

Cardiac Resynchronization Therapy and Left Ventricular Diastolic Function

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Abstract

Cardiac resynchronization therapy (CRT) improves systolic performance in heart failure (HF). However, the effects of CRT on left ventricular diastolic function were variable and not fully understood.

The available studies used different diastolic parameters derived from pulse and tissue Doppler techniques and more recently from deformation data.

The most studies showed that CRT improves diastolic function (data are more controversial regarding relaxation) but this seems to be dependent on improvement in systolic function.

Keywords: Cardiac resynchronization; 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].

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 [1-10].

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].

Therefore, a greater cardiac output after CRT relies not only on improved systolic emptying but also on better diastolic filling.

The effects of CRT on LV filling velocities (E-wave, E/A ratio) and Deceleration Time (DT) have been variable [3-5] and remain less studied.

Effects Of CRT On Left Ventricular Diastolic Parameters

The effects of biventricular pacing on LV diastolic function were less studied and whether its improvement plays an important role in the mechanism of response to CRT is unknown (Table 1).

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 [10-12].

In St John Sutton's study [5], neither peak A-wave velocity, E/A wave velocity ratio, nor isovolumic relaxation time changed significantly in the CRT group or in the control group from baseline to 6 months, whereas deceleration slope and deceleration time of the E-wave (during rapid filling) increased significantly at 3 and 6 months in the CRT group but did not change in the control group.

Other investigations have reported that the PWD-derived Ewave velocity decreases after CRT [7,13].

Waggoner et al. [13] 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 improvement in LVEF. These results are consistent with the preload-dependency of PWD-derived mitral inflow parameters.

Despite the benefits observed in LV diastolic filling and lower LV filling pressures after CRT, measurements of global or regional LV relaxation were not favorably altered and there were no changes in the relatively load-independent measurements of TDI derived Em and color M-mode flow propagation velocities, regardless of the response in LV volumes or LVEF. It is possible that recovery of LV relaxation is delayed after CRT and thus not yet evident at a short-term follow up of four months in this study.

The Verbrugge's study [14] focused on the diastolic filling time corrected to RR interval (DFTc) before and after CRT in 91 patients. They found that DFTc increase after CRT and reflects favourable reverse remodeling.

Recently, Alksoy et al. [15] described the effects of CRT on diastolic function in 54 heart failure patients. Echocardiographic parameters and brain natriuretic peptide (BNP) levels were assessed in responders and non-responders as defined by the occurrence of LV reverse remodelling 6 months after CRT.

They observed that echocardiographic indices such as the ratio between peak early Filling (E) and peak early diastolic longitudinal myocardial velocity (e'), left atrial volume, and BNP levels significantly improved only in responders to CRT.

Therefore, the main conclusion of this study was that improvement in diastolic function contributes to the overall benefit of CRT in responders. However, some important limitations were noted (small sample size, the majority of patients recruited in this study had an

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Received June 13, 2014; **Accepted** July 14, 2015, 2015; **Published** July 20, 2015

Citation: Kammoun I, Marrakchi S, Kachboursa S (2015) Cardiac Resynchronization Therapy and Left Ventricular Diastolic Function. J Clin Med Genom 3: 118. doi: [10.4172/2472-128X.1000118](https://doi.org/10.4172/2472-128X.1000118)

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| study | patients | Diastolicparameters | results |
|----------------------------|--------------|--|--|
| Sutton et al. [5] 2003 | 323 patients | E, A, E/A, DT, IVRT | No changes in A,E/A, IVRT, DT increased only in the CRT group |
| Waggoner et al. [13] 2005 | 50 patients | E, A, E/A, DT, DFT,e', E/e', Vp | reduction in E ,E/A and E/e' , increased DT and DFT in patients with improvement in LV systolic function. No changes in e' and Vp regardless of the systolic response . |
| Jansen et al. [17] 2007 | 52 patients | E, A, DT, DFT, E/e', E/Vp | short-term symptomatic benefit was related to decreased filling pressure at follow-up, improvement of diastolic function and significant decrease filling pressure observed only in patients with reverse remodeling |
| Alksoy et al. [15] 2010 | 54 patients | E/e' and left atrial volume | E/e' and left atrial volume significantly improved only in responders to CRT. |
| Doltra et al. [18] 2013 | 250 patients | E, A, E/A, DT, DFTc, S, D, S/D, E/e', left atrial volume | A decrease in E, E/A, E/e' and LA volume and an increase in DT and DFTc in the echocardiographic responders E and DT decreased in clinical responders without echocardiographic response. |
| Verbrugge et al. [14] 2013 | 91 patients | DFT corrected to RR interval | DFT _c increase after CRT in patients with reverse remodeling |
| Shanks et al. [20] 2011 | 188 | SRIVR and E/ SRIVR | improvement in diastolic functionwas only observed in responders to CRT and patients with non-ischaemic aetiology |

E, The peak rapid filling velocity [E wave]; A, peak atrial filling velocity [A wave]; DT, E wave deceleration time [DT]; DFT, diastolic filling time;E/A,E/A wave velocity ratio; IVRT, isovolumic relaxation time; e',Tissue Doppler e'velocity; E/e' , E/e' ratio; Vp ,color M-mode flow propagation velocity; S,the peak systolic velocity in the right upper pulmonary vein; D, peak diastolic [D] velocity in the right upper pulmonary vein; S/D, S/S ratio, SRIVR, diastolic strain rate during the isovolumic relaxation period; E/SRIVR, ratio E by SRIVR.

Table 1: principle studies on effect of CRT on diastolic function.

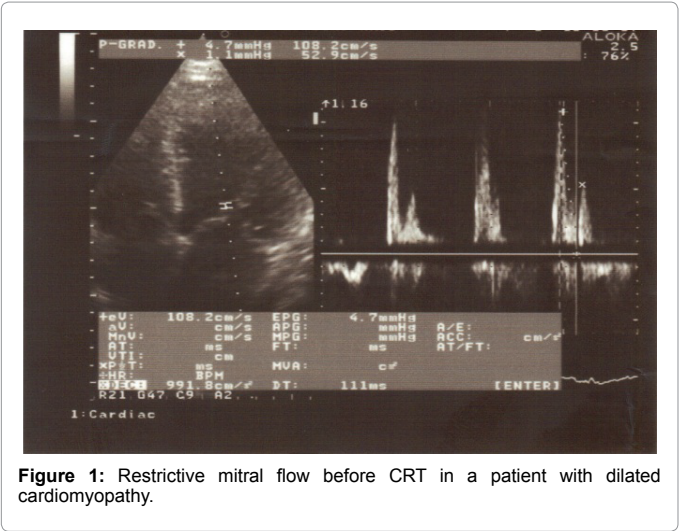


Figure 1: Restrictive mitral flow before CRT in a patient with dilated cardiomyopathy.

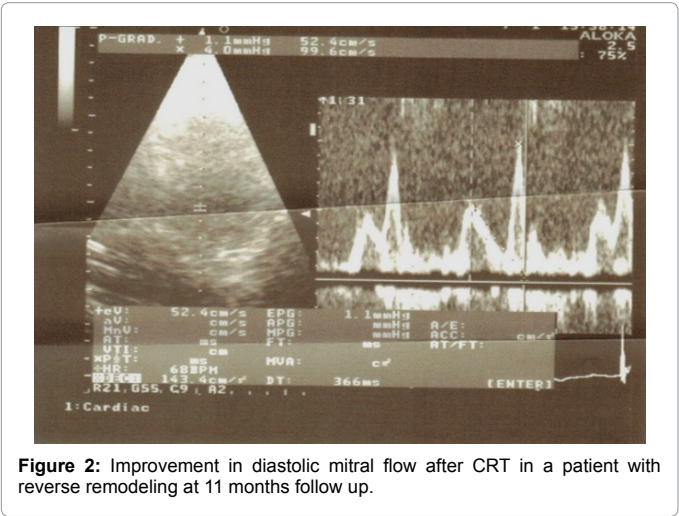


Figure 2: Improvement in diastolic mitral flow after CRT in a patient with reverse remodeling at 11 months follow up.

ischaemic aetiology of heart failure and only septal E/e' was significantly improved that can be influenced by regional dysfunction typical of ischaemic disease) [16].

In another study by Jansen et al. [17], they suggested that short-term symptomatic benefit was related to decreased filling pressure (estimated by E/Vp and E/e'). However, for longer-term symptomatic improvement and decreased filling pressures, LV reverse remodeling appeared mandatory.

Recently, Doltra et al. study [18], a more large study including 250 patients, confirmed that LV diastolic function improves with CRT in echocardiographic responders (defined by a reduction in left ventricular (LV) end-systolic volume of $\geq 15\%$ at 1-year follow-up). Clinical responders without echocardiographic response show improvement in some parameters of diastolic function. The authors suggested that clinical-only response to CRT is secondary to a real effect of the therapy and not a placebo effect.

An hemodynamic study was recently done by Kato et al. [19] They investigated whether improvement of invasive Left Ventricular (LV) hemodynamic diastolic parameters could identify CRT responders in 34 consecutive patients.

They found that an acute improvement in LV isovolumic relaxation time, as assessed by tau, was associated with favorable response to CRT and they concluded that assessment of invasive diastolic function could provide valuable information about CRT volume response.

The LV relaxation was recently studied, using new techniques, to characterize diastolic function after CRT. Shanks et al. [20] study (including 188 patients) assessed global load-independent LV relaxation properties with two-dimensional (2D) speckle-tracking imaging by measuring diastolic strain rate during the isovolumic relaxation period (SRIVR) and by calculating the ratio of peak transmitral E-wave to SRIVR (E/SRIVR).This study concluded that improvement in diastolic function was only observed in responders to CRT and patients with non-ischaemic aetiology.

The most studies, using different parameters, showed that CRT improves diastolic function (data are more controversial regarding relaxation) but this seems to be dependent on improvement in systolic function [21] (Figures 1and 2).

Diastolic Function and Prognosis after CRT

Waggoner et al. [22] was the first to investigate the predictive role of the septal E/e' ratio as a marker for increased LV filling pressures in patients after CRT.

Similarly, Soliman et al. [23] evaluated the value of baseline parameters derived from tissue Doppler imaging for event prediction in patients with heart failure secondary to ischemic and nonischemic cause who underwent cardiac resynchronization therapy in seventy-four consecutive patients. 21 patients (28%) had cardiac death or hospitalization for HF and these patients more often had an ischemic cause ($p < 0.05$), diabetes ($p < 0.05$), and restrictive filling ($p < 0.001$), less often had LV dyssynchrony ($p < 0.05$), and had higher septal and lateral E/e' ratios.

In a multivariable analysis, only the lateral E/e' ratio remained an independent predictor of cardiac outcome.

In Gradaus's study, patients with an increased left ventricular end-systolic diameter and concomitant restrictive filling pattern before CRT, had a significantly worse outcome [24]. Porciani et al. [25] showed that the persistence of restrictive filling pressure after CRT is associated to an extremely poor prognosis.

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 [26]. Then, diastolic function before CRT must be more studied as a predictor for response after CRT.

The recent study of Iron [27] including 42 patients, showed that patients with a less severe E/A ratio before CRT are more likely to improve their clinical condition as shown by the reverse remodeling.

Recently, Facchini et al. [28] investigated potential relations between left ventricular changes induced by CRT and the composite clinical endpoint of progressive heart failure and cardiac death over 3 years follow-up in 119 patients. The ventricular reverse remodeling, together with improvement in ventricular filling, rather than improvements of systolic function, can predict long-term clinical prognosis after CRT.

Conclusion

In conclusion, evaluation of the effects of CRT on LV function exploring not only systolic but also diastolic properties determines a more comprehensive approach to understanding the underlying mechanisms of CRT.

This may be helpful for management of CRT patients during follow-up and may have important prognostic implications.

The best diastolic parameter to predict reverse remodeling after CRT need large studies to be defined and then it can be included in multiparametric echocardiographic score for predicting CRT response and clinical outcomes.

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