Small left atrium and mild mitral regurgitation predict super-response to cardiac resynchronization therapy

Liliana Stefan†, Kamil Sedláček*†, Daniela Černá, Lukáš Krýže, Vlastimil Vančura, Tomáš Marek, and Josef Kautzner

Department of Cardiology, Institute for Clinical and Experimental Medicine (IKEM), Vědeřská 1958/9, Prague, Czech Republic

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Aims
Cardiac resynchronization therapy (CRT) can result in profound reverse remodelling. The goal of this study was to identify factors predictive of such beneficial response.

Methods and results
Super-response to CRT was defined as normalization or near normalization of left ventricular systolic function without recognized reversible causes of heart failure. In a retrospective study, we compared baseline demographic, electrocardiogram, and echocardiographic characteristics of super-responders (n = 21) with a population of unselected consecutive cardiac CRT patients (Control 1, n = 330) and another sex-, age-, and aetiology-matched control group (Control 2, n = 43). Compared with Control 1, super-responders had significantly smaller left ventricular end-diastolic diameter (65.4 ± 6.4 vs. 73.4 ± 9.3 mm, P = 0.0001), higher ejection fraction (0.25 ± 0.05 vs. 0.22 ± 0.04, P = 0.004), smaller degree of mitral regurgitation (MR; mean value 1.9 ± 0.9 vs. 2.6 ± 0.8, P < 0.0001), and smaller left atrium (LA; 42.8 ± 4.6 vs. 50.0 ± 6.5 mm, P < 0.0001). Septal flash and inter-ventricular mechanical dyssynchrony were both more frequent among super-responders than in Control 2 subjects (93.8 vs. 69.8%; P = 0.01, and 93.8 vs. 62.8%; P = 0.01, respectively). In a multivariate analysis, smaller LA diameter and milder MR remained independent predictors of super-response.

Conclusion
Super-response to cardiac CRT was associated with less advanced left-sided structural involvement as described by echocardiography. In particular, smaller LA and milder MR were independent predictors of pronounced reverse remodelling.

Keywords
Heart failure • Cardiac resynchronization therapy • Super-responder • Predictors

Introduction
Cardiac resynchronization therapy (CRT) has become an integral part of management of advanced heart failure in patients with left-bundle branch block (LBBB) and optimized medical therapy.1,2 Current experience suggests that significant clinical and/or echocardiographic response can be expected in 60–70% of subjects.3 Some studies have shown that a certain proportion of patients treated by CRT recover normal or near-normal left ventricular function, and improve considerably their functional status. This phenomenon is referred to as a super-response to CRT. More detailed analyses demonstrated that super-responders are predominantly patients with non-ischaemic dilated cardiomyopathy (NIDCM). A term LBBB-induced cardiomyopathy has been coined for patients in whom electrical conduction delay correctable by CRT plays a substantial role in development of heart failure.4,5 Other studies suggested higher prevalence of women among super-responders and less severe structural heart disease as predictors of pronounced CRT benefit.6–9

The goal of this study was to evaluate pre-implantation parameters associated with super-response to CRT using a retrospective analysis of a CRT database in our centre.

1 These two authors contributed equally to this work.
2 Corresponding author. Tel: +420 236 055 006; fax: +420 261 362 985, Email: kamil.sedlacek@medicon.cz
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Methods

Study population

The study population was selected from a local clinical research database which included 687 consecutive patients implanted with a CRT system between January 2001 and December 2010. Adequate follow-up with complete serial clinical assessment, electrocardiogram (ECG), and echocardiography, suitable for analyses in this study was available in 351 patients included in the database. Super-response to CRT was defined as near-normalization or normalization of the left ventricular ejection fraction (LVEF) to at least 45% during the available follow-up. Patients with recognized reversible causes of heart failure such as brady- and tachyarrhythmias, myocarditis, right-ventricular-pacing-induced cardiomyopathy, or evidence of toxic cardiomyopathy were excluded from the analysis. After identification of the super-responder group, the remainder of the consecutive patients in the CRT database with adequate complete baseline and follow-up dataset was used as a control group (Control 1). Another sex-, age-, and aetiology-matched subgroup from Control 1 was selected in order to avoid bias introduced by currently known response predictors such as female gender and NIDCM (Control 2). Matching was performed manually using 1:2 case to control ratio by analysing the whole cohort and identifying subjects fitting to pre-defined characteristics (heart failure aetiology and gender) and 5 years age strata.

Indication for CRT implantation was based on the Guidelines of the European Society of Cardiology. Implantation criteria included the following: chronic heart failure of New York Heart Association (NYHA) class III or IV, despite optimized pharmacological treatment, LVEF ≤ 35%, left ventricular end-diastolic diameter (LVEDD) ≥ 55 mm, and the QRS width ≥ 120 ms.

Cardiac resynchronization therapy devices from all major manufacturers (Biotronik, Medtronic, St Jude Medical and Guidant—Boston Scientific) were used. Unipolar or bipolar left ventricular leads were implanted in posterolateral, lateral, or anterolateral veins, predominantly at the mid-ventricular level. True anterior position was deliberately avoided at all times and anterolateral positions were typically considered suboptimal at that time. Patients were paced in unipolar or bipolar mode from their left ventricular lead. Right ventricular mid-septal pacing site position has been used routinely in our centre since 2001, both for pacemaker and implantable cardioverter defibrillator (ICD) right ventricular leads. Bipolar right atrial leads with active fixation were placed in the right atrial appendage. Selection of a specific type of device (biventricular pacemaker or biventricular ICD) was based on valid guidelines and clinical history. Individually tailored device programming was performed before discharge. Reprogramming of CRT devices during the follow-up occurs rarely in our centre and is typically performed only in the case of missing response to the therapy. Therefore, it was unlikely to occur frequently in super-responders or influence magnitude of their reverse remodelling. Obligatory baseline database entries included demographic characteristics (age, gender, aetiology of heart failure, clinical history, and medical therapy), functional class at baseline, ECG analysis (heart rate, ECG intervals, and presence and type of heart block), and echocardiographic parameters. Left ventricular end-diastolic diameter and left atrium (LA) anteroposterior dimensions were measured according to the recommendations of the American Society of Echocardiography.10 Left ventricular ejection fraction was calculated using the modified Simpson’s formula. The degree of mitral regurgitation (MR) was assessed semiquantitatively, using five classes (minimal, light, moderate, significant, and severe). One experienced echocardiographist (DC) reviewed retrospectively our institutional digital image database (EchoPAC, GE Healthcare) for dysynchrony assessment in super-responders and Control 2 population according to guideline recommendations.11 Septal flash, defined as an abnormal short-lived septal motion occurring during the isovolumic contraction time was used as an indicator of intra-ventricular dysynchrony. Inter-ventricular dysynchrony was defined as inter-ventricular mechanical delay (IVMD, difference between left- and right-ventricular pre-ejection periods measured from QRS to the onset of pulmonary and aortic flows, respectively) > 40 ms. Atrio-ventricular dysynchrony was assessed by means of the total left ventricular filling time < 40% of an RR interval. Patients were classified as having ischaemic dilated cardiomyopathy (IDCM) or NIDCM based on their medical history, echocardiography, and coronary angiography, if available. Follow-up visits in CRT patients typically occurred every 3–6 months during the first year after implantation and subsequently every 6–9 months in stable patients. With the exception of pre-specified study protocols, routine follow-up echocardiography in our centre was performed in 12 months after implantation and as clinically indicated thereafter.

This retrospective study complied with the Declaration of Helsinki. A signed informed consent was obtained from all subjects undergoing CRT implantation.

Statistical analysis

Data are expressed as mean ± standard deviation, or percentages, where applicable. Continuous variables were analysed using the t-test for independent samples and categorical variables using the χ² test. Differences between the baseline and follow-up values in outcome parameters were evaluated using the paired t-test. Linear regression was used to analyse relationship between echocardiographic values at baseline and response to CRT. Multivariate nominal logistic regression analysis was performed to identify independent predictors of super-response including significant univariate predictors in the model. A P value < 0.05 was regarded statistically significant. Analyses were performed using SPSS 16.0 and JMP 7 statistical softwares.

Results

Our institutional CRT database contained 351 patients with complete dataset for analysis. Among them, 40 (11.3%) fulfilled the echocardiographic criteria of super-response. After exclusion of patients with improvement attributable to reversible causes of heart failure, 21 (5.9%) true super-responders were identified. The remaining 330 patients were used as an unselected control group (Control 1). The age-, sex-, and aetiology-matched control group (Control 2) consisted of 43 individuals (Table 1).

Demographic characteristics

Baseline demographic characteristics were similar in super-responders and controls (Table 1). Duration of symptomatic heart failure was on average 28.6 months (median 24 months) in the super-responder group. Compared with Control 1, super-responders were more often women (42.8 vs. 12.3%, P < 0.0001) and their prevailing heart disease was NIDCM (76.2 vs. 42.7%, P = 0.01). In addition, they had more frequently hypertension (76.2 vs. 49.3%, P = 0.009) and lower serum creatinine (93.1 ± 21.2 vs. 108.0 ± 24.2, P = 0.03). However, the distribution of hypertensive subjects and creatinine levels were similar when the comparison with the matched Control 2 was performed.
Medication history was similar in super-responders and both control groups with exception of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, which were used in all super-responders but in a smaller percentage of control subjects (100% vs. 88.7% in Control 1 and 88.4% in Control 2, respectively, P < 0.05 for both comparisons).

**Electrocardiographic characteristics and left-ventricular lead position**

A comparison of electrocardiographic parameters is shown in Table 2. There were no statistically significant differences in baseline heart rate, PR interval, QRS width, and mean QRS axis when super-responders were compared with both control groups. In addition, super-responders and Control 2 had similar QRS width immediately after institution of CRT and QRS width difference before and after CRT institution (QRS delta). Paced rhythm was not present in the super-responder group at baseline compared with 19.7% in Control 1. A detailed analysis of ECGs in the super-responders and controls revealed overlapping spectrum of LBBB morphology, width, and axis which made it impossible to predict super-response based on specific LBBB patterns.

Distribution of left-ventricular lead positions was not statistically significantly different between the super-responders and Control 2. All left-ventricular leads in these groups were placed in basal or mid-ventricular segments. The most frequent lead position was lateral (68% in super-responders and 68.2% in Control 2).
and 58% in super-responders and Control 2, respectively). Antero-lateral position was used in 21% of super-responders and in 14% subjects of the Control 2 group. The remaining leads were implanted in postero-lateral positions (11 and 28% in super-responders and Control 2, respectively).

Echocardiographic characteristics

Comparison of pre-implant echocardiographic parameters demonstrated highly significant differences between the super-responders and control subjects (Table 3). Compared with Control 1, super-responders presented with higher baseline LVEF (0.25 ± 0.05 vs. 0.22 ± 0.04, P = 0.004), smaller LVEDD (65.4 ± 6.4 vs. 73.4 ± 9.3 mm, P = 0.0001), milder MR (mean value 1.9 ± 0.9 vs. 2.6 ± 0.8, P < 0.0001), and smaller LA diameter (42.8 ± 4.6 vs. 50.0 ± 6.5 mm, P < 0.0001). Similar differences were encountered in comparison between super-responders and Control 2 (LVEF 0.25 ± 0.05 vs. 0.22 ± 0.04, P = 0.01; LVEDD 65.4 ± 6.4 vs. 75.1 ± 10.7 mm, P = 0.003; MR 1.9 ± 0.9 vs. 2.5 ± 0.8, P = 0.006; and LA diameter 42.8 ± 4.6 vs. 47.0 ± 5.2 mm, P = 0.003).

Septal flash and inter-ventricular dyssynchrony were both more frequent among super-responders compared with Control 2, in which the dyssynchrony data were available (93.8 vs. 69.8%, P = 0.01 and 93.8 vs. 62.8%, P = 0.01, respectively). Distribution of atrio-ventricular dyssynchrony was similar between the cases and controls (Table 3).

Multivariate analysis

In a multivariate analysis with the Control 1 group including gender, heart failure aetiology, LVEF, LVEDD, MR degree, and LA dimension in the model (dyssynchrony analysis was not available for this comparison), three independent predictors of super-response were found: female gender (P = 0.02), mild MR (P = 0.004), and small LA dimension (P = 0.0004).

Mitrval regurgitation grade and LA diameter remained the only significant echocardiographic predictors (including dyssynchrony parameters) in the multivariate analysis using Control 2 (P = 0.02).

Follow-up data

The mean follow-up duration after CRT implantation was 51 ± 31 months (range 9–104; median 48 months) in the super-responders group, 30 ± 20 months (range 2–98; median 28 months) in the Control 1, and 32 ± 23 months (range 2–105; median 28 months) in the Control 2. During the follow-up, there were two deaths (9.5%) in the super-responders group (one from malignancy and another one from unknown cause) compared with 107 (32.2%) and 13 (30.2%) deceased patients in Controls 1 and 2, respectively.

Per definition, super-responders improved during the follow-up in LVEF (mean difference 27.1%, P < 0.0001), LVEDD (mean reduction 11 mm, P < 0.0001), and functional capacity (mean NYHA class improvement 1.0, P < 0.001). With the exception of three super-responders, who entered the study in an NYHA class II and remained stable throughout the follow-up, all others improved their exercise tolerance (≥1 on the NYHA class scale). The degree of MR did not change significantly (mean reduction 0.2, P = 0.2). Improvements over the follow-up period were less pronounced in the control groups (Control 1: NYHA class improvement 0.42, P < 0.0001; ejection fraction improvement 2.44% points, P < 0.0001; LVEDD decrease 2.05 mm, P < 0.0001; and MR reduction 0.1, P = 0.01). Figure 1 provides a visual demonstration of gradual changes in NYHA class, LVEF, LVEDD, and MR in the super-responders group compared with Control 1.

The paced QRS width at last follow-up was significantly narrower in the super-responders group than in the Control 2 group (148.6 ± 15.5 vs. 163.3 ± 19.8, P = 0.006). The time between CRT implantation and LVEF improvement in the super-responders group was 3 months for five patients (23.8%), between 3 and 12 months for 10 patients (58.8%), and 12 to 24 months for two patients (10.5%).
months in six other cases (28.6%), and >1 year in the rest of the group (10 patients or 47.6%).

**Discussion**

The principal finding of this study is that less advanced heart disease as identified by echocardiography is strongly associated with probability of super-response to CRT. Apart from known predictors such as NIDCM and female gender, echocardiographic predictors described in this study suggest that patients who have less advanced left heart involvement at baseline are particularly prone to marked reverse remodelling. Previously described predictors of super-response (smaller LVEDD and higher LVEF at baseline) were observed in this study in a univariate analysis. Super-responders had higher proportion of mechanical dyssynchrony as described by septal flash and IVMD. However, only smaller LA diameter and milder degree of MR were identified as independent predictors of super-response in the multivariate analysis, findings already reported in two other studies.6,9

Left atrium dilatation is a sensitive marker of chronic left heart disease. Pressure and/or volume overload associated with left ventricular involvement lead to gradual LA enlargement, electrical remodelling, and fibrosis. Considerable evidence has been collected demonstrating the relationship between increased LA size and cardiovascular morbidity and mortality.12,13 both in general population14 and in patients with left ventricular dysfunction.15,16 Furthermore, LA dilatation correlates with changes in electrophysiological properties such as prolonged inter-atrial and LA conduction times,17,18 and functional LA conduction blocks.19 In addition, it may be impossible to achieve left atrio-ventricular resynchronization using standard CRT configuration with only right-sided atrial lead in patients with pronounced LA conduction disturbances. In a study by Leclercq et al.,20 19% of patients in sinus rhythm required both right- and left-atrial pacing to achieve satisfactory cardiac resynchronization. More research is needed to enhance our understanding of how
dilated LA with variable conduction abnormalities influences outcomes in patients receiving CRT and whether addressing these pathophysiological mechanisms could improve the response to CRT. As with MR, begetting its own progression in a vicious circle of deterioration of the left ventricular function, LA enlargement might also independently limit positive effects of CRT and contribute to progression of left heart disease. Exactly which mechanisms might be instrumental in this effect, whether electrophysiological, haemodynamic, or neurohumoral remains at the moment beyond our understanding.

Reduction of systolic and diastolic functional MR by correction of atrio-ventricular and intra-ventricular dysynchrony, improved left ventricular mechanics and, in the long term, by reverse remodelling, is one of the fundamental beneficial mechanisms of CRT.21–24 On the other hand, significant secondary MR has recently been associated with the lack of response to CRT25,26 and reduced reverse remodelling.27 In a study by Cabrera-Bueno et al.,28 CRT reduced significant functional MR only in ~30% of patients with NIDCM and persistence of MR was associated with adverse clinical outcomes and lack of reverse remodelling. Further research is needed to answer the question whether patients with persistent MR after institution of CRT might benefit from hybrid approaches such as CRT combined with surgical or percutaneous mitral valve interventions.

While we confirmed female gender as a predictor of super-response in the multivariate analysis using a large unselected control group, NIDCM aetiology was not among independent predictors. About a quarter of super-responders presented with IDCM or valvular heart disease which is similar to numbers reported in other studies.8,29 In IDCM patients, pronounced clinical and echocardiographic response can only be expected when the amount of scar tissue in the left ventricle is small.8,30–32

No ECG predictors of super-response could be identified in this study. Super-responders had a baseline LBBB pattern comparable with the control group in this study and with representative populations in large randomized controlled trials of the CRT.3,8,33

We used exclusively echocardiographic definition of super-response (i.e. LVEF ≥ 45% on CRT) and saw a smaller fraction of super-responders in our CRT population (5.9%) than reported in the literature where it ranges between 10 and 39%.6–9,29 We believe that this difference can be explained both by more advanced heart disease in patients receiving CRT in our tertiary centre with a busy heart transplantation programme, and by strict exclusion of all cases with potentially reversible causes of heart failure.

Due to the study period of almost a decade, systematic assessment of mechanical dyssynchrony could only be completed by means of a retrospective analysis of digitally stored echocardiographic data. Therefore, it should be interpreted with caution. However, vast majority of super-responders presented with the signs of intra-ventricular and inter-ventricular mechanical dysynchrony. Septal flash has recently been shown to predict positive response if corrected by the CRT.34 Furthermore, correction of intra-ventricular dysynchrony has been associated with super-response in a study by Dreger et al.35 Inter-ventricular dysynchrony was predictive of response in the CARE-HF study26 and in NIDCM patients studied in our institution.36 Nevertheless, predictive value of dysynchrony measures for pronounced reverse remodelling was inferior to that of mild MR and smaller LA in the present study.

Recent large multicentre randomized trials have demonstrated the beneficial effect of CRT in patients predominantly in NYHA II class.13,37,38 In spite of the fact that less symptomatic heart failure patients were included in those trials, their echocardiographic baseline characteristics were similar to older studies including predominantly NYHA III/IV patients, e.g. the CARE-HF study. It might be interesting to study incremental benefits of CRT in patients with less advanced heart disease defined by echocardiographic measures, not by less severe symptoms.

This study has limitations that are common in retrospective single-centre analyses. It was confined only to patients who had an adequate baseline and follow-up dataset. Several variables might further help to analyse the super-response phenomenon but were not systematically available for analyses of this study population (e.g. systolic diameters and volumes, left ventricular pacing lead position, extent of myocardial scarring, or a detailed dyssynchrony assessment using novel techniques). Future studies should also pay more attention to detailed analysis of mechanisms of MR and use more sensitive measures of LA enlargement, such as LA volumes.

In conclusion, super-response to CRT is associated with less advanced left ventricular structural disease as defined by echocardiography. Specifically, smaller LA diameter and milder MR were found to be independent predictors of pronounced reverse remodelling. Concordant with evidence from other above-mentioned single-centre and large randomized trials, we suggest that introduction of CRT earlier in the course of heart failure and left heart remodelling process may result in more pronounced or even complete structural and functional improvement.

Conflict of interest: J.K. received consulting honoraria from Boston Scientific and Medtronic, and speaker honoraria from Biotronik, Boston Scientific, Medtronic, and St Jude Medical.

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