Effects of cardiac resynchronization therapy on disease progression in chronic heart failure

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Despite the alleviation of symptoms and longer survival conferred by pharmacological management of chronic congestive heart failure (CHF), this progressive syndrome remains associated with high morbidity and premature death. A new treatment of CHF should ideally alleviate symptoms, improve functional capacity, decrease mortality, and slow or reverse its progression without adding risks for the patient that outweighs the benefits. Growing evidence indicates that devices implanted to resynchronize ventricular contraction are a beneficial adjunct in the treatment of CHF. This review discusses the remodeling process, and its clinical and prognostic significance. We also discuss the impact of CRT, on remodelling and disease progression with a particular focus on patients with asymptomatic or mild heart failure (NYHA Class I-II).

KEYWORDS
Cardiac resynchronization therapy; Heart failure; Disease progression; Ventricular remodelling

Introduction

The natural history of chronic heart failure (CHF) is characterized by a progressive degradation of cardiac performance, unless the clinical course is interrupted by sudden cardiac death.1,2 Interventions, which lower mortality and morbidity in patients with CHF, have also had favourable effects on the continuous process of left ventricular (LV) remodelling. Cardiac resynchronization therapy (CRT) by biventricular stimulation has recently been introduced and tested in uncontrolled and controlled studies.3–7 Excepting the COMPANION and CARE-HF trials,5,7 the primary endpoints have been functional, based on changes in the quality-of-life, 6-min walk test, or peak VO₂.3,4 In addition to its significant effects on symptoms and exercise capacity, ancillary studies have shown that CRT may also reverse LV remodelling. For instance, in the Multi-site Stimulation in Cardiomyopathies (MUSTIC) trial, a significant decrease in LV dimensions was observed at 3 months of follow-up.8,9 This decrease was greater among patients with idiopathic cardiomyopathy, as was observed in the Multi-centre InSync Randomized Clinical Evaluation (MIRACLE) trial.4–10 CRT is an adjunctive treatment currently indicated for patients who remain symptomatic in New York Heart Association (NYHA) functional classes III or IV despite optimal drug therapy. The new challenge consists of preventing the development of severe symptoms, before patients are in advanced NYHA functional classes, and to show that the early delivery of therapy may prevent remodelling and disease progression. Although, implanting a CRT system in mildly symptomatic patients is not without possible adverse events related to the LV lead or to infection, the potentiality of clinical improvement and halting or reversing disease progression in these patients are estimated to outweigh these risks.11

This article reviews the mechanisms, and clinical and prognostic importance of LV remodelling. We also discuss the impact of CRT on LV remodelling. All randomized CRT studies published so far have been included. Pharmacological or surgical approaches are not treated in this review focused on CRT.

Causes and consequences of LV remodelling

Initially viewed as a simple haemodynamic disorder, CHF is now considered to be a complex syndrome associated with neuro-hormonal and cytokine activation that contribute to its progression.1,12,13 LV remodelling is a continuum from the onset of cardiovascular disease, such as myocardial infarction, hypertension, valvular disease, myocarditis or others, to end stage CHF. It includes several steps and different processes, which may be structural or functional.14 Its triggers include mechanical overload, activation of neuro-hormonal systems such as angiotensin and sympathetic/adrenergic stimulation, ischaemia and, perhaps, genetic factors, all of which promote electrophysiologic, ultrastructural, and anatomic adaptive or maladaptive processes. These complex and dynamic processes, beginning with cardiomyocyte hypertrophy, followed by fibrosis and deposition of extra-cellular matrix, and ending with myocytes necrosis or apoptosis, lead to LV dilation and...
changes in chamber geometry. Although the mechanisms responsible for this structural remodelling remain incompletely understood, pro-apoptotic molecules, endothelial nitric oxide synthase, extracellular matrix metalloproteinase, and tumour necrosis factor are among the many contributors. 15,16

Although LV is being functionally remodelled, it becomes more spherical. Initially, this adaptive process may help maintain stroke volume, though causes wall thinning, loss of myocardial contractility, and secondary mitral regurgitation (MR). 1,2 Cardiac imaging may easily assess changes in LV structure and function. 17,18 Echocardiography has especially become an appropriate tool for remodelling assessment. New post-treatments are available and current studies are using core-lab. Very strict protocol for image acquisition is requested and images are all analysed in the same core lab, applying rigorously the same techniques for remodelling quantification.7,9,18

During the ongoing remodelling process, changes in LV electrical activation frequently develop with secondary discoordination of myocardial contraction, which is strongly linked to morbidity and mortality.19 LV mechanical dysynchrony is responsible for regional heterogeneities of mechanical load and LV wall stress, and energetic metabolism. A 50% increase in LV lateral wall oxygen consumption was measured when left bundle branch block was created in an animal model.20,21 Studies of protein expressions and structural changes observed during the remodelling process, revealed that alterations in protein expression may also be regional, with a predominant dysregulation of myocardial proteins in the late-activated, high-stress, lateral wall. In a canine model, Spragg et al.22 showed that mechanical dyssynchrony polarizes the expression of ventricular proteins, calcium handling, and mitogen-activated phosphor-kinas in particular, generating trans-mural and trans-ventricular gradients in their expression. Interestingly, the myocardial protein dysregulation was predominant in the late-activated, high-stress lateral wall. That might contribute to regional LV heterogeneity of contractile function, as well as to electrical vulnerability. One small clinical study even suggests that this might have an impact on arrhythmia susceptibility.23

Prognostic importance of LV remodelling

A decline in LV function contributes to worsening symptoms and exercise intolerance, but also to increase serious morbidity and death by terminal pump failure or sudden cardiac death. The independent prognostic importance of LV remodelling has recently become a goal of CHF treatment.1 Previously, objectives of CHF treatment were largely concentrated on symptom relief, whereas present attention also encompasses slowing or halting disease progression. Furthermore, slowing or reversing cardiac remodelling appears closely related to relief of symptoms and improvements in prognosis. Therefore, treatment of LV remodelling while patients are in NYHA functional classes I or II should delay or reverse LV dilatation, and prevent the degradation of functional status. The provided benefits are expected to be larger than the potential risks of treatment.

Reversing LV remodelling by CRT

Impact of resynchronization therapy on LV remodelling

Resynchronization of atrio-ventricular, inter-ventricular, and left intra-ventricular dyssynchrony can be achieved by atrio-biventricular pacing, the LV being paced by a lead placed in a coronary sinus tributary draining the lateral or posterior LV wall. When patients were selected according to electrocardiographic criteria consistent with ventricular dyssynchrony, i.e. left bundle branch block and a QRS complex duration >120 ms, an immediate haemodynamic improvement was achieved with CRT.29–32 Furthermore, most non-controlled and multi-centre randomized trial designed for a 3–6 months follow-up demonstrated that CRT improves quality-of-life, exercise capacity, and reduces heart failure symptoms.3–7,31,33,34 Moreover, these studies consistently showed that these improvements are accompanied by reverse remodelling with 8–15% reduction in LVEDD and 4–7% increase in LVEF.35 In contrast, there is no evidence of electrical remodelling by CRT, as intrinsic QRS duration remains unchanged by CRT even after 12 months of treatment.8

Yu et al.25 reported a progressive improvement of LV fractional shortening and EF at 1- and 3-month by CRT. Moreover, isovolumic contraction time, diastolic filling time, and myocardial performance index gradually improved over the 3-month period. This beneficial effect was reversible if the pacemaker was turned off indicating an immediate effect by CRT. This change in time intervals by CRT probably is the prerequisite in initiating and maintaining the reverse remodelling process.9

These observations were accompanied by a decrease in the intra-ventricular asynchrony assessed by an index combining the time to peak systolic velocity recorded in systole for each LV wall in the basal and mid-lateral segment by Tissue Doppler imaging.36

Observational mechanistic studies

At present, the electrical dyssynchrony criterion by ECG was used to select patients for CRT. With this selection, 60–67% of patients respond to pacing.37 The studies performed so far indicate that electrical asynchrony is not always synonymous with mechanical asynchrony.38 Moreover, selected patients with ‘normal’ QRS duration but mechanical dyssynchrony have improved by CRT. As approximately 70% of implanted patients39 respond to CRT using the ECG criteria, attention is now focused in increasing the response rate by identifying mechanical criteria to predict the individual response to
pacing. To date, mechanistic studies have been performed in small numbers of patients using various imaging techniques and indexes to demonstrate mechanical asynchrony and to assess the effects of CRT on these indexes. 39–41 Therefore, there is a need for controlled clinical studies that evaluate these criteria before implementing them as selection criteria for CRT.

The mechanisms of myocardial mechanical asynchrony are multiple depending on the underlying aetiology and include a delayed LV regional contraction and relaxation. In many patients with left bundle branch block, the right ventricle contracts during LV end-diastole, leading to a ‘bulging’ of the septum into the LV. The LV septum is usually moving before the LV lateral wall. This asynchrony leads to a delay in contraction of the antero-lateral papillary muscle creating or aggravating functional MR related to LV enlargement. 42–45

Some studies have demonstrated the relationship between restoring mechanical synchrony by CRT and clinical improvements. In a sub-study of the InSync Italian registry, the magnitude of improvements in LV volumes, EF, right, and left side myocardial performance indices was related to the degree of resynchronization achieved by CRT. 46 In a 3-month study, Molhoek et al. 47 also emphasized that the relationship between magnitude of improvement and resynchronization achieved occurs irrespective of ischaemic and non-ischaemic aetiology. The follow-up time was actually very short (3 months) in this study.

In other studies, the impact of CRT on functional status and LV remodelling could be predicted most often by the use of Tissue Doppler imaging criteria to determine mechanical dysynchrony. An intra-left ventricular delay >65 ms before implantation, 48,49 or a myocardial dysynchrony index >32.6 ms,50 were proposed with an approximately 96% sensitivity, 77% specificity, and 88% accuracy to predict the effectiveness of CRT on reverse remodelling. 49 Pitzalis et al. 50 also derived a similar conclusion looking at the radial asynchrony on echocardiogram. An increase in LVEF was observed in 79% of patients with >130 ms delays between the septal and posterior walls in the parasternal long axis. These results were confirmed by Gorscan et al. 51 using tissue synchronization imaging but their observation also provides the opportunity to stress that an absence of acute improvement in LVEF or LV output does not mean that a beneficial reverse LV remodelling will not appear after weeks (about 6 months).

The echocardiographic evaluation of dysynchrony tends to reach the clinical routine practice. Nevertheless, no multi-centre large population-based series are confirming echocardiography or TDI-relevance in patient selection for CRT. Only CARE-HF trial considered echocardiographic mechanistic parameter in the inclusion criteria. These mechanistic criteria were requested for patients with QRS width between 120–150 ms. However, only 9% of the patients included in that study had QRS-width <150 ms. Thus, no significant conclusion can be done with regard to mechanistic criteria in CARE-HF. 7 Moreover, till date, patients have to be implanted based on electrocardiographic criteria of QRS duration ≥120 ms.

An effort to standardize the echocardiographic protocol(s) to assess asynchrony remains to be performed. 52

With regard to the ischaemic heart disease, the assessment of asynchrony in ischaemic heart and non-ischaemic cardiomyopathy might justify different kinds of evaluation, as the positioning of a pacing lead in front of a scarred tissue might not be as efficient as a hibernating or contracting segment.

Nevertheless, no study till date has demonstrated, in multi-centre large population-based series, the utility of echocardiography or TDI in patient selection for CRT. Thus, up-to-date, patients have to be implanted based on electrocardiographic criteria of QRS duration ≥120 ms.

Observations from randomized multi-centre studies

Patients in NYHA heart failure functional class III or IV

The echocardiographic sub-studies of randomized multi-centre trials have recently been reported and are summarized in Table 1. In MUSTIC, the decrease in LV dimensions observed at 3-month progressed further at 6- and 12-months of follow-up. 8,9 (Figure 1).

This observation was very recently confirmed in the extension study of CARE-HF, with a progressive LV volume reduction from baseline (LV end-diastolic volume 309 cm³, 367 patients) to 29-month follow-up (LV end-diastolic volume 221 cm³, 222 patients). 51 The short-term effects of CRT have been evaluated by serial echocardiograms in the VIGOR CHF trial, in which a mini-thoracotomy was performed for the placement of an epicardial LV lead. 52 After 12 weeks of CRT in 53 patients, LV diameters and LA volumes had decreased (an evolution consistent with reverse ventricular and atrial remodelling). Increases in LVEF and myocardial performance index were observed as well. In MIRACLE, 10 CRT caused a mean decrease in LV end-diastolic volume of 22.6 cm³ at 3-month, and 27.2 cm³ at 6 months, from a mean baseline volume of 295.6 ± 102.6 cm³. In addition, LVEF and diastolic function increased, and the severity of MR decreased significantly. The trend to progressive improvement over time was recently confirmed in the CARE-HF study with a longer follow-up. The LV end-systolic volume was reduced by a mean of 18% at 3-month and 26% at 18-month. As well, LVEF increased by 3.7% and 6.8%, respectively7 (Table 1).

The evidence from MUSTIC and MIRACLE 8,10 suggests that a greater magnitude of reverse remodelling is achieved in patients with non-ischaemic cardiomyopathy. In MUSTIC, the regression of LVEDD was greater at 3-month in the non-ischaemic group as compared with ischaemic patients with a mean difference in LVEDD of 5.1 mm after 3 months of CRT and of 8.9 mm after 9 months of CRT between aetiologies. 6,9 In MIRACLE, changes in LV end-diastolic volume and ejection fraction from baseline to 6-month of CRT were twofold greater in patients with non-ischaemic LV dysfunction than in patients with ischaemic cardiomyopathy. 10

Risk of CRT treatment

CRT is not without risks. Failure to implant the LV lead was relatively frequent, 7.5% (4) to 11% (5) in the initial experience but decreased up to 5% (7) in the most recent trials. It is also estimated that the implantation procedure is related to potential risks such as failure to implant LV lead, dissection or perforation of the coronary sinus, diaphragmatic stimulation, infection, and lead dislodgment. These risks
are 9–10% and mostly present themselves within 1 month following implantation. They surpass the risk of mere right ventricular (4%) or dual-chamber (7%) pacemaker implantations as observed in the CTOPP or UKPACE studies. The benefits in established populations (NYHA class III and IV CHF patients) for this treatment in terms of morbidity and mortality as evidenced by the CARE-HF trial with a 29 follow-up time are large enough for these risks to be considered acceptable. During follow-up, the most frequent adverse event was LV lead dislodgment that occurred in 3.8% (4) to 5.9% (7). Infection requiring device explantation was observed in 0.7% (7) to 1.2% (4).

Patients with mild CHF (NYHA class II)

In the CONTAK-CD trial, significant reverse remodelling could also be demonstrated in the small sub-group of NYHA class I-II patients after 6-months of CRT, even though benefits were less pronounced than in the much larger group of NYHA III-IV patients (Table 2). Similar observations were done in the MIRACLE-ICD II trial. One hundred eighty-six patients with NYHA I or II clinical status and an ICD indication were randomized to two parallel arms: CRT-on and CRT-off (control group). Functional improvement at 6-month was non-significant in the CRT arm but the clinical composite response that combines mortality, serious morbidity, and symptoms, was significantly improved thus indicating less disease progression. This global clinical improvement paralleled to an obvious benefit on LV remodelling with a significant increase in LVEF (4%) and decrease in LV volumes (mean reduction of 15% in LVESV) when no significant variations were observed in controls.

Ongoing and future trials to assess the effect of CRT on remodelling and disease progression in NYHA class I-II CHF patients

A consistent finding in the CRT trials designed with a 3–6-month follow-up is an 8–15% reduction in LVEDD and an increase in LVEF of 4–6% expressed in absolute value units. In the MIRACLE ICD II study, similar data were reported in NYHA class II patients. These preliminary observations
Table 3  Effects of CRT on L V function and dimensions in patients with moderate to severe heart failure (NYHA class III-IV)

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>Follow-up CRT</th>
<th>Follow-up Control</th>
<th>P</th>
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<tr>
<td>MUSTIC3 (n = 34)</td>
<td></td>
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<tr>
<td>LV EED (mm)</td>
<td>73 ± 8</td>
<td>64 ± 7</td>
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<td>&lt;0.001</td>
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<tr>
<td>LVESD (mm)</td>
<td>62 ± 8</td>
<td>53 ± 8</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Aortic ITV (cm)</td>
<td>14.9 ± 5.6</td>
<td>17.9 ± 6.6</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>PATH-CHF64 (n = 25)</td>
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<tr>
<td>LV EESD (mm)</td>
<td>63 ± 11</td>
<td>58 ± 11</td>
<td></td>
<td>0.007</td>
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<tr>
<td>FS (%)</td>
<td>12 ± 6</td>
<td>15 ± 7</td>
<td></td>
<td>Ns</td>
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<tr>
<td>CONTAK-CD59 (n = 227)</td>
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<tr>
<td>LVEDD (mm)</td>
<td>71.5 ± 10.5</td>
<td>−4.9 ± 1</td>
<td>−0.2 ± 1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>59.5 ± 11</td>
<td>−5.4 ± 1.1</td>
<td>−0.6 ± 1.1</td>
<td>0.002</td>
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<tr>
<td>LV EF (%)</td>
<td>21 ± 6</td>
<td>6 ± 1.1</td>
<td>2.3 ± 1.2</td>
<td>0.029</td>
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<tr>
<td>MIRACLE4 (n = 172)</td>
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<tr>
<td>LVEDD (mm)</td>
<td>295.6 ± 102.6</td>
<td>−27.2</td>
<td>+4.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>227.7 ± 93.7</td>
<td>−25.6</td>
<td>+0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>24.5 ± 6.8</td>
<td>+3.6</td>
<td>−0.4</td>
<td>&lt;0.05</td>
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<tr>
<td>CARE-HF7 (n = 409)</td>
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<tr>
<td>LVESVI (ml/m²)</td>
<td>121 (IQR: 92–151)</td>
<td>−84.4</td>
<td>−26.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>LV EF (%)</td>
<td>25 (IQR: 21–29)</td>
<td>+6.9</td>
<td>+2.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LVESD, Left ventricular end-systolic diameter; LVEDD, Left ventricular end-diastolic volume; LVESD, Left ventricular end-systolic volume; MIRACLE, LV end-systolic volume index.

In brackets are figured the changes observed in the control group of each randomized study in opposition to changes observed in the CRT group. MUSTIC and PATH-CHF were crossover studies without any control group.

Table 4  Effects of CRT on LV function and dimensions in patients with mild heart failure (NYHA class II)

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>Follow-up CRT</th>
<th>Follow-up Control</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>MIRACLE-ICD55 II (n = 85)</td>
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<tr>
<td>LVED volume (ml)</td>
<td>340 ± 151</td>
<td>300 ± 130</td>
<td>334</td>
<td>0.04</td>
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<tr>
<td>LVES volume (ml)</td>
<td>264 ± 138</td>
<td>223 ± 118</td>
<td>250</td>
<td>0.01</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>24.1 ± 6.6</td>
<td>27.9 ± 7.9</td>
<td>24.9</td>
<td>0.02</td>
</tr>
<tr>
<td>CONTAK–CD59 (n = 263)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>69.6 ± 10.5</td>
<td>−2.4 ± 0.8</td>
<td>0 ± 0.8</td>
<td>0.024</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>57.6 ± 10.5</td>
<td>−3.2 ± 0.8</td>
<td>−0.5 ± 0.8</td>
<td>0.014</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>21.9 ± 8</td>
<td>+4.7 ± 0.9</td>
<td>2.9 ± 0.9</td>
<td>0.16</td>
</tr>
</tbody>
</table>

LVESD, Left ventricular end-systolic diameter; LVED volume, Left ventricular end-diastolic volume; LVES volume, Left ventricular end-systolic volume; LVESVI, LV end-systolic volume index.

In brackets are figured the changes observed in the control group of each randomized study in opposition to changes observed in the CRT group.
suggest that CRT might favourably impact outcomes in patients with less severe symptoms of HF, LV systolic dysfunction, and ventricular dyssynchrony. To test this hypothesis, the REsynchronization reVErseS Remodelling in Systolic left vEntricular dysfunction (REVERSE) study has been initiated to assess the safety and efficacy of CRT in addition to optimal medical therapy, in patients with asymptomatic LV dysfunction (NYHA I ACC/AHA stage C) or mild heart failure (NYHA II). 25

The REVERSE study is a prospective, multi-centre, randomized, double-blind, parallel controlled clinical trial designed to establish whether CRT combined with optimal medical treatment can attenuate HF disease progression over at least 12 months compared with optimal medical treatment alone, in patients with mild HF. Inclusion criteria are: NYHA I ACC/AHA stage C or II HF, QRS-duration ≥ 120 ms, LVEF ≤ 40%, LVEDD ≥ 55 mm, and an optimized pharmacological regimen.

After successful implantation of an atrio-biventricular device (CRT pacemaker or CRT defibrillator according to the patient needs) approximately 500 patients from 100 centres in the United States, Canada and Europe will be randomized to CRT vs. no CRT and followed for at least 12 months (24 months in Europe). The primary endpoint is the HF clinical composite response, and LV end-systolic volume index is the first-order secondary endpoint. Enrolment started in September 2004 and is expected to be completed in 2006.

The MADIT CRT aims at investigating whether prophylactic CRT inhibits or slows symptomatic heart failure. Patients with previous myocardial infarction and NYHA II-III patients with non-ischaemic cardiomyopathy in NYHA II will be included if they have EF < 30%, sinus rhythm and QRS > 130 ms. The primary endpoint is the time to first all cause mortality or heart failure event analysed from randomization. This study will include 1820 subjects with an estimated follow-up time of 24 months.

In parallel to observations performed with pharmacological agents, the impact of CRT on inflammatory and remodeling markers has to be performed to emphasize the beneficial effect of this treatment on the remodelling process as expected from imaging mechanistic observations.21

Safety issues will have to be examined very carefully in these studies, as the risk-benefit balance could be less favourable in NYHA class I-II patients as compared with class III-IV (Tables 3 and 4).

Conclusion

LV remodelling is tightly related to prognosis and might be easily assessed by echocardiography. Pharmacological agents validated in the CHF treatment have demonstrated beneficial effects. CRT is now included in ACC/AHA and ESC guidelines as a validated treatment of refractory CHF.56,57 Aware of the potential reverse remodelling observed in patients treated with atrio-biventricular pacing, it might now be of interest to test the clinical value of CRT in NYHA I-II CHF patients. Combined CRT with optimal medical treatment might be able to attenuate disease progression and thus improve functional outcome and survival. This is the purpose of new ongoing studies like the REVERSE trial aimed at comparing CRT plus optimal medical therapy to optimal therapy in patients with asymptomatic or mild heart failure and ventricular dyssynchrony. Risk-benefit balance will be a key objective to assess these new trials.

Conflict of interest: none declared.

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