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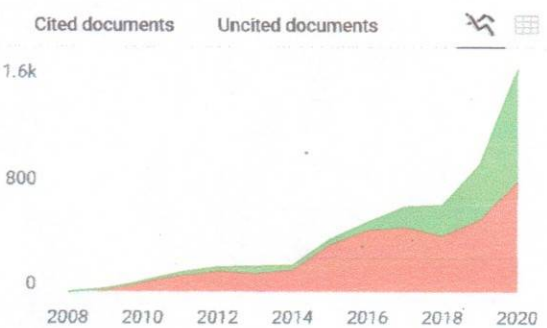
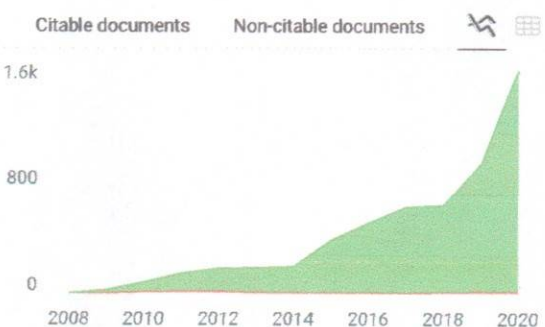
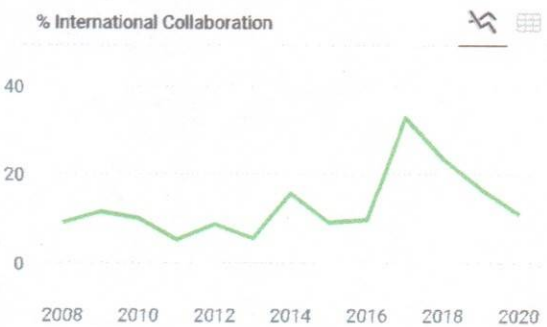
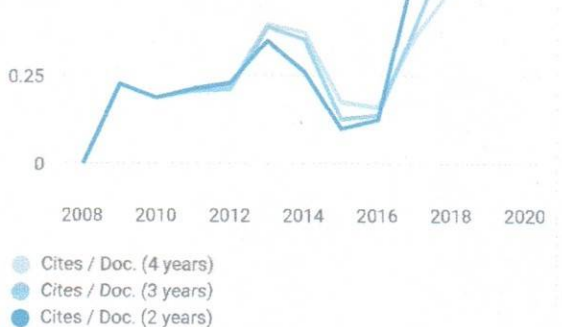
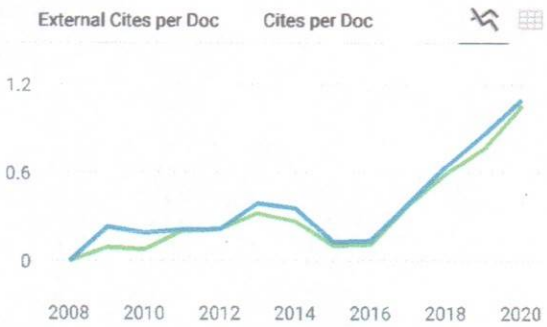
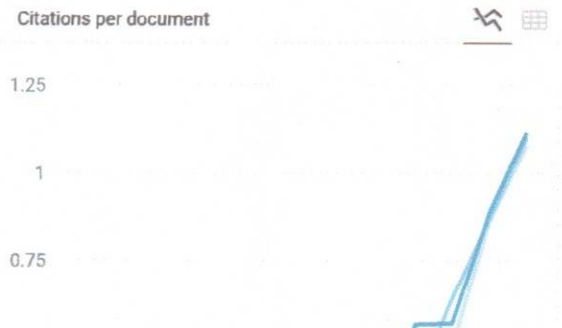
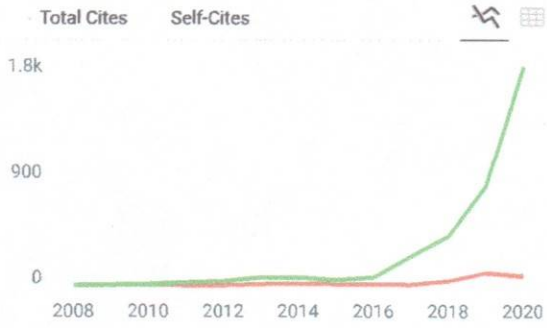
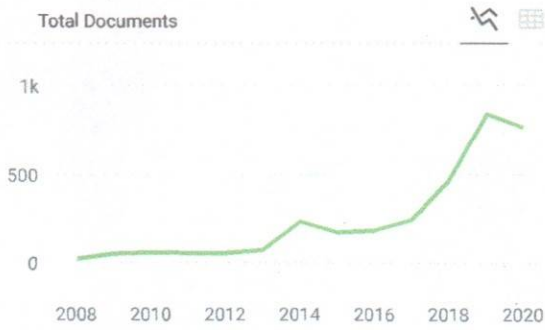
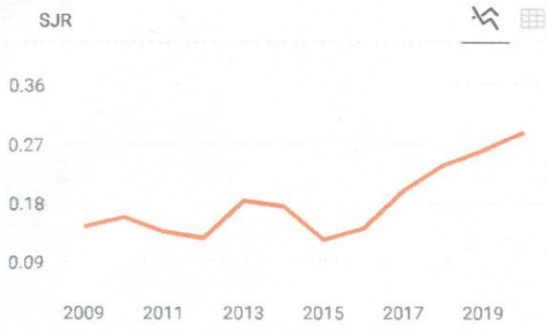
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The Role of Contractile Reserve by Stress Test Echocardiography for Predicting Cardiac Resynchronization Therapy Responder: Systematic Review and Meta-analysis

Achmad Lefi^{1*}, Ivana Purnama Dewi^{1,3}, Kristin Purnama Dewi², Eka Prasetya Budi Mulia¹, Agus Subagio¹, Budi Baktijasa Dharmadjadi¹

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Abstract

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Keywords: Contractile reserve; Cardiac resynchronization therapy; Cardiac resynchronization therapy responder; Stress test echocardiography; Dobutamine stress echo; Exercise test

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BACKGROUND: Up to one-third of patients who received resynchronization devices do not experience full benefit of cardiac resynchronization therapy (CRT). Echocardiography plays an important role in heart failure patients treated with CRT. Contractile reserve is a strong prognostic factor to predict positive response to CRT (CRT responder).

AIM: We perform a systematic review and meta-analysis of published data to assess the relationship between contractile reserve (CR) and response to CRT.

METHODS: We conduct a systematic search from major medical databases on all clinical trials published up to June 2020, written in English, full-text availability, and human subject. We used Newcastle-Ottawa Scale to measure the quality of evidence. We employed the Mantel-Haenszel random-effects meta-analysis of using RevMan 5.4.

RESULTS: We identified 17 studies involving 1399 patients. The type of stress was either dobutamine (n = 15) or exercise (n = 2). The presence of CR was associated with a higher chance of CRT responder (odds ratio [OR] 7.68, 95% confidence interval [CI] 4.27–13.82, p < 0.001) using a random-effects model. The ORs slightly differed when studies were analyzed separately based on the stress test type and definition of CR. CR, assessed with dobutamine stress echocardiography, defined as an increase in left ventricular systolic function (OR 5.10, 95% CI 2.29–11.32, p < 0.00001) was numerically lower than defined as increased LV contractility (OR 6.86, 95% CI 3.36–12.88, p < 0.00001). The presence of CR assessed with exercise stress test is associated with higher chance of CRT responder (OR 49.11, 95% CI 15.04–160.36, p < 0.00001). From our meta-analysis, we found non-ischemic has better response to CRT compare to patient with ischemic etiology (OR 0.41; 95% CI 0.31–0.55, p < 0.01).

CONCLUSION: The presence of CR during stress test echocardiography with either dobutamine or exercise stress test is associated with a higher chance of CRT responder.

Introduction

Congestive heart failure is a cardiovascular disease with an increasing incidence. Cardiac resynchronization therapy (CRT) is an adjunct therapy in the management of end-stage heart failure that is resistant to medical therapy. Studies with large sample sizes have reported benefits of CRT in patients with severe heart failure (New York Heart Association/NYHA class III/IV), decreased left ventricular systolic function (LVEF $\leq 35\%$); and wide QRS complex (> 120 ms) [1], [2]. The positive benefits of CRT include improvement of clinical complaints, stroke volume (SV), LVEF, mitral regurgitation, left ventricle (LV) remodeling, and survival rate.

One of the issues in CRT therapy is the identification of prospective patients who will get benefit from CRT implantation. The duration of the QRS complex

is still the only parameter indicative of CRT implantation in patients with severe symptomatic heart failure with a decreased ejection fraction [3]. Approximately 20–30% of CRT patients, selected based on QRS complex duration criteria, are non-CRT responder [4]. Other factors, such as myocardial viability, determine the placement of the CRT lead. Lead position in the scar tissue is a determinant of poor response to CRT [5]. LV pacing becomes less efficient because fibrotic tissue can modify myocardial contractility and electrical conduction of the heart [6]. Myocardial viability can be assessed by several non-invasive modalities, such as nuclear imaging, dobutamine stress echocardiography (DSE), and magnetic resonance imaging.

Contractile reserve (CR) is one of global myocardial contractility markers that are related to myocardial viability. CR assessment correlates with the extent of fibrosis and is a modality with high sensitivity and specificity in assessing the response to CRT

implantation [7]. CR is also a simple parameter that is easy to do in daily practice. Two meta-analysis about CR in predicting CRT responder were conducted by Ciampi *et al.*, and Kloosterman *et al.*, in 2017 [8], [9]. However, from the two meta-analyzes, the study results were quite heterogeneous. We performed an update meta-analysis by adding three studies with a quite large total sample from three studies. We also evaluate ischemic etiology as factors that related to CRT responder.

CR is a parameter measured by visual myocardium motion and/or LVEF changes by stress echocardiography (SE). The stimulus for SE can be done in 2 ways: Dobutamine or exercise. The aim of this article is to provide a critical assessment of existing studies of CR assessment in predicting CRT responder, provide clinically useful reference values in patients with heart failure, and test its accuracy through meta-analysis.

Methods

This study was conducted in a series of steps in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes guidelines, including searching for articles, assessing the quality of each article, extracting and analyzing data, as well as summary and interpretation of findings [10].

Literature search

We searched all articles assessing CR as a predictor in CRT candidate patients. The search was conducted systematically on various major medical databases (PubMed, Clinical Key, medRxiv, MEDLINE, Cochrane Library, and EMBASE) using keywords: "Contractile reserve," "myocardial viability," "cardiac resynchronization therapy," "CRT," "stress echocardiography," "dobutamine," and "DSE" in the title, abstract, and medical subject heading. Search parameters were limited to clinical trials, fully published studies or studies in progress if preliminary results were published, articles in English, and human studies. Lists of references from the literature matching the inclusion requirements have also been screened manually to find more relevant studies.

Study selection and outcome

We included all studies in which CR was assessed by DSE and/or exercise in response to CRT. The inclusion criteria are; (1) Human studies with adult sample with indications of CRT implantation according to heart failure guideline criteria (NYHA class III and/ or IV, LVEF <35%, and QRS complex \geq 120 ms); (2)

CRT and SE were performed in the same patient population; (3) availability of CR parameter data before and after CRT implantation; (4) clear definition of response to CRT either by clinical or echocardiography assessment; and (5) followed up for at least 6 months post CRT implantation. The exclusion criteria were (1) focus on specific populations (CRT super-responders, post-implantable cardioverter defibrillator implantation population, and patients with aortic stenosis or septal flash); (2) case report study, case series, review, editorial, or conference paper; and (3) missing required data.

Before full-text retrieval, three investigators independently screened and analyzed titles and abstracts. For final inclusion, two authors analyzed the full papers that theoretically met the inclusion/exclusion criteria for final inclusion.

The primary outcome was to predict CRT responder based on CR evaluation using SE. CR is defined as one or a combination of echocardiographic parameters: Increase LVEF and/or decrease myocardial wall contractility score (wall motion score index [WMSI]). The WMSI score is assessed based on a 16 or 17 segment model of LV recommended by the American Society of Echocardiography (ASE). Segments were scored from normal, hypokinetic, akinetic, and dyskinetic. CRT responses were assessed after CRT implantation and compared to preliminary data before CRT implantation. Positive response to CRT (CRT responder) was defined as both clinically (improvement of NYHA class, electrocardiography parameters, and pacemaker data) and by echocardiography parameters (increase LVEF and decrease left ventricular end-systolic volume).

Quality assessment and publication bias

Two investigators assessed the methodological quality of each included article using Newcastle-Ottawa Scale (NOS) for cohort studies [11]. The evaluation of NOS was carried out by considering several factors: Study selection, comparison, and outcomes. Publication bias was assessed using visual inspection of funnel plots and Harbord's regression test.

Data extraction and analysis

Two investigators extracted the data, including authors, year of publication, location, sample size, type of stress, CR criteria, duration of follow-up, and CRT responder criteria. All extracted data were recorded with a dedicated form on an Excel spreadsheet.

Meta-analysis with Mantel-Haenszel fixed-effects model using Review Manager (RevMan v5.3 2014) and Stata v.16 was conducted to assess the relationship between CR and response to CRT. The outcome assessment was measured using the odds

ratio (OR). We performed a subgroup analysis based on types of SE and definition of CR. The sensitivity analysis was performed by excluding studies assessed as having a high risk of bias. Evaluation of heterogeneity between and heterogeneity in the study was carried out using the chi-square test and I^2 . Random-effect model analysis was performed if the I^2 statistic showed more than 50% heterogeneity. Continuous data are presented as mean \pm SD and dichotomous variables are presented as percentages (%). The statistical significance was stated if the p-value was <0.05 . Restricted maximum likelihood random-effects meta-regression was performed for age, sex, LVEF, QRS duration, follow-up, and ischemic etiology.

Results

The initial systematic search returned 752 articles, and 37 relevant articles were added from the main article reference list, for a total of 789 articles. We got 80 full-text studies, and 47 duplicates were excluded, leaving 33 articles. Furthermore, screening the title and abstract according to the inclusion and exclusion criteria eliminated 7 articles. A thorough reading of the full articles of the most recent number of papers resulted in an exclusion of 9 articles, due to follow-up duration <6 months, specific study population, unavailability of stress test intervention data, and unclear definition of CR (Figure 1).

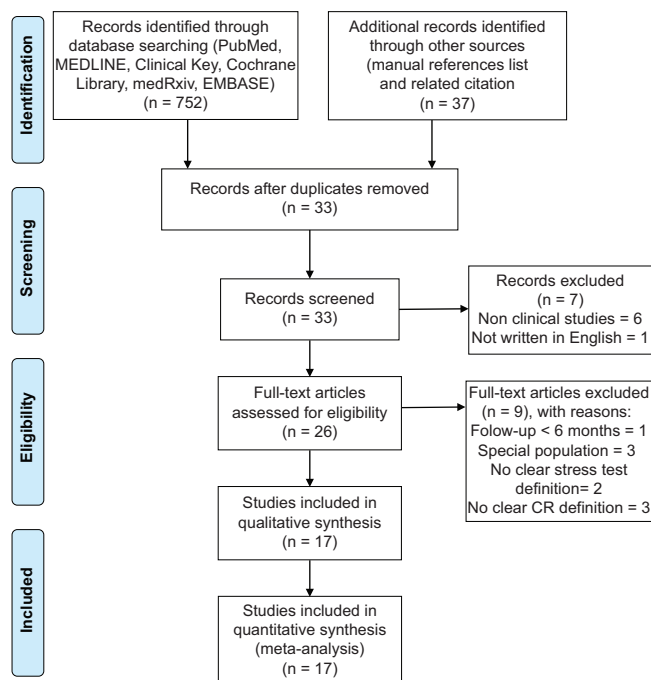


Figure 1: Literature search flow chart based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Seventeen studies with 1399 patients (mean age 66 ± 10 years and 74% men) were included in this meta-analysis. Baseline of the included studies,

populations are presented in Table 1. Ischemic etiology was present in 53% of patients, with mean LVEF at rest of $26 \pm 6\%$, and a QRS complex duration of 157 ± 24 ms. Fifteen studies assessed CR using the DSE and two studies using exercise. Low-dose dobutamine (up to 10 mcg) was obtained in four studies, medium dose (up to 20 mcg) in nine studies and high dose protocols (up to 40 mcg) were obtained in two studies. The mean follow-up duration was 12 months (Table 1). CR defined by increasing in LVEF was found in 9 studies, whereas CR defined by decreasing in WMSI after a SE stimulus was found in 8 studies. One study define CR as either increasing in LVEF or decreasing in WMSI [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28].

From a mean follow-up of 12 months, out of a total of 1399 patients, only 1356 patients were included by the end of the study. This is due to some patients died during follow-up or incomplete paired data at the end of the study. Total 935 patients (68%) were CRT responders based on clinical and echocardiographic criteria. Positive CR was obtained in 908 patients (67%). We found a higher patient prevalence of CRT responder with positive CR (735/935; 79%). Positive predictive value was 81% and negative predictive value was 56% (Table 2).

Although all articles were published in peer-reviewed journals, we assessed methodological quality using NOS (Table 3). Overall, all included studies have fair and good methodological quality. Visual inspection on funnel plot showed symmetry, which indicates no publication bias of all the included studies (Figure 2). Sub-group analysis based on dobutamine or exercise SE also showed symmetry in both sub-groups. Harbord's regression test showed no publication bias in overall included studied ($p = 0.105$) and dobutamine SE subgroup ($p = 0.116$). We did not perform Harbord's regression test on exercise SE because there were <10 studies.

The primary outcome of this meta-analysis was a response to CRT based on baseline CR. Seventeen studies involving 1365 patients reported CR and non-CR on CRT responders (Figure 3). Contractile reserved was obtained in 67% (908/1365) of CRT responder. CR group was associated with a higher CRT responder compared with the non-CR group (OR 7.68; 95% confidence interval [CI] 4.27-13.82; $p < 0.001$). There was significant heterogeneity ($I^2 = 73\%$; $p < 0.001$) for the entire population.

Fifteen studies involving 1250 patients reported CR and non-CR assessed by DSE on response to CRT (Figure 4). CR was found in 66% (831/1250) of patients who responded to CRT. CR group was associated with a higher CRT responder compared with the non-CR group (OR 5.90; 95% CI 3.37-10.34; $p < 0.001$). There was significant heterogeneity ($I^2 = 68\%$; $p < 0.001$). We also performed a subgroup analysis based on CR definition:

Table 1: Baseline characteristics of the studies

Author, Years	Country	n	Male (%)	Age (years)	LVEF (%)	QRS duration	Ischemic (%)	NYHA class III/IV (%)	Stress Type	Dobutamine dose (mg)	CRT Response (Responder)	Contractile reserved	Follow-up (months)
Da Costa, 2005 [9]	France	67	84	64 ± 10	26 ± 5	154 ± 30	34	60/40	Dobutamine	10	Clinical (NYHA, ECG, Pacemaker data)	Increase EF>1.25 fold	20
Ypenburg, 2007 [10]	Netherlands	31	87	71 ± 10	26 ± 7	191 ± 28	65	90/3	Dobutamine	10	Decrease LVESV≥15%	Increase EF>7.5%	6
Lim, 2007 [11]	France	19	74	64 ± 13	27 ± 8	154 ± 25	47	79/21	dobutamine	10	Decrease LVESV	Decrease WMSI≥0.25	6
Tuccillo, 2008 [12]	Italy	42	76	66 ± 9	27 ± 7	144 ± 23	43	88/12	Dobutamine	20	Decrease LVESV≥15%	Increase EF>25%	6
Rocchi, 2008 [13]	Italy	64	75	64 ± 11	29 ± 5	154 ± 25	31	95/5	Exercise	-	Decrease LVESV≥15% and/or increase LVEF>5% (absolute value)	Decrease WMSI≥0.25	6
Ciampi, 2009 [14]	Italy	69	71	70 ± 8	27 ± 6	150 ± 27	55	83/17	Dobutamine	40	Decrease LVESV≥15%	Decrease WMSI≥0.20	11
Lancellotti, 2009 [15]	Belgium	51	63	70 ± 9	27 ± 5	161 ± 25	67	3.1*	Exercise	-	Decrease LVESV≥15%	Increase EF>6.5%	6
Muto, 2010 [16]	Italy	231	72	67 ± 10	27 ± 6	149 ± 24	43	94/6	Dobutamine	20	Decrease LVESV≥10%	Increase EF>5 points	6
Senechal, 2010 [17]	Belgium	49	69	66 ± 12	19 ± 7	164 ± 30	69	67/33	Dobutamine	20	Decrease LVESV≥15%	Decrease WMSI≥0.25	6
Altman, 2011 [18]	USA	31	74	68 ± 12	28 ± 6	158 ± 22	65	90/10	Dobutamine	10	Decrease LVESV≥15%	Increase EF>20% (relative)	24
Gasparini, 2011 [19]	Italy	221	70	67 ± 10	27 ± 6	150 ± 25	43	95/5	Dobutamine	20	Decrease LVESV>10%	Increase EF>5 points	15 ± 5
Chaudhry, 2011 [20]	Netherlands	54	63	69 ± 11	18 ± 5	147 ± 20	59	3.2*	Dobutamine	20	Increase LVEF>5 points	Decrease WMSI≥0.31	7
Pugliese, 2012 [21]	Italy	104	64	71 ± 5	27 ± 4	142 ± 11	87	3.2*	Dobutamine	20	Decrease LVESV≥15% and/or increase LVEF>5%	Decrease WMSI≥0.20	6
Stankovic, 2013 [22]	Norway	58	78	63 ± 10	26 ± 6	175 ± 25	47	3.1*	Dobutamine	20	Decrease LVESV>10%	Increase EF>5%	41 ± 13
Mizia-Stec, 2013 [23]	Poland	129	76	62 ± 9	25 ± 6	164 ± 24	48	90/10	Dobutamine	20	Decrease LVESV≥15%	Decrease WMSI≥0.20	12
Murin, 2014 [24]	Slovak Rep	52	75	62 ± 11	26 ± 7	150 ± 24	48	100/0	Dobutamine	40	Decrease LVESV≥15% and/or increase LVEF>5%	Increase EF>7%	6
Plonska-Gosciniak, 2016 [25]	Poland	127	79	63 ± 9	25 ± 6	163 ± 23	48	76/9	Dobutamine	20	Decrease LVESV>10%	Increase EF>20% or decrease WMSI	12

*Mean NYHA class. CRT: Cardiac resynchronization therapy; ECG: Electrocardiography; EF: Ejection fraction; LVESV: Left ventricular end-systolic volume; NYHA: New York Heart Association; WMSI: Wall motion score index. LVEF: Left ventricular systolic function.

Table 2: CR with SE in patients with CRT responder and non-CRT responder

Author, Years	CRT+, CR +	%	CRT+, CR -	%	CRT-, CR +	%	CRT-, CR -	%	CRT+	%	CR+	%
Da Costa, 2005 [10]	28	42	19	28	6	9	14	21	47	70	34	51
Ypenburg, 2007 [11]	13	42	4	13	2	6	12	39	17	55	15	48
Lim, 2007 [12]	10	53	3	16	0	0	6	31	13	68	10	77
Tuccillo, 2008 [13]	25	59	0	0	2	5	15	36	25	60	27	64
Rocchi, 2008 [14]	41	64	2	3	5	8	16	25	43	67	46	72
Ciampi, 2009 [15]	29	49	5	7	13	22	12	20	34	59	42	71
Lancellotti, 2009 [16]	27	53	3	6	4	8	17	33	30	59	31	61
Muto, 2010 [17]	145	63	25	11	40	17	21	9	170	74	185	80
Senechal, 2010 [18]	30	61	1	2	7	14	11	23	31	63	37	63
Altman, 2011 [19]	11	35	3	10	9	29	8	26	14	45	20	65
Gasparini, 2011 [20]	144	70	16	8	22	11	22	11	160	78	166	81
Chaudhry, 2011 [21]	29	54	2	4	13	24	10	18	31	57	42	78
Pugliese, 2012 [22]	37	38	19	19	14	14	28	29	56	57	51	49
Stankovic, 2013 [23]	15	26	24	41	10	17	9	16	39	67	25	43
Mizia-Stec, 2013 [24]	62	48	42	33	5	4	20	15	104	81	67	52
Murin, 2014 [25]	22	43	6	12	3	6	20	39	28	55	25	49
Plonska-Gosciniak, 2016 [26]	67	53	26	20	18	14	16	13	93	73	85	67

CR: Contractile reserve; CRT: Cardiac resynchronization therapy; SE: Stress echocardiography.

Table 3: NOS quality assessment

Author, Years	Selection	Comparability	Outcome
Da Costa, 2005 [10]	****	*	***
Ypenburg, 2007 [11]	****	*	***
Lim, 2007 [12]	****	*	***
Tuccillo, 2008 [13]	****	*	**
Rocchi, 2008 [14]	****	*	***
Ciampi, 2009 [15]	****	*	***
Lancellotti, 2009 [16]	****	*	**
Muto, 2010 [17]	****	*	**
Senechal, 2010 [18]	****	*	***
Altman, 2011 [19]	****	*	**
Gasparini, 2011 [20]	****	*	***
Chaudhry, 2011 [21]	****	*	***
Pugliese, 2012 [22]	****	*	***
Stankovic, 2013 [23]	****	*	**
Mizia-Stec, 2013 [24]	****	*	**
Murin, 2014 [25]	****	*	***
Plonska-Gosciniak, 2016 [26]	****	*	***

NOS: Newcastle-Ottawa Scale.

Increased LVEF and decreased WMSI score. Sub-group analysis of nine studies included 842 patients which CR was assessed based on increased LVEF showed a similar result: CR group was associated with a higher CRT responder compared with non-CR group (OR 5.10; 95% CI 2.29–11.32; p < 0.001) with significant heterogeneity (I² = 77%; p < 0.001). Six studies included 408 patients, which CR was assessed based on decreased WMSI scores also showed a similar result: CR group was associated with a higher CRT responder compared with non-CR group (OR 5.90; 95% CI 3.37–10.34; p < 0.001) without significant heterogeneity (I² = 21%; p = 0.27).

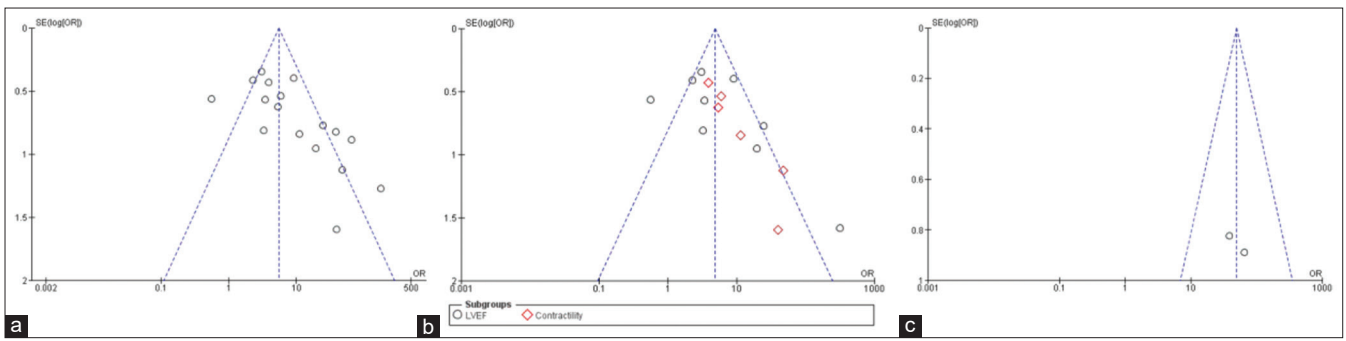


Figure 2: Funnel plots of study outcome showed no publication bias for (a) all included studies ($p = 0.105$); (b) dobutamine stress echocardiography ($p = 0.116$); (c) exercise stress echocardiography

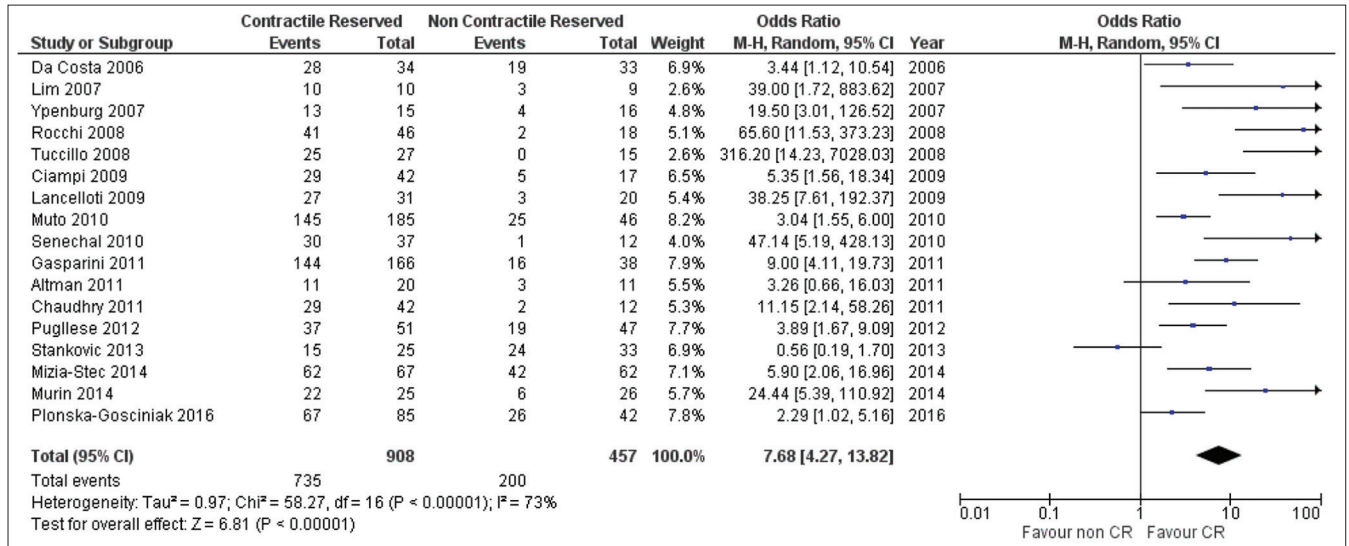


Figure 3: Forest plots of cardiac resynchronization therapy responder based on contractile reserve in all included studies

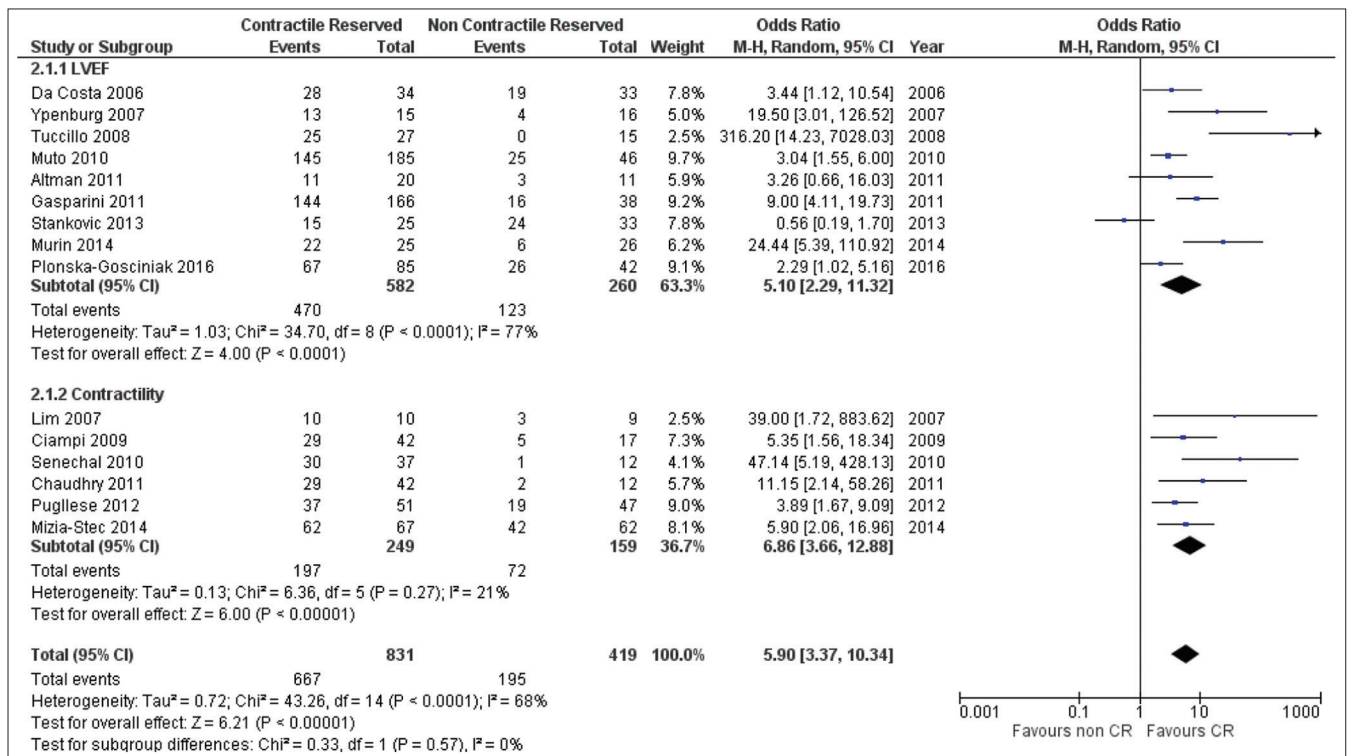


Figure 4: Forest plots of cardiac resynchronization therapy responder based on contractile reserve assessed by dobutamine stress echocardiography

Two studies involving 115 patients reported CR and non-CR assessed by exercise SE on CRT responder (Figure 5). CR was found in 67% (77/115) of patients who responded to CRT. CR group was associated with a higher CRT responder compared to non-CR group (OR 49.11; 95% CI 15.04–60.36; $p < 0.001$) without any significant heterogeneity ($I^2 = 0\%$; $p = 0.66$).

Random-effects meta-regression analysis showed that the association between CR and CRT responder was not significantly affected by age ($p = 0.451$), sex ($p = 0.612$), LVEF ($p = 0.978$), QRS duration ($p = 0.968$), follow-up ($p = 0.259$), and ischemic etiology ($p = 0.821$).

We also performed a group analysis of 13 studies that included ischemic etiology with CRT responder (Figure 6). The overall OR benefit of CRT in ischemic etiology was 0.41 (95% CI 0.31–0.55, $p < 0.01$) without significant heterogeneity ($I^2 = 32\%$; $p < 0.15$).

Discussion

CRT has shown considerable potential to improve outcomes in patients with severe chronic heart failure. Large studies showed that CRT could improve

symptoms of heart failure, LV function, exercise capacity, and reduce morbidity and mortality [29], [30]. Several previous studies have also demonstrated the efficiency of mechanical resynchronization in ischemic and non-ischemic cardiomyopathy. However, 40% of patients who underwent CRT implantation did not respond well enough so that other criteria were needed in selecting CRT patient candidates [29], [30]. Myocardial viability is one of the current factors in clinical practice. Myocardial viability can be measured by SE by looking at the presence of CR. The presence of CR increases the possibility of a positive CRT response and could be one of the considerations in selection of CRT candidates. SE defined groups with a better prognosis of enhancing clinical and functional conditions after CRT implantation in the CR evaluation [8].

In 2016, ESC guidelines regarding the diagnosis and management of heart failure, clinical symptoms, ejection fraction, and QRS complex duration are still major criteria for identifying heart failure patients as CRT candidates [3]. ESC guidelines suggest an exercise or pharmacological SE for the assessment of myocardial viability and/or myocardial ischemia but do not mention SE to identify CRT responder [3].

Mechanical dyssynchrony has been described as the regional contraction discrepancy or an uncoordinated, unequaled regional myocardial motion [31]. Left bundle branch block (LBBB) may trigger

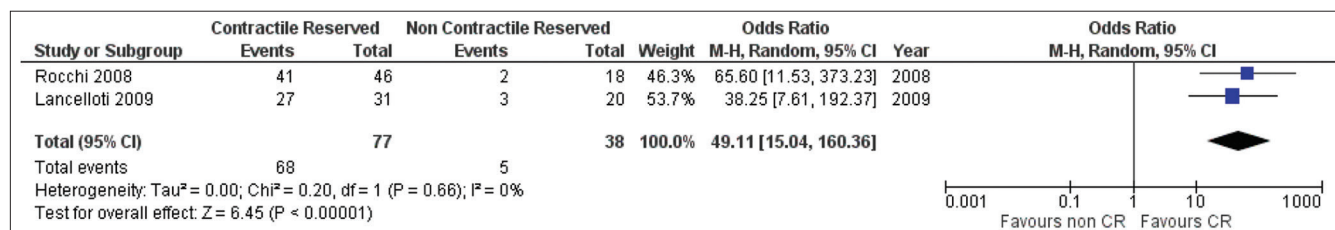


Figure 5: Forest plots of cardiac resynchronization therapy responder based on contractile reserve assessed by exercise stress echocardiography

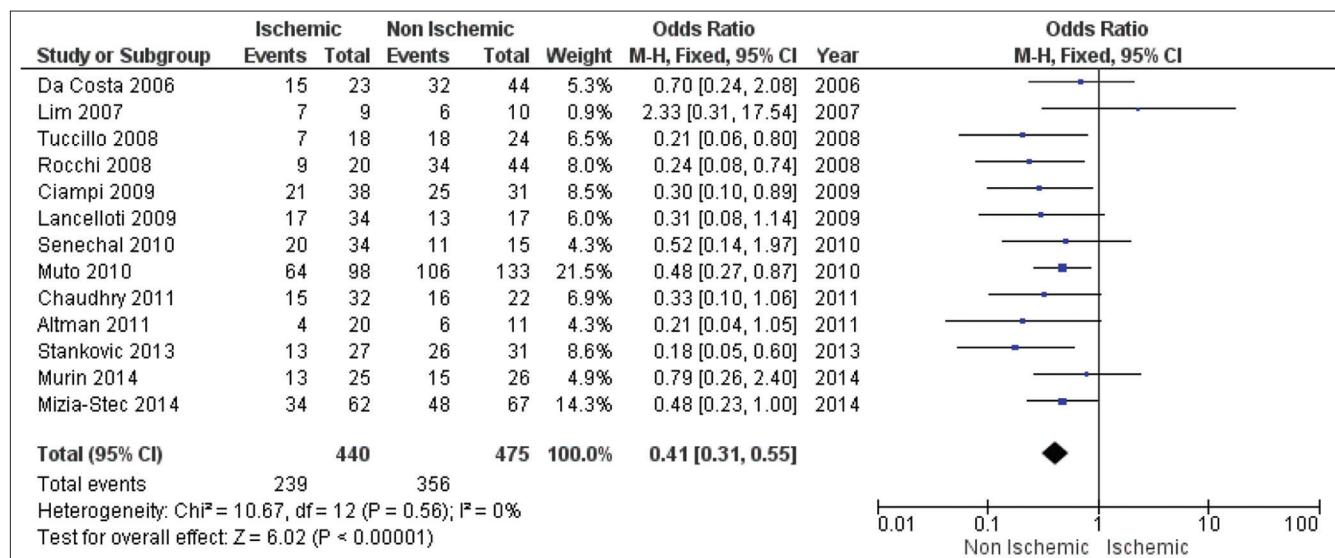


Figure 6: Forest plots benefit of cardiac resynchronization therapy towards ischemic etiology

a dyssynchrony. Not all ECG with LBBBs reflect a true delay in LV activation. A LV endocardial mapping study has demonstrated that up to one-third of LBBB patients are misdiagnosed [32]. The true LBBB activation induces a peculiar pattern contraction of opposing wall motions (septal flash) with apical rocking movement. Septal flash and apical rocking are two parameters that are widely recommended to assess mechanical dyssynchrony. However, these two parameters have disadvantages, such as; apical rocking sometimes depend on the RV function and there are differences between observers, also there is bias in translation of continuous process to on/off phenomenon in septal flash measurement [31]. Most studies investigated wall movement with echocardiography did not specify the cause of dyssynchronous conditions, whether it was due to electrical activation delayed (broad QRS) or the loading and/or contractile properties. This lack of relation between mechanical and electrical dyssynchrony presumably accounts controversy over echo-dyssynchrony measurement for patient selection and CRT response.

We conducted a systematic review and meta-analysis for the relationship between CR assessed by SE in predicting response to CRT. We found the clinical benefit of SE in CRT responder (OR 7.68; 95% CI 4.27–13.82; $p < 0.001$). Of the 15 studies assessing CR by DSE, the parameter of reduction in WMSI scores was slightly better than the increase in LVEF (OR 6.86 vs. 5.10) in predicting CRT responder. Contractile reserved assessed by exercise SE showed very high OR (OR 49.11; 95% CI 15.04–160.36; $p < 0.001$). However, only two studies evaluated contractile reserved assessed by exercise SE, more study is needed to draw a conclusion that exercise is better than DSE in predicting CRT responder.

Our results are consistent with previous studies and the recommendations of the European Association of Cardiovascular Imaging and ASE that clinical assessment of SE can be performed beyond coronary artery disease [8], [9], [32]. The absence of CR is a strong determinant of outcome and a potential marker of negative response to CRT [33]. Actually, no reliably echocardiographic dyssynchrony measurements have been shown to predict the CRT responder. Several studies even suggest that the CR tends to be a stronger response predictor and offers incremental value above dyssynchrony measurements [9], [21]. This result also shifts the topic of functional response to the myocardial substrate from mechanical and electrical dyssynchrony. It is possible that similar information can be obtained with other techniques myocardial viability testing with metabolic, structural, or functional markers, such as delayed enhancement, nuclear imaging, or low-dose dobutamine magnetic resonance [8].

CR appears to be present independently of HF etiology. Previous meta-analysis found that there were no significant differences in the proportion of patients

with ischemic and non-ischemic cardiomyopathy [9]. From our meta-analysis, we found that patient with non-ischemic etiology has better respond to CRT compare to patient with ischemic etiology (OR 0.41; 95% CI 0.31–0.55, $p < 0.01$). This indicates the myocardium itself has a lack of contractility due to metabolic and/or ultrastructural changes in ischemic patient. In any event, monitoring of the CR tends to be an essential modality for ensuring the response in patients expected to have a high response rate of non-ischemic etiology [9].

Limitations of this meta-analysis were the substantial heterogeneity between studies. This heterogeneity could be due to different SE administration (exercise and dobutamine), different CR parameters, and different CRT responder criteria. For the SE group with dobutamine, heterogeneity could be caused by different dobutamine doses, ranging from 10 to 40 mcg. For the same stress at the same dose, the CR parameters differed across studies (EF and WMSI), and when the parameters were the same, varied cutoffs were used in each studies (Table 1). Heterogeneity was substantially decreased in the dobutamine study with WMSI parameter ($I^2 = 21\%$) compared with EF ($I^2 = 77\%$) and overall analysis ($I^2 = 68\%$).

Conclusion

Our meta-analysis shows that the presence of CR assessed by both dobutamine and exercise SE is associated with a better positive CRT response. These results can serve as the basis for updating the guidelines for the management of severe heart failure, which currently recommends clinical symptoms, ejection fraction, and QRS complex duration to identify CRT candidates.

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