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Effect of Cardiac Resynchronization Therapy on Left Ventricular Diastolic Function

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Abstract

Aims: Cardiac Resynchronization Therapy (CRT) improves systolic performance in Heart Failure (HF). However, the effects of CRT on Left Ventricular (LV) diastolic function were variable and not fully understood. The aim of this study was to determine the effects of cardiac resynchronization therapy on LV diastolic filling pattern and the relation between the diastolic filling pattern and the response to CRT.

Methods and Results: Twenty nine patients (mean age, 66 ± 8 years; 26 men; mean LV ejection fraction 25±7%) with severe HF were included. Measurements included LV volumes and Ejection Fraction (EF), pulsed-wave Doppler (PWD)-derived transmitral filling indices (E- and A-wave velocities, E/A ratio, Ewave deceleration time).

Clinical responders were defined as survived patients with an improvement by one or more NYHA functional class, echocardiographic response to CRT was defined as a decline in LV end-systolic volume >15% during follow-up. In clinical responder group, both diastolic and systolic LV volumes decreased significantly (p=0.02 and p<0.001 respectively) and LVEF increased significantly (p=0.001) in 26 of 29 patients (89%) and were accompanied by reduction in mitral E-wave velocity and E/A ratio (both p<0.001), and increased A-wave velocity and Ewave deceleration time (p=0.03 and p<0.001). In echocardiographic responders, reverse remodelling (52%) was coupled to the improvement in LV diastolic function but diastolic filling pattern improved also in 42% in patients without reverse remodelling.

Conclusion: Left ventricular diastolic indices after CRT improved in the clinical responder group, but there was no significant change in these indices among non-responders. CRT enhances diastolic filling patterns in both echocardiographic responder and nonresponder patients. This may be related to improvement in symptoms even in echocardiographic nonresponders who were clinical responders.

Keywords

Cardiac resynchronization therapy, Responders, Diastolic function

Introduction

Cardiac Resynchronization Therapy (CRT) can be an adjunctive treatment in patients with medically refractory heart failure symptoms, severe Left Ventricular (LV) systolic dysfunction, and an interventricular conduction delay.

CRT has been shown to improve symptom class, exercise capacity, quality of life, and systolic function [1]. The LV diastolic function is physiologically coupled to LV systolic performance and is an important determinant of symptoms and outcomes in patients with LV systolic dysfunction [2]. The effects of CRT on LV filling velocities (E-wave, E/A ratio) and Deceleration Time (DT) have been variable [3-5].

The aims of this study were to evaluate the effects of CRT on LV diastolic filling pattern and to whether an association existed between improvement of LV diastolic function and the response to CRT.

Methods

Study population

A total of 29 patients (mean age, 66 ± 8 years, 86% male) with New York heart Association (NYHA) functional class III or IV HF symptoms despite maximal medical therapy, LV ejection fraction ≤35%, sinus rhythm, and intraventricular echocardiographic asynchrony were enrolled in the study, between June 2004 and April 2008.

Clinical evaluation

Clinical evaluation included assessment of NYHA class, and measurement of the QRS duration on the surface ECG using the widest QRS complex.

Echocardiography

A commercially available ultrasound system was used (Aloca 5000 and ATL 3000) for the echocardiography studies. Two-dimensional (2D) measurements included LV volumes at end-diastole and end-systole from the apical four and two-chamber views (method of discs), LVEF calculated by the biplane method, The PWD-derived transmitral velocities were obtained at the mitral leaflet tips according to American Society of Echocardiography guidelines [6]. Measurements included the early diastolic (E) and atrial (A) wave velocities, the E/A ratio, and the E-wave DT. Mitral regurgitation was assessed by PISA method to determine ERO (effective regurgitant orifice) and RV (regurgitant volume). The extent of intraventricular dyssynchrony was defined if the maximal difference between the time intervals from Q-wave to peak Sm at each annular site is superior to 65ms [7] or if there is an overlap of the lateral wall [8].

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Table 1: Baseline echocardiographic characteristics of the patients

EDD (mm)	70 ± 8
ESD (mm)	61 ± 7
EDV (ml)	177 ± 54
ESV (ml)	134 ± 48
LVEF (%)	25 ± 7
Mitral regurgitation≥II	16 (55%)
Ewave (m/s)	0.83 ± 0.25
Awave (m/s)	0.49 ± 0.22
E/A ratio	2 ± 1.4
Ewave DT (ms)	166 ± 71
Diastolic dysfunction (I,II,III)	(7/7/16)

Table 2: The PWD-derived parameters of diastolic function improved significantly in the clinical responder group.

	Clinical responders: n=26		
	preCRT	postCRT	p
Ewave (m/s)	0.82 (±0.24)	0.57 (±0.26)	<0.001
Awave (m/s)	0.5 (±0.23)	0.69 (±0.24)	0.001
E/A ratio	2.1 ± 1.5	1.1 ± 1	<0.001
DT (ms)	170 ± 74	267 ± 88	<0.001

CRT device implantation

CRT device implantation included pacemaker-only and -defibrillator CRT devices. First, the Right Ventricular (RV) lead was implanted using the cephalic vein or the subclavian vein. The LV pacing lead was inserted transvenously via the subclavian route if an appropriate coronary sinus branch was present. Otherwise, an epicardial approach was used and the lead was placed at the lateral LV free wall using a limited thoracotomy. The right ventricular lead was positioned at the apex and the right atrial lead in the atrial appendage.

Definition of response

Clinical responders were predefined as survived patients with an improvement by one or more NYHA functional class. Echocardiographic responders were those who reduced LV end-systolic volume by >15% during follow-up.

Statistical analysis

All statistical analysis was performed using SPSS software (version 15.0); continuous variables are expressed as mean ± one standard deviation. A comparison of the clinical and echocardiographic variables prior to and after CRT was performed using paired and unpaired Student t test and Pearson correlations as appropriate. Statistical significance was determined as a p value of < 0.05.

Results

Clinical parameters

29 patients (age 66 ± 8 years, 86% male) were included. The aetiology of heart failure was primarily nonischemic (79%). Medications included angiotensin-converting enzyme inhibitors in 89%, beta-blockers in 76% and potassium-sparing diuretics in 48%.

The QRS duration was prolonged (≥120ms) in 65% (left bundle branch block in 18 and non specific intraventricular conduction disturbance in one patient).

The LV pacing lead was placed in a mid-lateral or posteriolateral vein in the majority of patients (86%), and 4 patients' required thoracotomy. 6 patients (20%) had an implantation of a pacemaker-defibrillator. There were no complications from CRT device implantation.

All patients were restudied at a mean of 8 ± 2 months after CRT; 26 (89%) were clinical responders. These clinical responders were often in class III of NYHA (62%), with non ischemic aetiology (73%).

Echocardiographic parameters

The echocardiographic parameters of all patients are resumed in the Table 1. LV end-diastolic and end-systolic diameters and volumes decreased significantly in the clinical responder group (70 ± 5 vs 67 ± 10mm, p=0.02 and 61 ± 8 vs 55 ± 10mm, p<0.001 respectively for diameters, 181 ± 56 vs 150 ± 52ml, p=0.02 and 138 ± 49 vs 104 ± 50ml, p<0.001 respectively for volumes).

The LV ejection fraction increases significantly only in responder group (26 ± 5 vs 34 ± 12, p=0.001). The PWD-derived parameters of diastolic function improved significantly (decreased E-wave velocity and E/A ratio; increased A-wave velocity and DT) in the clinical responder group (Table 2) (Figure 1 and Figure 2).

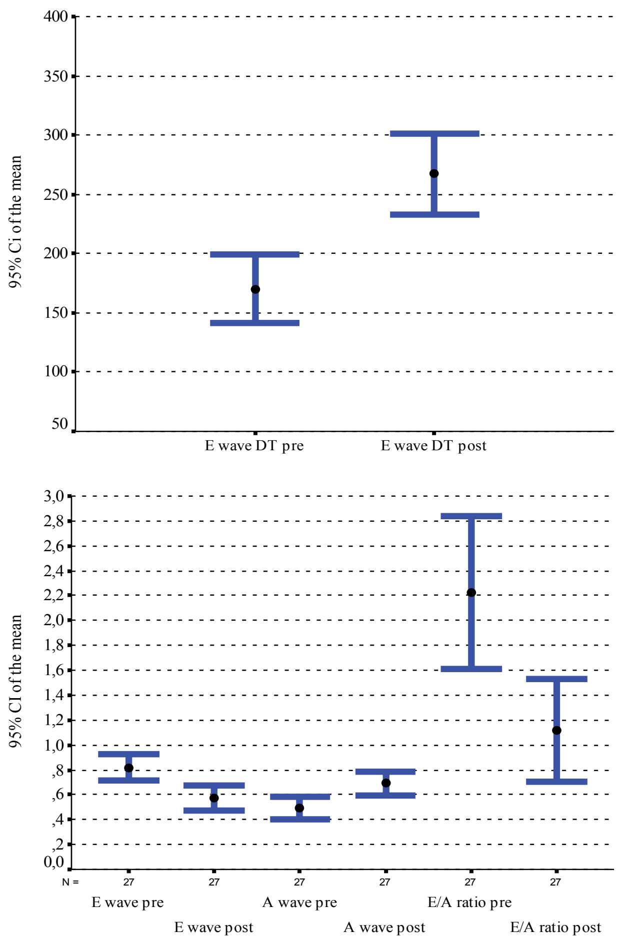
A restrictive diastolic filling pattern before CRT was noted in 16 patients (55%) and did not predict clinical response (p=0.15). It was more frequent in echocardiographic nonresponders (63% versus 37%) but remained insignificant (p=0.08). A cut-off value of DT at 180ms predict significantly an echocardiographic response (p=0.017).

Reverse remodelling, occurring in 52%, was coupled to the improvement in LV diastolic function in all patients (Figure 3 and Figure 4) but diastolic filling pattern improved also in (6/11) in clinical responders without reverse remodelling , and parameters of diastolic function (Ewave, E/A ratio and Ewave DT) were significantly improved even in non echocardiographic responders (Table 3).

Then CRT enhances diastolic filling patterns in both echocardiographic responder and nonresponder patients. This may be related to improvement in symptoms even in echocardiographic nonresponders who are clinical responders.

Discussion

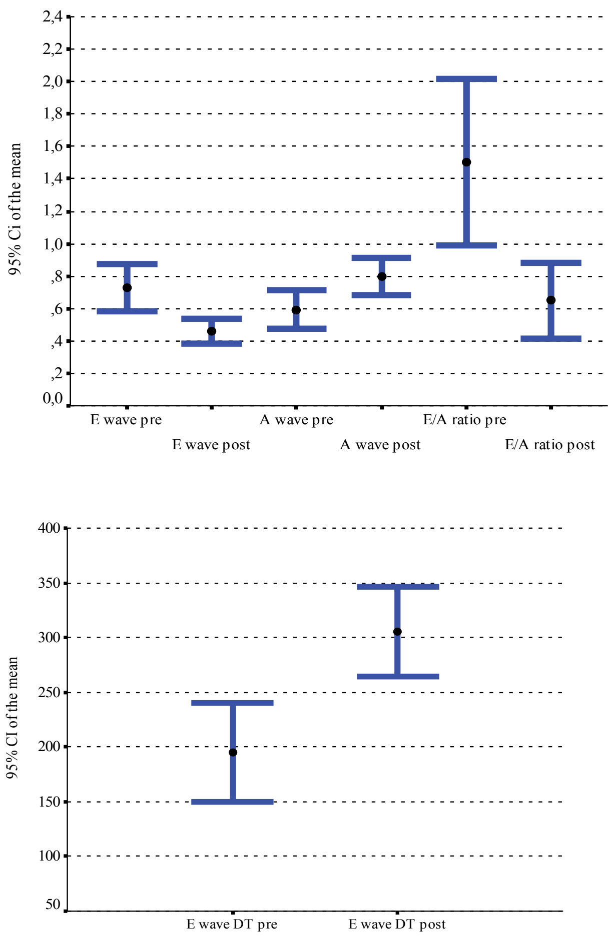
Cardiac Resynchronization Therapy (CRT) has become a



Figures 1 and 2: A significant improvement of diastolic parameters after CRT in clinical responders

Table 3: Comparison of echocardiographic parameters between echocardiographic responders and non-responders

	Echocardiographic responders: n=15			Echocardiographic nonresponders: n=14		
	preCRT	postCRT	p	preCRT	postCRT	p
EDD (mm)	68 ± 8	64 ± 10	0.005	71 ± 8	70 ± 8	0.37
ESD (mm)	60 ± 8	51 ± 10	0.001	62 ± 7	61 ± 5	0.44
EDV (ml)	172 ± 48	126 ± 46	0.001	182 ± 64	174 ± 41	0.75
ESV (ml)	129 ± 39	78 ± 40	0.001	139 ± 58	133 ± 40	0.52
LVEF (%)	27 ± 6	40 ± 11	0.001	25 ± 4	25 ± 6	0.77
Ewave (m/s)	0.72 ± 0.26	0.46 ± 0.13	0.001	0.95 ± 0.2	0.77 ± 0.28	0.014
Awave (m/s)	0.59 ± 0.21	0.79 ± 0.2	0.035	0.41 ± 0.19	0.53 ± 0.22	0.08
E/A ratio	1.5 ± 0.92	0.65 ± 0.42	0.003	2.87 ± 1.68	1.89 ± 1.23	0.03
DT (ms)	195 ± 82	305 ± 74	0.003	136 ± 46	197 ± 83	0.008
rPISA (cm)	0.46 ± 0.21	0.18 ± 0.19	0.003	0.69 ± 0.15	0.54 ± 0.14	0.02
ERO (mm²)	12 ± 7	4.2 ± 4	0.001	28 ± 22	15 ± 8	0.001
RV (ml/b)	15 ± 8	4.2 ± 4.4	0.003	25 ± 12	17 ± 9.5	0.001



Figures 3 and 4 : Improvement of diastolic parameters in echocardiographic responders

therapeutic option for patients with severe heart failure (HF), particularly in cases that are refractory to conventional medical treatment [9,10].

Various studies have demonstrated improvement in functional class and quality of life, with increased exercise tolerance and fewer hospitalizations for heart failure and, as shown in the CARE-HF trial, reduced mortality [1,9]. The effects of CRT on LV diastolic function were less studied.

The main findings of our study are as follows: the PWD-derived parameters of diastolic function improved significantly in the clinical responder group and diastolic filling pattern improved in 42% in patients without reverse remodelling, and then CRT enhances diastolic filling patterns in both echocardiographic responder and nonresponder patients.

Prior studies that have evaluated the effects of CRT on LV diastolic function by use of PWD-derived transmitral filling parameters have reported variable results; the mitral E-wave velocity or E/A ratio may not be significantly altered [11-13].

Other investigations have reported that the PWD-derived E-wave velocity decreases after CRT [14,15]. Deceleration slope and deceleration time of the E-wave increased significantly at 3 and 6 months in the CRT group but did not change in the control group which is consistent with improved diastolic function in the CRT group [15]. Waggoner showed that CRT decreases the mitral E-wave velocity and the E/A ratio only in those patients who exhibit significant decreases in LV volumes and significant improvements in LVEF [16].

In our study, reverse remodelling, occurring in 52%, was coupled to the improvement in LV diastolic function but diastolic filling pattern improved also in 42% in patients without reverse remodelling, then enhancement of diastolic filling patterns after CRT may explain improvement in symptoms in the absence of reverse remodelling.

Similar to our results, Jansen and Aksoy suggested that patients with reverse remodelling and symptomatically improved patients without reverse remodelling showed decreased filling pressures after CRT [17,18]. Recently, Doltra's study demonstrated that patients with clinical but no echocardiographic response had significant improvement in E-wave and deceleration time and non significant improvement in other parameters [19].

In our study, the restrictive diastolic filling pattern before CRT was more frequent in echocardiographic non responders (63% versus 37%). The more frequent restrictive mitral patterns in the non responders suggests that these patients were at a more advanced stage of heart failure, which was confirmed by their higher pro-BNP and lower oxygen consumption in Galrinho's study [20]. Then, diastolic function before CRT must be more studied as a predictor for response after CRT.

Study Limitations

The major limitation of this study is the relatively small sample size. One third of the patients had a QRS duration <120ms and inclusion criteria for CRT were based on the mechanical asynchrony but this may be explain the high rate of clinical response. Inclusion period was before the publication of PROSPECT study which not supported echocardiographic criteria.

Conclusion

Cardiac resynchronization therapy improves LV diastolic filling in the clinical and echocardiographic responders. Enhancement of diastolic filling pattern in clinical responders without reverse remodelling may explain improvement of symptoms in these patients.

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