Cardiac resynchronization therapy in left ventricular hypertrabeculation/non-compaction and myopathy

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Aims Little is known how patients with left ventricular hypertrabeculation/non-compaction (LVHT) and heart failure respond to cardiac resynchronization therapy (CRT).

Methods and results Included in this retrospective study were 8 out of 102 patients (3 female, age range 43–78 years), in whom LVHT was diagnosed and in whom a CRT system was implanted. All eight patients were investigated neurologically and in seven of them a myopathy was found. The mean follow-up after CRT implantation was 39 (4–68) months. All patients improved by one or more New York Heart Association (NYHA) classes, and two by two NYHA classes. The left ventricular end-diastolic diameter decreased by 5% in 2 patients, by 6–10% in 3 patients, by 12% in 1 patient, and by 30% in 2 patients. The left ventricular systolic function, as assessed by the fractional shortening, did not change in 2 patients, increased by 10% in 2 patients, by 59% in 1 patient, doubled in 2 patients, and showed a five-fold increase in 1 patient. Two patients died during follow-up.

Conclusion CRT by biventricular pacing in LVHT, heart failure, and myopathy leads to improvement in functional capacity in all patients and improvement of systolic function in half of the patients. The weak response of LVHT patients to CRT may be due to inappropriate selection or comorbidities, in particular, neuromuscular disorders.

KEYWORDS Cardiomyopathy; Heart failure; Myopathy; Cardiac resynchronization therapy; Biventricular pacemaker

Introduction Cardiac resynchronization therapy (CRT) has been shown to be a promising therapy in patients with heart failure and intraventricular conduction delay.1 However, up to now, it remains unclear why apparently suitable patients do not respond to CRT.2

Left ventricular hypertrabeculation/non-compaction (LVHT) is a cardiac abnormality of unknown aetiology characterized by prominent left ventricular trabeculations and deep intertrabecular recesses. Left ventricular hypertrabeculation/non-compaction is frequently associated with neuromuscular disorders. LVHT is assumed to be congenital, although in several cases it has been reported to develop during life-time.3 LVHT is frequently associated with heart failure and systolic dysfunction, which have also been identified as prognostic factors in LVHT.4,5 Only little is known about the response of LVHT patients with heart failure to CRT.6–9 Thus, we report about our cohort of LVHT patients who have received a CRT system.

Patients and methods Included in this retrospective study were all patients in whom LVHT was diagnosed in the echocardiographic laboratory of the KA Rudolfstiftung between June 1995 and November 2006. Two-dimensional and Doppler echocardiographic criteria for the diagnosis of LVHT were (i) more than three trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in one echocardiographic image plane, and (ii) intertrabecular spaces perfused from the ventricular cavity, as visualized on colour Doppler imaging. Trabeculations were defined as structures with the same echogenicity as the myocardium and moving synchronously with the ventricular contractions.3 The clinical characteristics of the included patients have been published previously.5,10 In December 2006, the records of the patients were screened and the treating cardiologists were contacted to assess how many of the patients had received a CRT system and how their symptoms and echocardiographic parameters had changed since CRT implantation. The medication at the last follow-up visit was registered.
Results
Between June 1995 and November 2006, LVHT was diagnosed in 102 patients (30 females, mean age 53 ± 16 years, range 14–94) among 38 370 transthoracic echocardiographic examinations. Ninety-three of these cases, diagnosed until December 2005, have been published previously. 10

Eight of these 102 patients received a CRT system (Medtronic Inc., MN, USA/Guidant Inc., IN, USA). The clinical characteristics of these patients are listed in Table 1. In all patients, coronary angiography was carried out and was normal. Echocardiography did not show any regional wall motion abnormalities. Seven patients were in sinus rhythm, and one patient (Nr.8) had atrial fibrillation. In seven patients, the ECG showed a left bundle branch block, and in one patient (Nr.2), an incomplete right bundle branch block and left ventricular hypertrophy. Cardiac resynchronization therapy was implanted in patient Nr.2 because severe asynchrony had been demonstrated by tissue-Doppler imaging. An interventricular delay of 24 ms was assessed, which decreased after CRT to 4 ms, and an intraventricular delay of 84 to 38 ms, respectively. 6

All patients were in advanced stages of heart failure despite pharmacotherapy. One patient (Nr.1) was already on the waiting list for heart transplantation, the other patients refused cardiac transplantation (Nr.2 and Nr.6) or were considered inappropriate candidates for cardiac transplantation because of mannose-binding lectin deficiency with recurrent infections (Nr.7), chronic alcohol abuse (Nr.5), or increased age (Nr.3, Nr.4, and Nr.8). In five of the eight patients, the CRT system was combined with an implantable cardioverter defibrillator (ICD) because of ventricular tachycardia (Nr.1, Nr.2, Nr.5, and Nr.7) and prophylactic (Nr.4). All eight patients were investigated neurologically and in seven of them a neuromuscular disorder was found as listed on Table 1. One had Becker muscular dystrophy, two mitochondrial myopathy, and four non-specific myopathy.

The mean follow-up after CRT implantation was 39 months, ranging from 4 to 68 months. All patients improved in their subjective capacity by one or more New York Heart Association (NYHA) classes, and two of them (Nr.1 and Nr.6) by two NYHA classes. In contrast to subjective capacity, the response to CRT varied considerably when looking for left ventricular remodelling. The left ventricular end-diastolic diameter decreased by ≤5% in 2 patients (Nr.5 and Nr.7), by 6–10% in 3 patients (Nr.1, Nr.2, and Nr.8), by 12% in 1 patient (Nr.4), and by >30% in 2 patients (Nr.3 and Nr.6). The left ventricular systolic function, as assessed by the fractional shortening, did not change in 2 patients (Nr.2 and Nr.5), increased by 10% in 2 patients (Nr.7 and Nr.8), by 59% in 1 patient (Nr.3), doubled in 2 patients (Nr.1 and Nr.4), and showed a five-fold increase in 1 patient (Nr.6). Neither the duration of follow-up nor the width of the base QRS nor the change of QRS-width due to pacing correlated with clinical or echocardiographic improvement.

Pharmacotherapy was continued in all patients. Only after implantation of the CRT system in patient Nr.3 and patient Nr.4, digitalis could be added; in patient Nr.4, an ACE-inhibitor initiated, and the dosage of beta-blocking agents increased, since the patients did not tolerate it before CRT implantation because of hypotension and bradycardia. In patient Nr.8, it was difficult to achieve frequency control of his atrial fibrillation despite amiodarone, which had to be discontinued because of hyperthyroidism.

Complications related to CRT system implantation occurred in two patients: patient Nr.3 developed a haemorrhagic pericardial effusion requiring pericardiocentesis and surgical drainage 3 months postoperatively. Cytological examination of the effusion showed no signs of malignancy or infection. Her further course was uneventful. In patient Nr.7, it was not possible to introduce the left ventricular pacing lead through the coronary sinus, thus an epicardial lead had to be placed by thoracotomy. The postoperative course in this patient was complicated by a haematotherax and the necessity for prolonged mechanical ventilation.

Two of the eight patients died during follow-up. Both of them died in the hospitals where the regular follow-up visits were carried out. Patient Nr.7 died 16 months after CRT implantation from recurrent respiratory infections due to Methicillin-resistant Staphylococcus aureus, renal insufficiency necessitating haemodialfiltration, and eventually hepatic failure. At autopsy, no colonization was found on the CRT system and its leads. Patient Nr.2 developed renal failure and septicamia with Staphylococcus epidermidis. Cardiac transplantation was considered as an ultimate treatment option, but refused by the surgeons because of the septicaemia. Despite intensive therapy, he died of multi-organ failure 4 months after CRT implantation. Since post-mortem examination was not carried out, it remains uncertain whether the S. epidermidis septicaemia was due to the CRT system or another source.

Altogether, all patients profited from CRT when measured by functional status, and four of them improved by functional status as well as by echocardiography.

Discussion
This case series shows that in LVHT patients with systolic dysfunction and heart failure despite pharmacotherapy, CRT by biventricular pacing may lead to improvement in functional capacity in all patients and systolic function in half of them.

CRT by biventricular pacing is a recent and promising therapy for heart failure patients with an intraventricular conduction defect. 1,11 However, up to now, it remains unclear why apparently suitable patients do not respond to CRT. Rates of non-response to CRT are often quoted as 20–30%, but it is assumed that this is an underestimate. 2 To assess the responder rate to CRT in the presented patients, only echocardiographic measurement and NYHA class were available. 12

The therapeutic effect of CRT was most prominent in the NYHA class. This subjective improvement may not only be caused by CRT, but also by a placebo effect in response to implantation of the CRT device, as observed in almost 30% of the patients in the MIRACLE trial. 13 The therapeutic effect of CRT was less prominent on echocardiographic parameters. The effect on left ventricular remodelling was least in both patients who eventually died (Nr.2 and Nr.7). Also patient Nr.5 can be regarded as a non-responder, most probably due to continuation of his heavy alcohol abuse. Alcohol abuse may have a direct toxic effect on the myocardium and additionally lead to lack of adherence to the prescribed pharmacotherapy. 14 The poor response to CRT in...
<table>
<thead>
<tr>
<th>Patient</th>
<th>Nr.1</th>
<th>Nr.2</th>
<th>Nr.3</th>
<th>Nr.4</th>
<th>Nr.5</th>
<th>Nr.6</th>
<th>Nr.7</th>
<th>Nr.8</th>
</tr>
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<tbody>
<tr>
<td>Age at implantation/sex</td>
<td>43/m</td>
<td>44/m</td>
<td>78/f</td>
<td>71/f</td>
<td>53/m</td>
<td>68/f</td>
<td>46/m</td>
<td>71/m</td>
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<td>MP</td>
<td>BMD</td>
<td>MP</td>
<td>Normal</td>
<td>Hypertension</td>
<td>Alcohol abuse</td>
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<td>NSMP</td>
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<tr>
<td>Extra-cardiac comorbidities</td>
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<td>None</td>
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<td>Infecions, MBL deficiency</td>
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<tr>
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<td>LBBB</td>
<td>IRBBB</td>
<td>LBBB</td>
<td>LBBB</td>
<td>LBBB</td>
<td>LBBB</td>
<td>LBBB</td>
<td>LBBB, AF</td>
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<td>QRS before CRT (ms)</td>
<td>160</td>
<td>120</td>
<td>150</td>
<td>170</td>
<td>170</td>
<td>200</td>
<td>180</td>
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<tr>
<td>QRS after CRT (ms)</td>
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<td>130</td>
<td>130</td>
<td>140</td>
<td>170</td>
<td>160</td>
<td>150</td>
<td>140</td>
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<tr>
<td>LVEDD (mm)/FS before CRT (%)</td>
<td>97/11</td>
<td>82/11</td>
<td>81/17</td>
<td>60/10</td>
<td>84/7</td>
<td>88/6</td>
<td>97/11</td>
<td>65/10</td>
</tr>
<tr>
<td>LVEDD (mm)/FS at last follow-up (%)</td>
<td>89/22</td>
<td>76/11</td>
<td>54/27</td>
<td>53/20</td>
<td>80/7</td>
<td>52/39</td>
<td>95/12</td>
<td>60/11</td>
</tr>
<tr>
<td>FU duration</td>
<td>65 months</td>
<td>Died after 4 months</td>
<td>62 months</td>
<td>7 months</td>
<td>43 months</td>
<td>68 months</td>
<td>Died after 16 months</td>
<td>48 months</td>
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<td>Medication at last follow-up</td>
<td>Unchanged</td>
<td>Digitalis added</td>
<td>ACE-inhibitor and digitalis added</td>
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<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged</td>
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<tr>
<td>NYHA class before CRT</td>
<td>IV</td>
<td>IV</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>IV</td>
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<tr>
<td>NYHA class at last follow-up</td>
<td>II</td>
<td>III</td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>CRT system</td>
<td>InSync Sentry, Medtronic</td>
<td>InSync Marquis, Medtronic</td>
<td>Contak TR, Guidant</td>
<td>InSync Sentry, Medtronic</td>
<td>Contak Renewal, Guidant</td>
<td>Contak TR, Guidant</td>
<td>InSync Sentry, Medtronic</td>
<td>InSync Sentry, Medtronic</td>
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<tr>
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<td>Lateral vein</td>
<td>Lateral vein</td>
<td>Lateral vein</td>
<td>Lateral vein</td>
<td>Lateral vein</td>
<td>Lateral vein</td>
<td>Epicardial</td>
<td>Lateral vein</td>
</tr>
</tbody>
</table>

CRT, cardiac resynchronization therapy; ICD, implantable cardioverter/defibrillator; MP, mitochondriopathy; BMD, Becker muscular dystrophy; NSMP, non-specified myopathy; LBBB, left bundle branch block; IRBBB, incomplete right bundle branch block; AF, atrial fibrillation.
Patient Nr.8 might be due to poor frequency control in atrial fibrillation. At present, it is uncertain if CRT is as beneficial in atrial fibrillation as in sinus rhythm, since patients with atrial fibrillation have been excluded from large studies.1,11,13

It is of interest that systolic function improved more in females than in males. This observation is in accordance with other reports which described that females with dilative cardiomyopathy respond better to CRT implantation than males.15

Death occurred in 25% of the patients. Both of these patients suffered from comorbidities: one patient (Nr.2) from advanced motor impairment due to Becker muscular dystrophy, the other (Nr.7) from a non-specified myopathy and recurrent infections due to mannose-binding lectin deficiency.

Whether non-response to CRT was due to the underlying myopathy is difficult to assess. Heart failure due to systolic dysfunction is a frequent manifestation of cardiac involvement in myopathies.16 Usually, these patients respond well to conventional pharmacological therapy.16,17 Since systematic neurological examinations are not reported in the studies about CRT, it cannot be assessed how many of these patients had suffered from heart failure due to cardiac involvement of an underlying myopathy.1,11,13

Reports about response to CRT in heart failure due to myopathy is confined to one patient are also included in the present series.6 Since in the present series, three of the four patients who responded well to CRT also suffered from a myopathy, it can be concluded that also patients with myopathy may respond to CRT. Furthermore, there are indications that CRT improves exercise capacity attributable to skeletal myopathy by attenuating the chronic sympathetic activation of heart failure.18

Limitations of the study were the small number of patients and that it was retrospective. The decision for CRT system and ICD implantation was not based on a uniform protocol but on the decision of the treating cardiologists. Because of technical reasons and lack of standardization at the time of implantation, tissue Doppler data about asynchrony are lacking for most of the patients. Owing to the heavily trabeculated left ventricles, estimation of left ventricular systolic function and calculation of systolic volume were difficult to assess by planimetry and calculation of the left ventricular ejection fraction, hence only left ventricular fractional shortening was calculated. For the evaluation of the response to CRT, important parameters such as results of 6-minute-hall walking test, peak VO₂, and serum levels of natriuretic peptides are lacking.

In conclusion, this study shows that CRT by biventricular pacing leads to improvement in functional capacity in all patients and systolic function in half of the patients with LVHT, heart failure, and myopathy. The weak response of LVHT patients to CRT may be due to inappropriate selection or comorbidities, in particular, neuromuscular disorders. Since LVHT is a rare disorder, a multicentre study of CRT in LVHT patients would be desirable to obtain more reliable results.

Conflict of interest: none declared.

References

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