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What is the Lowest Value of Left Ventricular Baseline Ejection Fraction that Predicts Response to Cardiac Resynchronization Therapy?

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Background: Cardiac resynchronization therapy (CRT) is an effective treatment option for patients with refractory heart failure. However, many patients do not respond to therapy. Although it has been thought that there was no relation between response to CRT and baseline ejection fraction (EF), the response rate of patients with different baseline LVEF to CRT has not been evaluated in severe left ventricular systolic dysfunction. We aimed to investigate any difference in response to CRT between the severe heart failure patients with different baseline LVEF.

Material/Methods: In this study, 141 consecutive patients (mean age 59±13 years; 89 men) with severe heart failure and complete LBBB were included. Patients were divided into 3 groups according to their baseline LVEF: 5–15%, Group 1; 15–25%, Group 2, and 25–35%, Group 3. NYHA functional class, LVEF, LV volumes, and diameters were assessed at baseline and after 6 months of CRT. A response to CRT was defined as a decrease in LVSVi (left ventricular end-systolic volume index) ≥10% on echocardiography at 6 months.

Results: After 6 months, a significant increase of EF and a significant decrease of LVESVi and LVEDVi after 6 months of CRT were observed in all groups. Although the magnitude of improvement in EF was biggest in the first group, the percentage of decrease in LVESVi and LVEDVi was similar between the groups. The improvement in NYHA functional class was similar in all EF subgroups. At 6-month follow-up, 100 (71%) patients showed a reduction of >10% in LVESVi (mean reduction: −15.5±26.1 ml/m^2) and were therefore classified as responders to CRT. Response rate to CRT was similar in all groups. It was 67%, 75%, and 70% in Group 1, 2, and 3, respectively, at 6-month follow-up (p>0.05). There was no statistically significant relation between the response rate to CRT and baseline LVEF, showing that the CRT has beneficial effects even in patients with very low LVEF.

Conclusions: It seems there is no lower limit for baseline LVEF to predict non-response to CRT in eligible patients according to current guidelines.

MeSH Keywords: Cardiac Resynchronization Therapy • Stroke Volume • Ventricular Remodeling

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Background

Cardiac resynchronization therapy (CRT) is considered an important treatment option for selected patients with severe chronic heart failure (CHF) [1–3]. CRT improves heart failure symptoms, functional capacity, and quality of life [4–6]. Despite current guidelines recommending CRT for patients with left ventricular ejection fraction (LVEF) ≤35% [7,8], it was recently shown that CRT produced reverse remodeling and similar clinical benefit in patients with mild HF, QRS prolongation, and LVEF >30% compared to subjects with more severe left ventricular systolic dysfunction [9]. However, the response rate of patients with different baseline LVEF to CRT has not been evaluated in severe left ventricular systolic dysfunction. We aimed to investigate any difference in response to CRT between severe heart failure patients with different baseline LVEF and to find if any lowest value of baseline LVEF predicts non-response to CRT.

Material and Methods

Patients

The study population consisted of 141 consecutive patients (mean age 59±13 years; 89 men) with severe heart failure and QRS duration >120 ms scheduled for implantation of a CRT device. Inclusion criteria were severe heart failure New York Heart Association (NYHA) class III or IV, LVEF ≤35%, and LBBB. The etiology of heart failure was considered ischemic in the presence of ≥50% stenosis in 1 of the major epicardial coronary arteries on coronary angiography. Ischemic heart disease was present in 62 (44%) patients. All patients received optimal pharmacological treatment before and after pacemaker implantation.

Written informed consent was obtained from all patients. The study was approved by the local Ethics Committee.

Cardiac resynchronization therapy device implantation

All pacemaker implantations were performed by left infraclavicular approach. Right atrial and right ventricular leads were implanted using a transvenous approach. LV leads were inserted by a transvenous approach through the coronary sinus into a cardiac vein of the free wall. Eighty-nine patients received biventricular pacemaker (InSync III, Medtronic Inc, Minneapolis, USA) and 52 patients received a biventricular cardioverter-defibrillator (InSync ICD, Medtronic Inc, Minneapolis, USA). The atrioventricular interval was optimized by Doppler echocardiography immediately after implantation.

Echocardiography

Patients were imaged in the left lateral decubitus position with a commercially available system (VIVID 7, General Electric-Vingmed Ultrasound, Horten, Norway). Images were obtained with a 2.5-MHz broadband transducer at a depth of 16 cm in the parasternal and apical views (standard long-axis, 2- and 4-chamber images). Standard 2-dimensional and color Doppler data triggered to the QRS complex were saved in cine-loop format. The 2- and 4-chamber images were used to calculate left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV), and values were indexed to body surface area. LVEF was calculated from the conventional apical 2- and 4-chamber images using the biplane Simpson`s technique [10].

Transthoracic echocardiography was performed before pacemaker implantation and repeated 6 months later. All echocardiographic measurements after CRT implantation were made with the device in active pacing mode. Echocardiographic response to CRT was defined as a decrease in LVSVi (left ventricular end-systolic volume index) ≥10% on echocardiography at 6 months [11].

Clinical response was defined as improvement in NYHA class.

Statistical analysis

All analyses were performed with the statistical software program SPSS V.13.0. Continuous data are expressed as mean ±SD. Patients were divided into 3 groups according to their baseline LVEF: Group 1 was <15%, Group 2 was 16–25%, and Group 3 was 26–35%. Comparison of the continuous parametric variables between LV EF subgroups was performed using a independent-sample t test or the χ^2 test for the ordinal variables. Echocardiographic and clinical findings at baseline and 6 months were compared with each other using Wilcoxon signed-rank test. For comparison of echocardiographic parameters between responders and non-responders, Mann-Whitney U test and χ^2 test were used. Variables associated with CRT response in univariate analysis were entered into a forward stepwise logistic regression model. A value of $p<0.05$ was considered statistically significant.

Results

Baseline patient characteristics of the groups are summarized in Table 1.The mean QRS duration of the patients was 151±21 ms and all of them had LBBB morphology. No difference in baseline patient characteristics was observed between groups except LVEF, LVEDD, LVESD, LVEDV, LVESV, LVEDVi (left ventricular end-diastolic volume index), and LVESVi (left ventricular end-systolic volume index).

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Table 1. Baseline patient characteristics divided by EF.

	Group1 (n=51)	Group (n=60)	Group (n=30)
Age (year)	59±12	60±13	59±13
Male (n,%)	34 (67)	36 (60)	19 (63)
Ischemic (n,%)	26 (51)	27 (45)	9 (30)
Hypertension (n,%)	32 (60)	45 (75)	18 (60)
Diabetes (n,%)	8 (16)	15 (25)	6 (20)
CRT-ICD implanted (n,%)	21 (41)	18 (30)	10 (33)
NYHA (mean)	3.3±0.5	3.3±0.4	3.1±0.4
QRS duration (ms)	151±18	152±20	149±20
LVEDD (mm)	73±9*,‡	68±8**	61±7
LVESD (mm)	62±9*,‡	55±8**	47±9
LVEDV (ml)	286±80*,‡	242±63**	191±48
LVEDVI (ml/m^2)	153±42†,‡	133±40**	104±28
LVESV (ml)	200±68*,‡	153±50**	105±46
LVESVI (ml/m^2)	107±36*,‡	84±30**	57±26
LVEF (%)	13±2*,‡	21±3**	30±2

* p<0.005 when compared to group 2; † p<0.05 when compared to group 2; ‡ p<0.001 when compared to group 3; ** p< when compared to group 3.

Table 2. Echocardiographic parameters and functional status of patients in group 1, 2 and 3 before and after cardiac resynchronization therapy.

	Group 1		Group 2		Group 3		p
	Baseline	6 mo	Baseline	6 mo	Baseline	6 mo	
LVEF (%)	13±2	22±10	21±3	29±7	30±2	39±8	p<0.01
LVEDD (m)	73±9	69±10	68±8	64±8	61±7	57±9	p<0.01
LVESD (m)	62±9	58±12	55±8	50±9	47±9	43±11	p<0.01
LVEDV (ml)	286±80	255±86	242±63	210±58	191±48	167±59	p<0.01
LVESV (ml)	200±68	174±79	153±50	125±53	105±46	90±55	p<0.01
LVEDVI (ml//m^2)	153±42	136±45	133±40	115±37	104±28	90±35	p<0.01
LVESVI (ml/m^2)	107±36	92±42	84±30	69±32	57±26	49±32	p<0.01
Delta EF		72±83*,†		42±40		31±23	
Delta EDVI		–11±17		–13±16		–14±15	
Delta ESVI		–14±26		–17±26		–15±28	
NYHA (mean)	3.3±0.5	2.6±0.6	3.3±0.4	2.6±0.5	3.1±0.4	2.4±0.5	p<0.01

* p<0.05 when compared to group 2; † p<0.05 when compared to group 3. LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; LVEDV – left ventricular end-diastolic volume; LVESD – left ventricular end-systolic diameter; LVESV – left ventricular end-systolic volume; NYHA – New York Heart Association.

At 6-month follow-up, significant improvement in LVEF, LVEDV, LVESV, LVEDVi, and LVESVi was observed in 3 patient groups when compared to baseline (Table 2). A significant increase of EF and a significant decrease of LVESVi and LVEDVi after 6 months of CRT were observed in all groups. Although the magnitude of improvement in EF was largest in the first group, the

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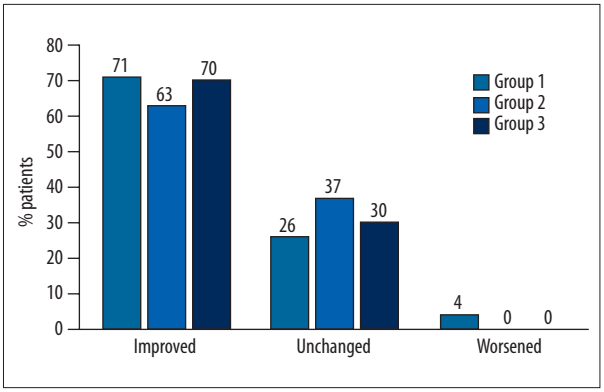

Figure 1. The changes in NYHA functional class in three groups.

percentage of decrease in LVESVi and LVEDVi was similar between the groups. At 6 months, there was an improvement of clinical status for the overall study group (from 3.2±0.5 to 2.6±0.6, p<0.001). The improvement in NYHA functional class was similar in all EF subgroups (Figure 1).

At 6 months, 100 (71%) patients showed a reduction of >10% in LVESVi (mean reduction: –15.5±26.1 ml/m^2) and were therefore classified as responders to CRT. Response rate to CRT was similar in all groups. At 6 months, it was 67% in Group 1, 75% in Group 2, and 70% in Group 3 (p>0.05). At baseline, clinical characteristics, as well as LV volumes and EF, were similar between responders and non-responders (Table 3). There was no statistically significant relation between CRT and baseline LVEF, showing that the benefit of CRT did not vary with baseline LVEF in severe heart failure. Although all patients had LBBB, the baseline QRS duration was shorter in non-responders but the difference was not statistically significant. However, the QRS duration was the only parameter associated with the response to CRT in the entire study population (r=0.20, p=0.16).

Discussion

Our study showed that CRT had similar beneficial effect on ventricular function and functional capacity in all stages of LVEF in patients with LVEF ≤35%.

Previous studies revealed improvement in moderate-to-severe left ventricular dysfunction [12,13]. Sub-studies have recently investigated the impact of LVEF on response to CRT in different LVEF groups; most of these studies examined the effect of CRT in patients with LVEFs beyond the current guidelines recommendations (>35%) [9,14,15]. In a retrospective analysis of the PROSPECT study, patients with core laboratory-measured LVEF >35% were compared with those whose LVEF was <35% [14]. PROSPECT was a multicenter, prospective, nonrandomized study to evaluate the ability of echocardiographic dyssynchrony measures to predict clinical and structural improvement after CRT. Patient enrolment was based on recent NYHA functional class III–IV, QRS duration ≥130 ms, and optimal background medical regimen [16]. The retrospective analysis of PROSPECT suggested that patients with LVEF >35% improved to a comparable degree as those with LVEF <35% [14]. Linde et al. [9] showed that the beneficial effect of CRT on ventricular function and on time to death or first hospitalization occurs across

Table 3. Demographic and echocardiographic parameters of patients according to response to CRT.

	Group 1		Group 2		Group 3	
	Responder (n=34)	Non-responder (n=17)	Responder (n=45)	Non-responder (n=15)	Responder (n=21)	Non-responder (n=9)
Age (year)	59±13	58±10	59±12	63±17	57±13	62±12
Male (n,%)	21 (62)	13 (77)	26 (58)	10 (67)	14 (67)	5 (56)
Ischemic (n,%)	15 (44)	11 (65)	20 (44)	7 (47)	6 (29)	3 (33)
QRS duration (ms)	154±18	145±17	154±21	145±16	151±24	144±9
NYHA (mean)	3.2±0.5	3.4±0.5	3.2±0.4	3.4±0.5	3.1±0.4	3.1±0.3
LVEF (%)	13±2	13±2	21±3	21±3	30±2	29±3
LVEDD (m)	72±9	74±9	68±8	67±8	60±6	63±8
LVESD (m)	61±10	63±9	55±8	54±9	46±7	48±12
LVEDV (ml)	279±79	298±84	244±64	237±64	185±41	204±63
LVESV (ml)	196±67	209±72	155±48	149±58	100±34	116±67
LVEDVI (ml//m^2)	150±39	159±47	133±39	131±44	99±22	114±38
LVESVI (ml/m^2)	105±35	110±39	85±28	83±36	53±18	65±39

LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; LVEDV – left ventricular end-diastolic volume; LVESD – left ventricular end-systolic diameter; LVESV – left ventricular end-systolic volume; NYHA – New York Heart Association.

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the full spectrum of LVEF studied in REVERSE, with indications of a similar benefit in patients with LVEF >30% to those with LVEF <30%. There was no statistically significant interaction between CRT and LVEF, indicating that there was no evidence that the benefit of CRT varied with LVEF. Although this study compared the effect of CRT between patients with LVEF >30% and those with LVEF <30%, similar to our findings, improvements in ventricular function produced by CRT were independent of LVEF. In a recent sub-study of the MADIT-CRT trial, Kutyifa et al. [15] investigated echocardiographic response with CRT, defined as percent change in LVEDV in 3 prespecified LVEF groups: >30%, 26–30%, and <25%. Although the clinical benefit of CRT-D was evident regardless of baseline LVEF, patients with mild HF with LVEF <25% at baseline had an increased risk for subsequent HF or death compared with patients with LVEF 26–30% or LVEF >30%. Unlike our study, the echocardiographic response was increased with increasing LVEF in MADIT-CRT. All of the above studies indicate that CRT might benefit patients with better LVEF. In contrast, we noticed similar echocardiographic response with CRT defined as a decrease in LVSVi in all LVEF groups. Although a variety of measures were used to define the response to CRT, a significant proportion of cases (20–30%) do not respond to the therapy [16–19]. Response rate to CRT was 67% in Group 1, 75% in Group 2, and 70% in Group 3, consistent with results of other studies investigating response rate in patients with mild HF and LVEF >30% [9,16].

It is well known that nearly half of all patients with dilated cardiomyopathy have conduction delays, such as a LBBB, which lead to contractile dyssynchrony [20,21] and meta-analyses of 15 large CRT clinical trials found that QRS duration predicts two-thirds of responders [22]. Consistent with this, the duration of the basal QRS complex was associated with the response to CRT but not basal EF in our study. Data suggest that the strongest predictor for the beneficial effect of CRT may be the degree of LV dyssynchrony, not EF. Additionally, recent studies showed a similar beneficial effect of CRT on ventricular function and clinical outcome in patients with LVEF >30% to those with LVEF <30% [9,14]. Based on these studies and our findings, LVEF may not be a criterion in the future guidelines to select CRT candidates in patients with heart failure and LV dyssynchrony. Although there is no lower limit of LVEF associated with non-response to CRT, it is important to explore the upper limit of LVEF associated with response to CRT, because its definition may lead to reform of the CRT indication.

Study limitation

We acknowledge that there were some limitations in this study. One limitation of our study was the single-center, nonrandomized design. Second, the study sample was small. Third, we did not investigate the survival in our patients. However, considering improvements in functional capacity and left ventricular remodeling, our data support implantation of biventricular pacemaker in patients with heart failure, LBBB, and very low LVEF.

Conclusions

Our study demonstrates that there is no lower limit for LVEF associated with non-response to CRT in eligible patients according to current guidelines. CRT has beneficial effects in heart failure patients, even those with very low LVEF.

Disclosures

No conflicts of interests to disclose.

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