



Does presence of left ventricular contractile reserve improve response to cardiac resynchronization therapy? An updated meta-analysis

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ABSTRACT

Background: Up to a third of patients undergoing cardiac resynchronization therapy (CRT) do not have a clinical or echocardiographic response. It is also unclear, whether contractile reserve (CR) could predict CRT response. This meta-analysis examines whether the presence of CR improves response to CRT and whether this is modulated by other clinical factors.

Methods: Search of PubMed/EMBASE/Cochrane databases for articles examining response to CRT stratified by the presence or not of CR. End-point classified as clinical or echocardiographic response. The analysis compared response to CRT (echocardiographic or clinical) between patients with or without CR.

Results: 824 patients in 12 studies were included. The presence of left ventricular CR was associated with a significant reduction in echocardiographic non-responders to CRT compared to patients without CR (OR: 0.16, 95% CI 0.08–0.33, $p < 0.00001$). The presence of left ventricular CR was associated with a significant reduction in clinical non-responders to CRT compared to patients without CR (OR: 0.23, 95% CI 0.14–0.37, $p < 0.00001$). Sensitivity analysis showed no difference in response when pooling studies using left ventricular ejection fraction (LVEF) or non-LVEF markers of CR. Meta-regression showed that CR was associated with lower rates of non-responders and this was more pronounced in patients with a narrower mean QRS complex.

Conclusions: Identification of CR is associated with improved response to CRT. Importantly, QRS width is a potential moderator variable which can explain part of the heterogeneity in echo response. The combination of CR and QRS width may modulate the response to CRT.

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1. Introduction

Heart failure (HF) remains one of the most common causes of morbidity in the developed world with a prevalence of 1–2% in the adult population [1]. Introduction of medical therapies targeting the neuro-hormonal pathway including angiotensin converting enzyme inhibitors, aldosterone antagonists and beta-blockers has led to a reduction in mortality over the past few decades. However, 5 year mortality remains high [2]. Cardiac resynchronization (CRT) therapy is recommended in symptomatic patients with an ejection fraction $\leq 35\%$ and QRS duration ≥ 150 ms with left bundle branch block morphology who are already receiving optimal medical therapy [3,4]. Its use is associated with improvement in symptoms, quality of life, reduction in heart failure

hospitalization and improved prognosis [5,6]. More than a third of patients do not respond to CRT therefore predictors of response may be useful to better select patients likely to benefit [7].

Improvement in left ventricular (LV) and inter-ventricular synchrony is associated with improved LV myocardial performance and ejection fraction [8]. Echocardiographic markers of LV dyssynchrony were observed to be powerful predictors of response to biventricular pacing in small predominantly single centre studies [9]. Multi-centre trials, to date, have failed to confirm this observation [10]. The presence of significant quantity of scarred and non-viable myocardium is unlikely to lead to improved LV performance after CRT [11,12]. The clinical value of the extent of recruitable myocardium to predict response to CRT is poorly defined. Studies have used a variety of different imaging modalities and techniques to measure contractile reserve [13–29]. Interpretation of studies is difficult due to multiple different definitions of response; these include clinical assessment of functional capacity (New York Heart Association Class), echocardiographic measures of left ventricular remodeling/performance (LV size, volume or ejection fraction) and

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prognostic markers (heart failure admissions, freedom from heart transplant). Furthermore, response to CRT may occur at variable times in different individuals therefore studies may underestimate response if the follow-up period is short.

The aim of the present meta-analysis is to assess whether contractile reserve can predict response to CRT in symptomatic heart failure patients and whether this response is influenced by clinical markers or imaging specific parameters.

2. Methods

2.1. Search strategy

PubMed, EMBASE, and Cochrane databases were searched using the search term expression: (“contractile reserve” AND “cardiac resynchronization” AND “heart failure” AND “stress echocardiography”). Articles published from inception until April 2016 were eligible for inclusion. Reference lists of all accessed full-text articles were further searched for sources of potentially relevant information. Authors of full-text papers and congress abstract authors were also contacted by email to retrieve additional information. Articles were screened by two independent reviewers (NP and SB).

2.2. Study selection

Only longitudinal studies performed in humans were considered for inclusion. The population, intervention, comparison and outcome (PICO) approach was used [30]. The population of interest included patients with advanced heart failure implanted with CRT devices, and the intervention was assessment of contractile reserve. Comparisons were performed between patients with and without contractile reserve. The outcomes of interest were presence of clinical and/or echocardiographic response to CRT. Minimum follow-up duration was 6 months. The methods sections of evaluated studies were reviewed to confirm the suitability and composition of the reported endpoint.

Each study was required to state the method of determining contractile reserve, the definition of contractile reserve, the proportion of patients with and without contractile reserve in each of the outcome groups. Contractile reserve could be defined either by change in LV ejection fraction, wall motion score index, myocardial strain or pressure–volume relationship. Exclusion criteria included cohorts of patients with moderate/severe valve disease, recent myocardial infarction or revascularization, non-English text. When data on the same cohort of patients was published in more than one full-text article, only the most recent publication was included. Three independent reviewers (NP, SB, RP) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated to determine the eligibility of the study for the review and meta-analysis. Agreement of at least two reviewers was required for decisions regarding inclusion or exclusion of studies. An agreement, between the three reviewers was mandatory for the final classification of studies.

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group [31]. The following data were extracted for characterizing each patient sample in the selected studies, whenever available: age, gender, % of males, and other baselines collected in Table 1, and data on DSE or contractile reserve assessment, and follow-up (Table S1).

2.3. End-points

The presence of an echocardiographic or clinical response to cardiac resynchronization therapy. Data on the definition of clinical and echocardiographic response was collected for each study. Exact response defined by each study is in Table S1.

2.4. Statistics

Odds ratio and 95% confidence interval was calculated for each end-point using a random effects model. Statistical heterogeneity was assessed and quantified using the Cochran Q test and the I² statistic. *p* values < 0.05 were considered significant. All values were two-sided. Statistical analysis was performed using Review Manager 5.3. Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I² statistic, respectively. The I² statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. Values of <25%, 25% to 50% and >50% are by convention classified low, moderate, and high degrees of heterogeneity, respectively.

Sensitivity analyses were performed for assessing potential sources of heterogeneity. Only conditions which were fulfilled by at least 2 studies, and gathering at least 15% of the whole meta-analysis population were considered appropriate to be tested. Funnel plot and meta-regression analyses were obtained using Comprehensive Meta-Analysis software (Version 2). Funnel plots were used for evaluating the presence of publication bias and traced for comparisons including >10 studies (minimum number for assuring the appropriateness of the method [32]). The Egger test was also performed for assessing for publication bias. This analysis was performed using Stats Direct, Version 3.0.124. A meta-regression (using the Unrestricted ML method) was performed using Comprehensive Review 2 for comparisons involving >10 studies for assessing the possible association of modulator variables with the two endpoints.

3. Results

3.1. Study selection and search results

Fig. S1 illustrates the search strategy and selection of studies for the purpose of this meta-analysis. A total of 824 patients in 12 studies were identified (Table 1). All studies except one [26] combined ischaemic and non-ischaemic heart failure patients, while one study did not clarify [27]. The overall proportion of patients with non-ischaemic heart failure patients was 57.2%. Mean patient age was, 65.3 ± 3.4 years and there was a male preponderance. Most of the patients were at least NYHA class III. All studies apart from three [17,19,22] were single-centre. Data were prospectively collected in all studies.

3.2. Assessment of contractile reserve and definition of response

The method used to identify contractile reserve was either low dose dobutamine [13,17–22,24–27] or high dose dobutamine (14). The response criteria were either echocardiographic or clinical. Among the studies used for our analysis, 2 studies used only clinical criteria [21,25], 5 studies used only echocardiographic criteria [13,22,24,26,27], while the rest of the studies used a combination of both clinical and echocardiographic. The presence of contractile reserve was based on the analysis of LVEF [13,17,18,20–22,26] wall motion analysis [25,27], pressure–volume relationship (PVR) [14], and LV systolic strain analysis [24].

Clinical response criteria ranged from hospitalization, and improvement in NYHA class, to death or transplant, and were assessed in 6 studies. All included studies had at least 6 months of follow-up (Table S1).

Table 1

Studies examining the role of contractile reserve in patients undergoing cardiac resynchronization therapy.

Study	Centres	Design	Number (with/without CR)	Age (years)	Males	LVEF	NYHA	QRS width (msec)	Ischaemic CM	AF
Da Costa 2006 [21]	Single-centre	Prospective cohort	67 (47/20)	70	83.6% (56)	26	3.4 ± 0.5	190	34.3% (23)	26.5% (18)
Lim 2007 [25]	Single-centre	Prospective cohort	19 (13/6)	64	73.7% (14)	27	3.2 ± 0.4	154	47.4% (9)	0%
Ypenburg 2007 [13]	Single-centre	Prospective cohort	31 (17/14)	64	87.1% (27)	26	3.6 ± 0.6	154	65% (20)	6.4% (2)
Senecal 2010 [27]	Single-centre	Prospective cohort	49 (31/18)	66	69% (34)	19	3.4 ± 0.5	164	N/A	0%
Altman 2011 [18]	Single-centre	Prospective cohort	31 (10/21)	68	74% (23)	28	3.1 ± 0.3	158	65% (20)	0%
Chaudry 2011 [20]	Single-centre	Prospective cohort	54 (31/23)	69	63% (54)	18	3.2 ± 0.5	147	59.3% (32)	0%
Ciampi 2011 [14]	Single-centre	Prospective cohort	69 (49/20)	69	72% (50)	26	3.2 ± 0.4	150	59% (41)	0%
Gasparini 2012 [17]	Multi-centre	Prospective cohort	221 (177/44)	67	70% (156)	27	3.1 ± 0.2	150	42.5% (94)	0%
Vukajlovic 2012 [26]	Single-centre	Prospective cohort	55 (7/48)	59.3	83.6% (46)	16.9	3.0 ± 0.5	173.7	0% (0)	16.4% (9)
Mitro 2014 [24]	Single-centre	Prospective cohort	41 (24/17)	61.9	80.5% (33)	26.3	3 ± N.A	152.1	60% (25)	16% (7)
Mizia-Stec 2014 [19]	Multi-centre	Prospective cohort	129 (67/62)	62	76% (98)	24.6	NA	164.3	48% (62)	0%
Stankovic 2014 [22]	Multi-centre	Prospective cohort	58 (39/19)	63	77.6% (45)	26	3.1 ± 0.3	175	47% (27)	17% (10)

Data are presented as number and percentage or mean. Abbreviations. N: number of subjects; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; CM: cardiomyopathy; AF: atrial fibrillation; N/A: non-available; CR: contractile reserve.

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