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.

Keywords: contractile reserve, cardiac resynchronization therapy, heart failure

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-hormomal 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 ≤ 35% and QRS duration ≥150 milliseconds 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 hospitalisation 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 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.

Methods

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).

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).

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 are in Table-S1.

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 less than 25%, 25% to 50% and greater than 50% are by convention classified low, moderate, and high degrees of heterogeneity, respectively.

Sensitivity analyses was 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 more than 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 more than 10 studies for assessing the possible association of modulator variables with the two endpoints.

Results

Study selection and search results

Figure-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.

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).

Prediction of Response to Cardiac Resychronisation Therapy

When considering an echocardiographic response to cardiac resynchronization therapy the presence of contractile reserve was associated with a significant reduction in non-responders compared to a lack of contractile reserve (Odds ratio 0.16, 95% Confidence Interval 0.08–0.33, $p<0.00001$) (Figure 1). There was major heterogeneity between studies ($I^2=69\%$), but minimal publication bias ($p=0.1$).

When considering a clinical response to cardiac resynchronization therapy the presence of contractile reserve was associated with a significant reduction in non-responders compared to a lack of contractile reserve (Odds ratio 0.23, 95% Confidence Interval 0.14 – 0.37, $p<0.00001$) (Figure 2). There was no significant heterogeneity between studies ($I^2=13\%$). There was significant publication bias ($p=0.02$).

Sensitivity analyses for stress echocardiography response

All sensitivity analyses are presented in Table 2. The pooling of single-centre studies shows that the absence of CR was significantly associated with non-response after CRT implantation (OR: 0.13; 95%CI 0.07-0.22, $p<0.00001$, $I^2=0\%$). However, in multi-centre studies this was no longer significant (OR: 0.31; 95% CI 0.06 – 1.56, $p=0.15$). In addition, in patients with atrial fibrillation, contractile reserve was no longer a significant predictor of response to CRT (OR: 0.12; 95%0.01-1.18, $p=0.07$).

Meta-regression

The assessment of potential moderator variables through meta-regression is shown in Table-S2. Among the examined variables, only the QRS width was a significant moderator variable, and explained part of the heterogeneity seen in echo response. Presence of CR was associated with lower rates of non-responders, with our analysis suggesting that the narrower the mean QRS complex, the more pronounced the relative reduction in non-responders among studies (Figure-S2). For example, in studies with a mean QRS width of 165ms, log OR was -1.5 and OR corresponded to 0.22, and in studies with a mean QRS width of 150ms, log OR was -2.62, which corresponded to a further reduction in non-responders, OR=0.07 (Figure-S2).

Discussion

The present meta-analysis shows that in symptomatic heart failure patients who meet guideline criteria for CRT, measurement of contractile reserve predicts both an echocardiographic and clinical response to therapy. In particular, the lack of left ventricular contractile reserve predicts a low likelihood response. Sensitivity analysis shows that the effect is consistent whether left ventricular systolic function (LVEF) or left ventricular end-systolic volume (LVESV) reduction is chosen as the marker of improvement. However, in patients with AF the effect of CR on CRT response is uncertain. Moreover, meta-regression analysis showed that QRS width could explain part of the observed heterogeneity seen in echo response.

Intraventricular conduction delays are common and occur in about a third of patients with heart failure [33]. This leads to asynchronous contraction between right and left ventricles, reduced ejection fraction and LV performance indices. Biventricular pacing improves these parameters [8]. Pivotal studies demonstrating CRT leads to an improvement on symptom status, quality of life and mortality have used a QRS duration of >120msec as criteria of dyssynchrony [5, 6]. However, using these criteria up to a third of patients are deemed non-responders to CRT. Tissue Doppler markers of mechanical left ventricular dyssyncrony were thought to be a good predictor of response to CRT [9]. However, the PROSPECT multi-centre trial showed previously validated markers had limited predictive power most probably due to lack of inter-observer reproducibility [10]. Resynchronization is unlikely to occur if there is significant infarcted/non-viable myocardium. Indeed, the extent of scar tissue has now been shown to be related the degree of CRT response [11]. Therefore, a viability marker may improve our ability to predict response to CRT. A recent meta-analysis by Kloosterman et al. [34] examined the effect of CR on echocardiographic response to CRT only. However, a clinical response related to symptom status/functional class is important and therefore we examined the effect of CR on both echocardiographic and clinical responses to CRT.

The region of maximal mechanical delay varies between patients [35]. Positioning of the LV lead at the most delayed site away from scar leads to a greater likelihood of response [36]. Two randomized studies showed placement of LV lead at the site of maximal mechanical delay improves response in terms of both symptoms, LV remodeling and prognosis [36, 37]. Using this strategy, TARGET trial response improved from 55% to 70% however this still left a significant proportion of non-responders [37]. More recently, several investigators have combined strain assessment of mechanical delay with scar assessment to guide lead placemen [38, 39]. Although the response rate improves there remains 20 – 30% non-responder rate. Another key factor determining this may inability to engage recruitable myocardium due to localised fixed/functional conduction block [40]. In our study, there was also a small proportion of patients with lack of contractile reserve who were echo responders. Further studies looking at the stepwise and sequential assessment of mechanical dyssynchrony, myocardial contractile reserve and optimal positioning of LV lead may provide the solution. The sensitivity analysis showed the association between contractile reserve and CRT response was attenuated when only considering multi-centre studies. This reinforces the need for a robust test with low inter-observer and test re-test variability for use in routine practice and for clinical decision making.

CRT in patients with a narrow QRS duration (<130msec) has been associated with a poor outcome [41]. The mean QRS duration in the studies we analyzed had a broad QRS duration (mean QRS width 147msec to 190msec). Within this group, the fact that in studies with a broader mean QRS complex, the presence of CR displayed a lower effect size with regard to echocardiographic response, seems to suggest that in patients with a broader QRS complex the presence of CR may not be as important, as these patients are more likely to respond anyway. Conversely, in patients with a narrower QRS complex, and thus less pronounced electrical dyssynchrony, the presence of CR may be of more importance for predicting echo response, which suggests that assessing CR may have more clinical impact in patients with lower degrees of electrical dyssynchrony.

The present results are hypothesis generating and although these can be considered as preliminary, they are still promising. This meta-analysis has several limitations which should be highlighted. First, endpoint definition (both for clinical and echocardiographic response), differed across studies. This reflects that there is no universal agreement on what the definition of response to CRT should be. Furthermore, data on separate components of the combined clinical endpoint (i.e. mortality, transplant, heart failure admissions), was not available frequently, precluding a more correct pooling of data. Second, the threshold for defining the presence contractile reserve varied among studies. There is likely to be a spectrum of response to CRT and therefore analyzing data which has dichotomized patients into responders and non-responders may miss patients who have benefited from therapy but not reached artificial derived thresholds. Given the heterogeneity between studies in this meta-analysis, large randomized, studies examining using pre-defined definitions of contractile reserve with reproducibility data on hard end-points (mortality) are required.

Conclusions

Identification of left ventricular contractile reserve is associated with improved response both clinically and echocardiographically to CRT. Importantly, contractile reserve was associated with higher response rates and this was more pronounced in patients with less pronounced electrical dyssynchrony (narrower mean QRS width). It seems that combination of CR and QRS width may modulate the response to CRT, however this needs further evaluation by future trials.

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Conflict of Interest: None

Figure legends

Figure 1. Forrest Plot comparing echocardiographic response cardiac resynchronization therapy between patients with and without contractile reserve.

Figure 2. Forrest Plot comparing a clinical response to cardiac resynchronization therapy between patients with and without contractile reserve.

Tables

Table 1. Studies examining the role of contractile reserve in patients undergoing cardiac resynchronization therapy

Table 2. Sensitivity analyses on CRT echo response.

Supplementary data

Figure-S1. Search and selection process for study inclusion.

Figure-S2. Meta-regression showing the relationship of QRS duration to odds of response to CRT.

Table-S1. Studies examining the role of contractile reserve in patients undergoing cardiac resynchronization therapy: focus on methods

Table-S2. Meta-regression on CRT echo response.

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