Long-Term Echocardiographic Outcome in Super-Responders to Cardiac Resynchronization Therapy and the Association With Mortality and Defibrillator Therapy

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Super-response to cardiac resynchronization therapy (CRT) is associated with significant left ventricular (LV) reverse remodeling and improved clinical outcome. The study aimed to: (1) evaluate whether LV reverse remodeling remains sustained during long-term follow-up in super-responders and (2) analyze the association between the course of LV reverse remodeling and ventricular arrhythmias. Of all, primary prevention super-responders to CRT were selected. Super-response was defined as LV end-systolic volume reduction of ≥30% 6 months after device implantation. Cox regression analysis was performed to investigate the association of LV ejection fraction (LVEF) as time-dependent variable with implantable-cardioverter defibrillator (ICD) therapy and mortality. A total of 171 super-responders to CRT-defibrillator were included (mean age 67 ± 9 years; 66% men; 37% ischemic heart disease). Here of 129 patients received at least 1 echocardiographic evaluation after a median follow-up of 62 months (25th to 75th percentile, 38 to 87). LV end-diastolic volume, LV end-systolic volume, and LVEF after 6-month follow-up were comparable with those after 62-month follow-up (p = 0.90, p = 0.37, and p = 0.55, respectively). Changes in LVEF during follow-up in super-responders were independently associated with appropriate ICD therapy (hazard ratio 0.94, 95% CI 0.90 to 0.98; p = 0.005) and all-cause mortality (hazard ratio 0.95, 95% CI 0.91 to 1.00; p = 0.04). A 5% increase in LVEF was associated with a 1.37 times lower risk of appropriate ICD therapy and a 1.30 times lower risk of mortality. In conclusion, LV reverse remodeling in super-responders to CRT remains sustained during long-term follow-up. Changes in LVEF during follow-up were associated with mortality and ICD therapy. **(Am J Cardiol 2016;■:■−■)**

Cardiac resynchronization therapy (CRT) reduces mortality and morbidity in patients with advanced heart failure, reduced left ventricular (LV) function, and prolonged QRS duration.[1] In general, CRT implantation induces LV reverse remodeling. However, patients experience this response to CRT in varying degrees. Women, patients with nonischemic heart disease, a prolonged QRS duration, and/or left bundle branch block (LBBB) are most likely to experience more pronounced LV reverse remodeling.[2,3]

Furthermore, patients who experience most pronounced LV reverse remodeling and (near) normalization of systolic heart function, so called super-responders, have most advantageous clinical outcome and survival.[4] Furthermore, the risk of ventricular arrhythmias is reduced after CRT implantation; it is of clinical importance to determine whether super-responders still require implantable-cardioverter defibrillator (ICD) treatment.[5] We previously reported that super-responders required ICD therapies especially after long-term follow-up.[6] On the one hand, it can be expected that with (near) normalization of the systolic heart function the increased risk of ventricular arrhythmias disappears, in contrast, CRT implantation often leaves the pathological substrate untreated.

Subsequently, it is unexplored whether possible ventricular arrhythmias during long-term follow-up are associated with patients' deteriorating. Therefore, the aim of this study was twofold; (1) to evaluate LV reverse remodeling in super-responders during long-term follow-up and (2) to analyze the association between the course of LV volume or function and ventricular arrhythmias or survival.

Methods

All patients who received a CRT-defibrillator (CRT-D) device at the LUMC (the Netherlands) from January 2000 to May 2012 were recorded in the departmental Cardiology Information System (EPD-vision, LUMC). Eligibility for the device was based on the current international guidelines.[7] For the present study, only echocardiographic super-responders to CRT were included. Super-response

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This study is funded by the Department of Cardiology, Leiden University Medical Center, the Netherlands.

See page 7 for disclosure information.

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0002-9149/16/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2016.07.041

was defined as decreased LV end-systolic volume (LVESV) ≥30% determined 6 months after implantation. In addition, patients were excluded from the study when one of the following criteria was met: secondary prevention ICD implantation; Cardiac Resynchronization Therapy-Pacemaker treatment before CRT-D implantation; congenital or monogenetic heart disease; decompensated heart failure at the time of device implantation; myocardial infarction <3 months before device implantation; or LV reconstructive surgery.

Follow-up visits were planned periodically every 3 to 6 months or more frequently when clinically indicated. If follow-up visits were not performed for more than 6 months, follow-up was considered incomplete. These patients were included in the current analysis up to their final outpatient follow-up visit. All consecutive follow-up visits were prospectively registered up to January 2015. Follow-up visits included clinical assessment and device interrogation performed under supervision of electrophysiologists or device cardiologists. Echocardiographic evaluation was only performed when clinically indicated at the discretion of the treating physician.

During device interrogation, device printouts were analyzed and ICD therapies were registered. ICD therapies were classified using intracardial electrograms. ICD therapy (antitachycardia pacing and shock) was only considered appropriate when occurring in response to sustained ventricular tachycardia or ventricular fibrillation, otherwise ICD therapy was considered inappropriate (triggered by sinus or supraventricular tachycardia, nonsustained ventricular arrhythmias, T-wave oversensing or lead dysfunction). Appropriate ICD therapy or appropriate ICD shock were considered the primary end point and all-cause mortality, the secondary end point.

All CRT-D devices were implanted transvenously. The devices used were manufactured by Biotronik (Berlin, Germany), Boston Scientific (Natick, Massachusetts, formerly CPI, Guidant [St. Paul, Minnesota]), Medtronic (Minneapolis, Minnesota), or St Jude Medical/Ventritex (St. Paul, Minnesota).

In general, the defibrillators were programmed with 3 different zones: ventricular arrhythmias from 150 to 155 beats/min to 185 to 190 beats/min were detected in a monitoring zone in which no therapy was programmed (30 to 32 intervals were needed for detection or 8/10 with a 2.5-second [s] initial delay depending on the manufacturer); ventricular arrhythmias faster than 185 to 190 beats/min were programmed with 2 bursts to terminate the arrhythmias, followed by shock if the arrhythmias continue (22 to 30 intervals were needed for detection or 8/10 with a 2.5-second initial delay depending on the manufacturer). In the final zone programmed to detect arrhythmias exceeding 205 to 210 beats/min, shock was the primary therapy (12 to 30 intervals were needed for detection or 8/10 with a 1.0-second initial delay depending on the manufacturer). Zone limit were adjusted when clinically indicated. Furthermore, supraventricular tachycardia discriminators were enabled and atrial arrhythmia detection was set to >170 beats/min.

Before and 6 months after CRT-D implantation, all patients underwent comprehensive echocardiographic evaluation. During follow-up, echocardiographic evaluations were repeated when clinically indicated at the discretion of the treating physician and following a systematic data acquisition protocol. The echocardiographic evaluation performed 6 months after implantation is defined short-term echocardiographic outcome, and from that time to the last additional echocardiographic evaluation is defined as long-term echocardiographic outcome.

Two-dimensional and color Doppler echocardiographic images were obtained using commercially available systems (Vivid 7 and E9, GE-Vingmed Ultrasound, Horten, Norway) equipped with 3.5-MHZ and M5S transducers. Measurement of the LV end-diastolic volume (LVEDV), LVESV, and LV ejection fraction (LVEF) was based on the Simpson's method using the apical 2- and 4-chamber views (EchoPac 113, GE Medical Systems, Horten, Norway).

The current analysis includes echocardiographic super-responders of CRT, as determined by the extent of LV reverse remodeling. This subgroup was predefined as CRT-D recipients with a decreased LVESV ≥30% 6 months after implantation. After long-term follow-up, the response status was reevaluated by comparing baseline and long-term echocardiographic evaluation, subgroups were negative responders (LVESV increase), nonresponders (LVESV decrease 0% to 15%), responders (LVESV decrease 15% to 30%), and super-responders.

Table 1
Clinical characteristics at implantation in super-responders to cardiac resynchronization therapy

	All Included (N=171)
Clinical parameters	
Age (years)	67±9
Men	112 (66%)
BMI (kg/m^2)	26±4
Coronary heart disease	63 (37%)
NYHA functional class	
II	47 (27%)
III	114 (67%)
IV	10 (6%)
QRS duration (ms)	170±20
Left bundle branch block	137 (80%)
Atrial fibrillation/flutter (History)	51 (30%)
Creatinine clearance (ml/min)	73±30
Hypertension	81 (47%)
Diabetes Mellitus	33 (19%)
Smoker	65 (38%)
Echocardiographic parameters	
Left ventricular end diastolic volume (ml)	220±72
Left ventricular end systolic volume (ml)	168± 61
Left ventricular ejection fraction (%)	24±6
Medication	
ACE inhibitors /AT II antagonists	152 (89%)
Aldactone	80 (47%)
Amiodarone	24 (14%)
Beta-blockers	128 (75%)
Sotalol	15 (9%)
Calcium antagonists	12 (7%)
Diuretics	137 (80%)
Statins	89 (52%)

ACE = angiotensin-converting enzyme; AT = angiotensin; BMI = body mass index; NYHA = New York Heart Association.