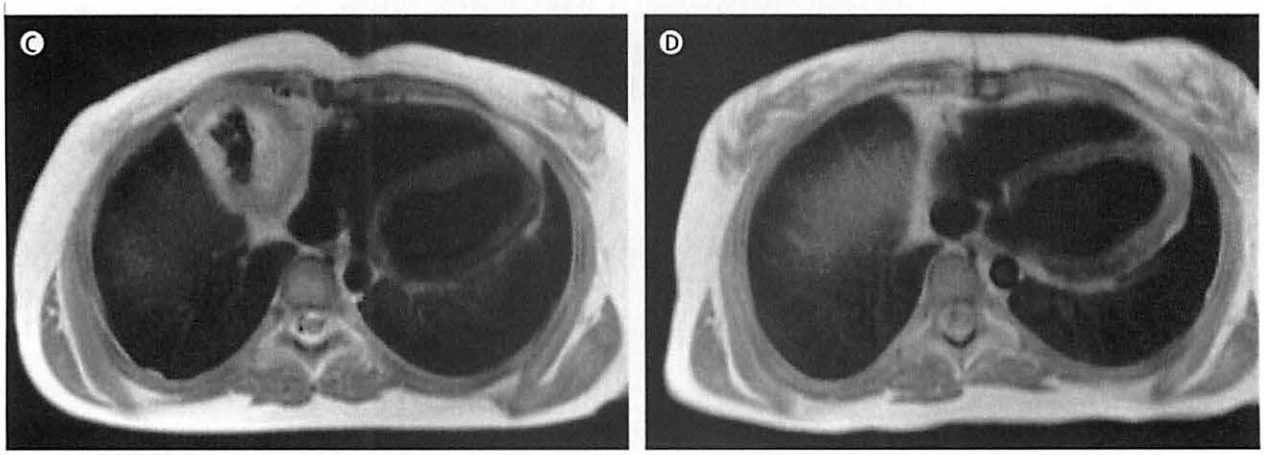
Introduction

Hannah Clark, was an 8-month girl when she developed dilated cardiomyopathy with severe heart failure (HF). Hannah, who is now 13, had a "piggyback" transplant operation in 1995, when a new heart was inserted in parallel to her own failing one. The surgeons used heterotopic transplantation in order to preserve the hypertrophied recipient right ventricle to deal with increased pulmonary vascular resistance, which is known to take months or years to regress. Other important consideration for heterotopic transplantation in this case was the ability to use a size-mismatched donor organ, since a reduction in the transplant-waiting period was deemed necessary.[1]

The donor organ had to be removed 3-1/2 years ago because of relapsing EBV-associated post-transplant lymphoproliferative disorder (PTLD). Since the surgery, Clark has made a full recovery from the PTLD and now has normal cardiac function.

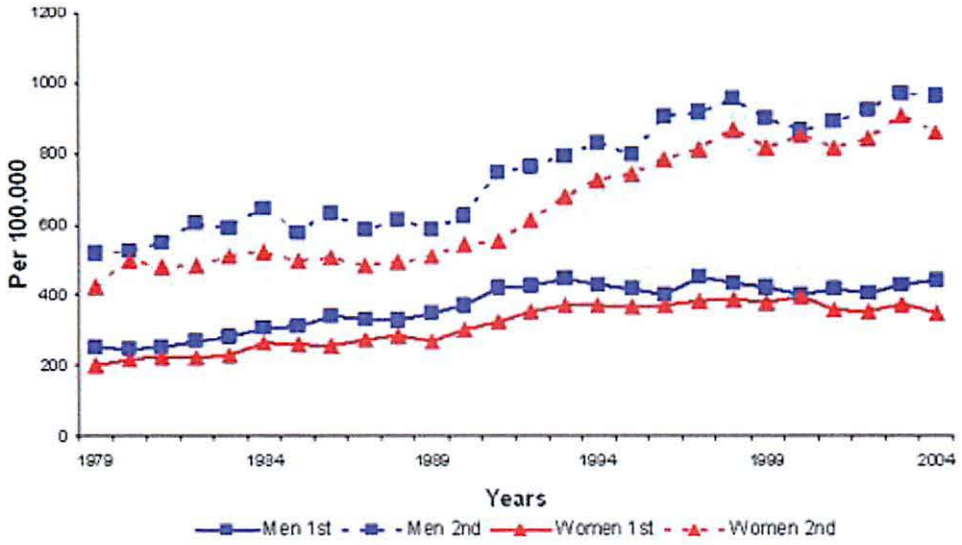


MRI shows half-Fourier acquisition single-shot turbo-spin echo images, positioned in a similar axial plane both before (C) and after (D) explantation of the transplanted heart. Panel C shows the native heart in the patient's left chest (right side of image), and the left ventricular cavity of the smaller, poorly functional transplanted heart in the patient's right chest. Stasis of blood caused the high signal artifact within the ventricular cavity of the transplanted heart. [1]

I view this case as the ultimate example of HF remission. Yet it is clear that with only 2500 donor hearts available in the US every year, this type of operation would not be possible in the great majority of patients with HF.

Heart failure remains an important health care problem in the US, accounting for over 3.8 million hospitalization per year[2] at cost that exceeds 50 billion dollars per year. With the aging of the U.S. population, advanced therapeutic interventions and improved survival for patients with acute myocardial infarction and other forms of heart disease, it is expected that heart failure

hospitalizations will continue to increase in the future. As such, therapeutic strategies to prevent hospitalizations for HF are necessary.



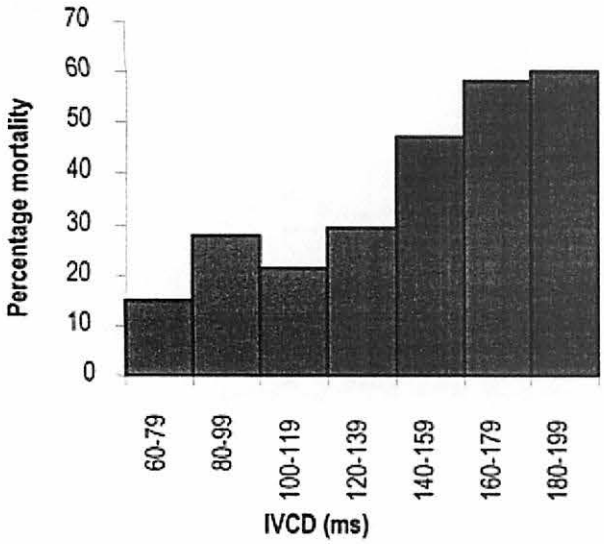
Age-Adjusted Hospitalization Rates for Heart Failure. National Hospital Discharge Survey, 1979–2004Trends of age-adjusted heart failure hospitalization rate (per 100,000) from 1979 to 2004 among patients with heart failure as the first-listed or additional (2nd to 7th) diagnosis for men and women. [2]

Not all is negative; in fact HF mortality has decrease significantly over the most recent decades.[3, 4] This is in part by the introduction of diverse pharmacological and device based therapies, such as ACE inhibitors, beta-blockers, aldosterone blockers and implantable defibrillators (ICD). More recently, cardiac resynchronization therapy (CRT) has become another important therapeutic option for treating HF.

Cardiac Resynchronization Therapy

Background

A high incidence of intraventricular conduction abnormalities (IVCD) has been reported in patients with HF, which directly correlates with HF severity. For example, in patients with HF and preserved ejection fraction (EF), only 8% show conduction abnormalities, compared to 38% of patients with moderate to severe left venrtricular dysfunction.[5] Furthermore, mortality also correlates with the presence of conduction delays. As demonstrated by Shamin and colleagues, mortality was worse as the width of the QRS increased (figure below).[6]



Graded increase in mortality with increasing intraventricular conduction delay.[6]

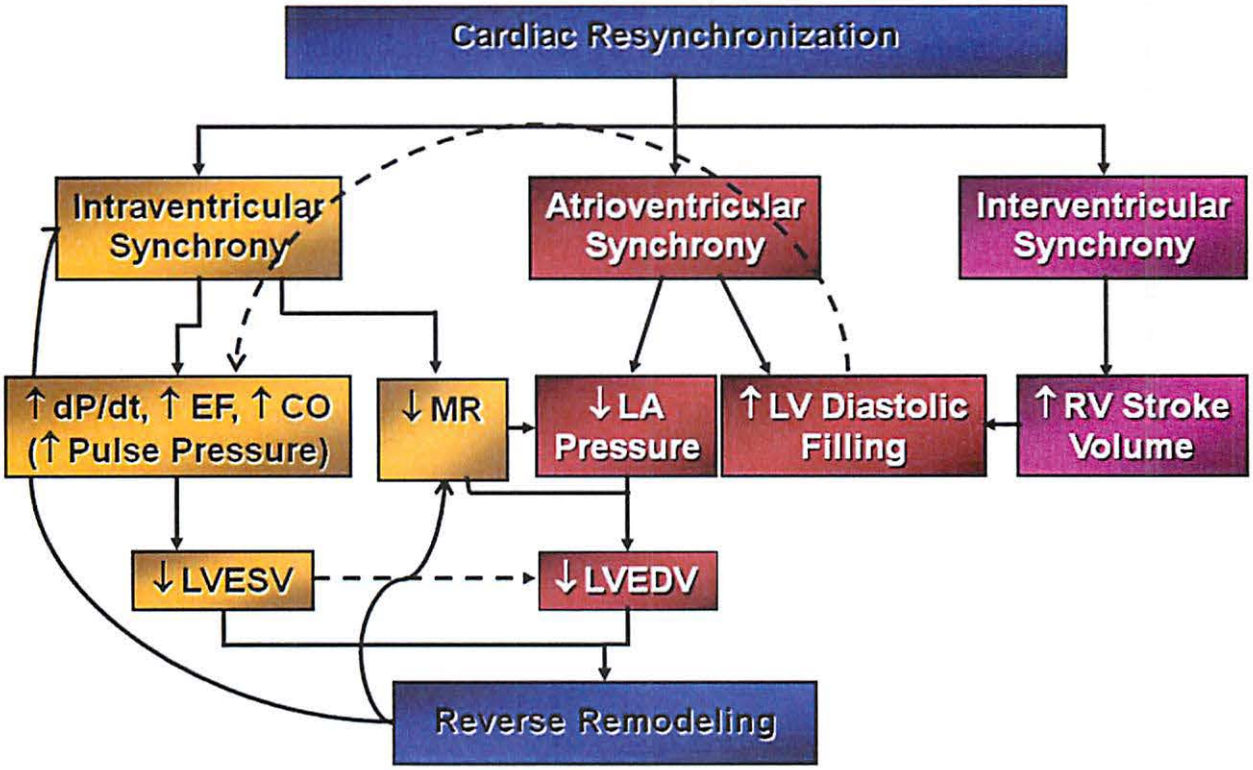
When the ventricle contracts in the presence of IVCD, segmental fractional shortening occurs in a rather disorganized way compared to normal conduction. . Early septal LV shortening occurs when total LV pressure is low, whereas late lateral LV shortening occurs late after total LV ejection. This leads to protracted mitral regurgitation due to asymmetry in papillary muscle contraction, a decline in systolic function of about 20%, diminished force of contraction and stroke volume and diminished cardiac efficiency.

Other data was also suggestive of the detrimental effects of IVCDs. Patient with structural heart disease who undergo standard right ventricular apical pacing experience a significant increase in HF hospitalization.[7] These findings were confirmed in the DAVID trial.[8] This landmark study was designed with the hopes of demonstrating that dual chamber ICD s were more effective than a single chamber ones, as it was though that pacing would have allowed for advancing beta blocker dose, and as such improving HF outcomes. Yet, the study was terminated early as the opposite was seen, in fact at one year, not only heart failure hospitalization almost doubled, but mortality increased from 6.5% in the control group to 10.1% in the pacing group.[8] The dramatic results were most likely related to the high percentage of RV apical pacing observed in the intervention group (55.7% of the time versus 2.9% in the control). Since the publication of this trial, RV apical pacing is considered deleterious in patients with structural heart disease and should be avoided as much as possible.

Proposed Mechanisms

The proposed mechanisms of CRT were described by Yu and colleagues. They demonstrated that biventricular pacing improved LV synchronicity by ensuring a delayed, yet synchronous, contraction so that intraventricular synchrony is improved. As a result of improved synchrony, systole becomes more effective, and ejection fraction, cardiac output, and other parameters of

cardiac function are improved. By synchronizing the contraction, mechanical mitral regurgitation attributable to distortion of mitral apparatus is reduced. As a result, LV end-diastolic pressure and volume are decreased. A second mechanism is the shortening of isovolumic contraction time after optimization of the atrioventricular delay. The effective diastolic filling time is increased, which, in turn, increases the stroke volume. A less important mechanism is the improvement of interventricular synchrony between the left and right (RV) ventricles. This benefit may mediate through ventricular interdependence. This results in the gain in RV cardiac output and, hence, the LV filling is augmented. The end effect of reverse remodeling will additionally improve cardiac synchrony and decrease secondary mitral regurgitation, forming a positive feedback loop as demonstrated below.[9]



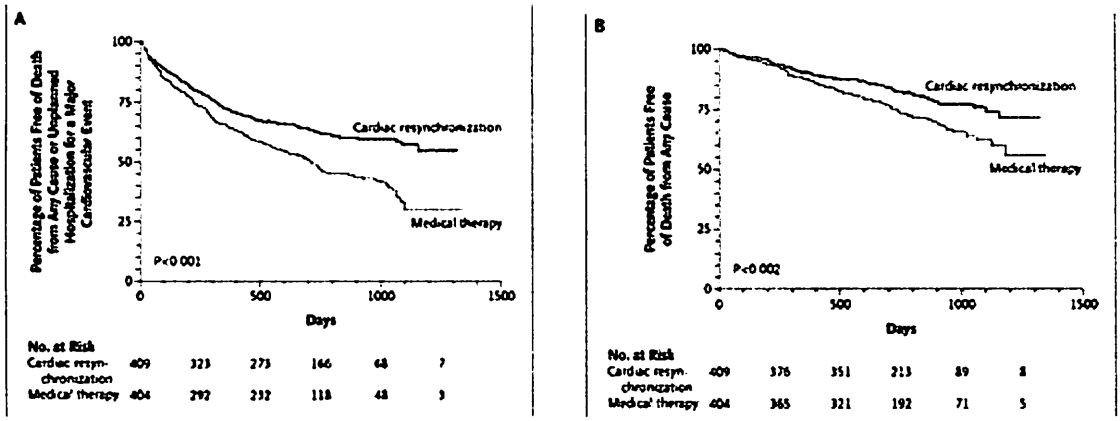
In addition, more recent studies have shed light into cellular and molecular mechanisms of CRT. Upregulation of contractility regulating genes has been demonstrated with long term CRT therapy, which goes in parallel with reverse remodeling .[10] Using a canine model of pacing-induced dyssynchronous HF, Aiba et al demonstrated that CRT partially restored dyssynchronous heart failure-induced ion channel remodeling, abnormal Ca^{2+} homeostasis and attenuated the regional heterogeneity of the action potential duration.[11] In a separate study, Chakir et al demonstrated upregulation of the β1-andrenergic receptors and restoration of normal balance between catecholamine stimulation and myocyte adrenergic responsiveness.[12] As such, these

and other studies show that in CRT responders, improvements in LV structure are accompanied by LV myocyte recovery, with restoration of electrophysiology currents, calcium handling and β adrenergic reserve [13]

Clinical Trials and Clinical Data

Up to date, over 100 clinical studies have looked in to the clinical efficacy of CRT in HF. Of these, 14 are randomized-controlled clinical trials involving a combined total of 4420 patients, all of which were included in a recent systematic review and meta-analysis.[14] In this analysis, CRT demonstrated to improve ventricular function and remodelling, HF symptoms, and exercise capacity, while also reducing frequency of heart failure hospitalizations by 37% and death by 22%. The magnitude of these benefits were found similar to those reported for angiotensin-converting enzyme inhibitors or β-blockers and are additive to the benefit of such medical therapies.[14]

In my view, one of the most important trial was CARE-HF,[15] as prior to its publication there was debate whether CRT would improve hard HF endpoints, such as hospitalizations and survival. One important aspect of this trial was that patients were followed longer than in previous trials (average 29.4 months). The study demonstrated conclusively that CRT did improve hospitalizations for HF, as well as survival. More importantly, it showed that the benefit continues to be visible over the long term, as Kaplan–Meier estimates curves continued to diverge (see figure below). Subsequent CRT analyses would take this observation in consideration.[15]



Furthermore, although patients with ischemic cardiomyopathy showed worse outcomes compared to patients with nonischemic cardiomyopathy, they did show similar relative benefit from CRT.[16]

CRT has a high initial cost, compared to pharmacological therapies, and early cost analysis that only took into consideration short term benefit data made CRT appear expensive. Subsequently, a cost analysis was published by Yao and colleagues based on the CARE HF study. [17] When the long term benefit is considered over the life of the device, CRT is cost effective in all age groups when compared to medical therapy alone, ranging from $9653 per quality-adjusted life-year in 55-year-old patients to US $10 792 in 75-year-old patients. Combined CRT-ICD devices were also found to be cost-effective when compared against medical therapy (US $24 360 per quality-adjusted life-year gained), but the cost-effectiveness ratios were less favorable in older patients (US $21 370 in 55-year-old patients vs US $30 408 in 75-year-old patients). The incremental cost-effectiveness of combined CRT-ICD devices vs CRT-alone devices, however, was markedly higher (US $64 777). Yet no data is available to support CRT only devices in patients with indications for ICD.

There is downside. Although the periprocedural risk of complications is modest (similar to the risk reported for patients undergoing implantation of conventional dual-chamber pacemakers), there is a 6% risk of device or lead problems and a 2% risk of infection in the first 6 months after CRT implantation. Furthermore, in about 7% of patients, the LV lead cannot be implanted due to anatomical limitations. Also, patients with CRT devices require more frequent replacements as battery longevity is significantly shorter than in standard pacemakers.

Based on the aforementioned data, CRT is currently indicated in HF patients with the following characteristics:

- NYHA Class III or IV
- QRS>130 msec
- LVEF<36%
- Stable medical regimen
  - ACEI
  - ß-blockers

Nonresponders

Despite the stated benefits, a number of key clinical research questions remain, perhaps most importantly the issue of why apparently suitable patients do not respond to CRT.[18] Rates of non-response to CRT are often quoted as 20–30%, but the published data suggest that this is an underestimate. The non-responder rates in the studies using subjective end point (such as functional capacity) as the main definition of response are generally lower (10-25%) than in the studies which used an objective parameter of left ventricle (LV) remodeling as the definition (up to 46%). This difference is related to the well-recognized significant placebo response to device

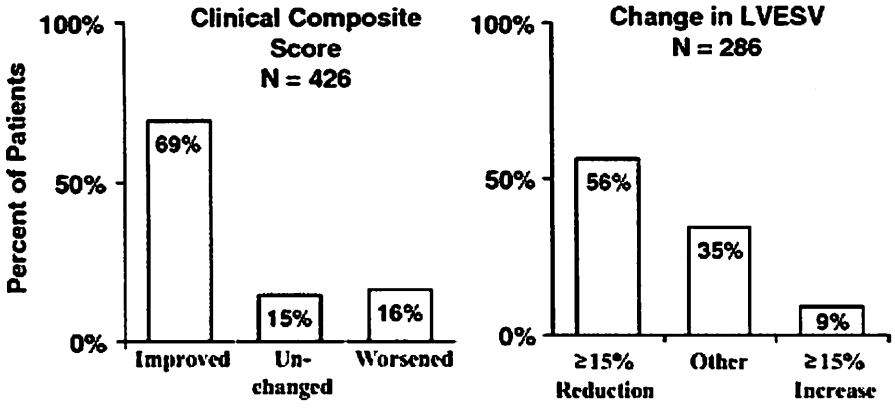
implantation. For example, in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, 28% of patients in the control group (inactive CRT) had a placebo response as assessed by improvement by one or more NYHA class. Of patients in the active CRT arm, 63% had an improvement in NYHA class and hence the placebo subtracted efficacy of CRT was only 35%.[19]

As such, more recent studies have emphasized the use of objective measures of response, such as LV remodeling. Nevertheless, even a conservative 30% nonresponse rate is a very significant number as the procedure is expensive, and technically difficult with an inherent risk of complications. As such, the issue of better patient selection has been a topic of extensive debate and research.

Predictors of Response

Since the objective of CRT is to reestablish synchrony, initial research focused on the presence and magnitude of mechanical dyssynchrony as a predictor of response. Earlier studies suggested that HF patients with similar electrocardiogram appearances may have quite different patterns of mechanical dyssynchrony and as a result may respond variably to CRT. For example Breinhardt et al. looked at correlating mechanical dyssynchrony and acute hemodynamic response to CRT in 33 patients with QRS duration of more than 150 ms.[34] Echocardiograhy was used to assess the difference between the lateral and septal wall motion. They identified two different types of mechanical dyssynchrony. The type 1 mechanical dyssynchrony pattern was very similar to the pattern in controls with normal hearts (no intraventricular conduction delay) and these patients failed to show acute improvement in hemodynamic function following CRT. Type 2 patients had significantly delayed lateral wall motion and exhibited the most acute hemodynamic benefit from CRT.[20] These and other data suggested that there was a group of patients who meet conventional electrical dyssynchrony (i.e. wide QRS) criteria but who did not have major mechanical dyssynchrony, therefore would not derive benefit from CRT.

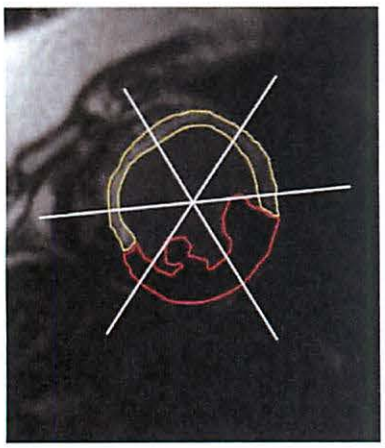
Then the PROSPECT study results were published, which rebutted prior thinking.[21] This trial represents the first large-scale, multicenter, clinical trial evaluating the performance of twelve commonly used echocardiographic measures of mechanical ventricular dyssynchrony to predict responsiveness to CRT. Four hundred and ninety eight patients with standard CRT indications were enrolled across centers in Europe, Hong Kong, and the United States. The composite endpoint improved in 69% of patients (a composite score combining subjective and objective clinical variables), where as 56% improved in the objective measure of LVESV (left ventricular end systolic volume) reduction of ≥15% at 6 months compared with baseline (figure below).



In regards to echo predictors, the PROSPECT concluded that none of the echocardiographic measures of ventricular dyssynchrony as applied in this study were able to distinguish responders from nonresponders to a degree that should affect clinical decision making[21] Thus, current clinical criteria, including the ECG, remain the standard for CRT patient selection. .As such, other predictors of response are required.

The first indication of the underlying cardiac substrate as a predictor of response came from the sub studies of the main CRT trials. For example, in the MIRACLE study, reverse remodeling at 12 months was see less often in patients with ischemic HF etiology, as compared to nonischemic HF.[22] In the CARE-HF trial, ischemic patients demonstrated relative improvements similar to the nonischemic cohort in the short term, both in terms of reduced mitral regurgitation and improved LVEF. However, in the long-term, LV function improved to a lesser extent in ischemic HF patients, presumably reflecting the inability of ventricular scar tissue to remodel favorably. The patients with ischemic HF also showed a worse prognosis overall.[23] It is likely that extensive left ventricular scar tissue attenuates clinical and structural response rates to CRT despite the presence of cardiac dyssynchrony and could be a potential confounder of results in CRT studies.[24]

Since scar tissue does not seem to remodel, integration of cardiac dyssynchrony and magnetic resonance imaging (MRI) for evaluating presence, location, and size of the scar in patients with ischemic cardiomyopathy may be a useful modality in patient selection for CRT. So far the data has been consistent with this theory, as recent studies have shown that a high scar burden would correlate with lack of response to a high degree.[25] For example, White and colleagues used delayed enhancement MRI and reported that a cutoff value of 15% percent total scar provided a sensitivity and specificity of 85% and 90%, respectively, for clinical response to CRT. Similarly, septal scar < or =40% provided a 100% sensitivity and specificity for response (see figure below).[26]



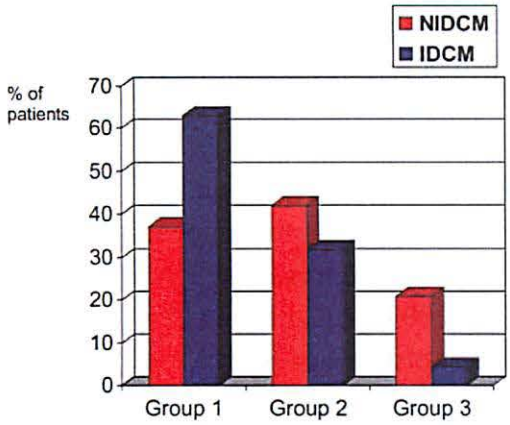
Short-axis delayed-enhancement magnetic resonance image showing a large area of scarred **(bright)** myocardium in the septal, anteroseptal, and anterior walls. Area planimetry of viable myocardium **(red line)** and scarred myocardium **(yellow line)** was performed as illustrated

Hyper-responders and Heart Failure Remission

Hyper-responders

Whereas early studies indicated that patients with ischemic cardiomyopathy and large scar burden were less likely to respond, other studies demonstrated very high response rates on different populations. An example is the population with pacemaker mediated cardiomyopathy. Leon and colleagues, on a 2002 study, demonstrated their experience after they upgraded 20 pacemaker-dependent patients with HF to CRT systems. The NYHA functional classification improved 29%, the left ventricular ejection fraction increased 44%, the LV diastolic diameter decreased 6.5% ($p < 0.003$) and the end-systolic diameter decreased 8.5% ($p < 0.01$). Furthermore, the number of hospitalizations decreased by 81%.[27]

Subsequent experience demonstrated that "complete" functional recovery associated with normalization of LV function could be observed, giving rise to the concept of "hyper-responders." The term was applied to patients in whom ejection fraction improved by over 20%. This finding was observed mainly in the subgroup of patients with nonischemic HF and left bundle branch block.[28] Although ischemic HF patients can be also show hyper-response, it is much less likely and even more unlikely for them to achieve full remission (see figure below).



Percentage of patients with ischemic dilated cardiomyopathy (IDCM) and nonischemic dilated cardiomyopathy (NIDCM) according to evolution after cardiac resynchronization therapy. Group 1 = no improvement of left ventricular ejection fraction (LVEF). Group 2 = 1%–19% increase of LVEF. Group 3 = >20% increase of LVEF. [28]

Similarly, Gasparinin and colleagues followed 520 consecutive HF patients from 1999 to 2006. Over a median follow-up of 28 months, 26% of patients achieved LV remission (rate: 16 per 100 person-years). At multivariate analysis, non-CAD etiology, LVEF 30% to 35%, and LV end-diastolic volume < 180 mL were strongly associated with HF remission phase.[29]

It is important to emphasize that the findings of exceptional CRT benefit in HF patients with non-CAD etiology and moderately compromised LV function are not intended to "question" standard guideline CRT indication criteria. Rather, the identification of strong predictors of HF remission allows to better define what can be "expected" from CRT on the basis of simple baseline variables.

Contractile Reserve as a Predictor of Response

These experiences bring up the issue of "Cardiac Substrate Selection" as benefit derived from CRT might depend on the extent of viable myocardium. Myocardial contractile reserve has been shown to provide important prognostic information in both ischemic and nonischemic cardiomyopathy, and for predicting response to other therapies, such as beta blockers. Ypenburg and colleagues demonstrated that a 7.5% increase in LVEF with low dose dobutamine predicted reverse remodeling after CRT.[30] In this study, the response rate in the patients with contractile reserve (cutoff 7.5%) was 87%, supporting the hypothesis that a substantial amount of "alive" myocardium is needed to obtain improvement in LV function after CRT, and points out how the lack of viability in the myocardium, mainly due to the presence of a relevant amount of scar tissue, reduces or even nullifies the benefits of CRT in HF patients.

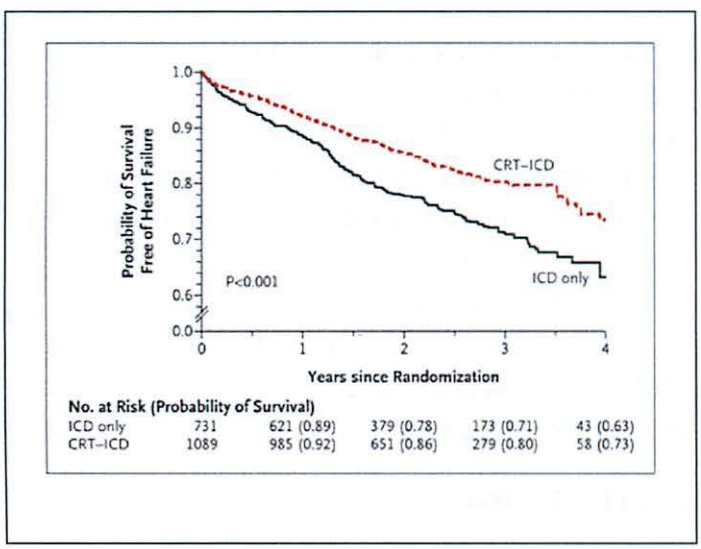
Expanded Indications: REVERSE and MADIT CRT trials

The large, long-term, observational study published by Gasparinin [29] suggests that, during a long-term follow-up, a consistent proportion of patients may experience remission of HF symptoms and of LV systolic dysfunction after CRT. The temporal pattern of this process is gradual and continuous through time and appears to be predicted by some specific and easily

recognizable preimplant characteristics, mainly nonischemic etiology and less advanced disease process. As such, a logical follow up question would be whether patients should receive CRT therapy earlier in the disease process, meaning in milder forms of HF?

REVERSE and MADITT CRT address this question. REVERSE is a double-blind study designed to evaluate the effects of CRT plus optimal medical therapy vs. optimal medical therapy alone, in patients with NYHA class I/II (mild) HF. Preliminary long term results (2 years) on the first 262 patients from European centers were presented at the 2009 ACC meeting.[31] Although there was no improvement in quality of life and 6 min walk test distance or NYHA class, there was a 62% reduction in the composite endpoint of death or worsening heart failure. The relative benefit was similar to that observed in CARE-HF.[31]

Full results of MADIT CRT study were recently published.[32] The study enrolled 1820 patients with ischemic or nonischemic cardiomyopathy, an ejection fraction of 30% or less, a QRS duration of 130 msec or more, and New York Heart Association class I or II symptoms. Patients were randomly assigned in a 3:2 ratio to receive CRT plus an ICD (1089 patients) or an ICD alone (731 patients). During an average follow-up of 2.4 years, the primary end point occurred in 17.2% of patients in the CRT–ICD group and in 25.3% of patients in the ICD-only group (hazard ratio in the CRT–ICD group, 0.66; 95% confidence interval [CI], 0.52 to 0.84; P=0.001). The benefit did not differ significantly between patients with ischemic and those with nonischemic cardiomyopathy. The superiority of CRT was driven by a 41% reduction in the risk of heart-failure events, a finding that was evident primarily in a prespecified subgroup of patients with a QRS duration of 150 msec or more.[32].



Kaplan–Meier Estimates of the Probability of Survival Free of Heart Failure.[32]

REVERSE and MADIT CRT, reinforced by a *post hoc* analysis of patients in CARE-HF,[33] suggests that the benefits of CRT on morbidity and mortality are not confined to patients with severe HF symptoms. Similar to beta-blockers, CRT may be now regarded as a therapy to

prevent worsening heart failure. These results suggest that it is likely that in the future CRT indications will expand to class I-II patients. Yet, because of the serious concerns about cost, perhaps only patients with very wide QRS (over 150msec) will be considered candidates.

Conclusions

Cardiac resynchronization is effective therapy for heart failure. In selected candidates, long lasting heart failure remission has been observed. Current trials are looking into initiating this form of therapy earlier in the CHF process. In the future, cardiac substrate selection might be used for better patient selection and cost reductions.

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