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CLINICAL INVESTIGATIONS

Changes in parameters of right ventricular function with cardiac resynchronization therapy

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Background: Studies have shown that cardiac resynchronization therapy (CRT) significantly improves right ventricle (RV) size and function in patients with heart failure (HF).

Hypothesis: CRT does not lead to improvement in RV function independent of baseline clinical variables.

Methods: A systematic search of studies published between 1966 to August 31, 2015 was conducted using Pub Med, CINAHL, Cochrane CENTRAL and the Web of Science databases. Studies reporting tricuspid annular plane systolic excursion (TAPSE) or RV basal strain or RV long axis diameter or RV short axis diameter or RV fractional area change (FAC), before and after CRT, were identified. A meta-analysis was performed using random effects with inverse variance method to determine the pooled mean difference in various parameters of RV function after CRT. Meta-regression analysis was performed to test the relationship between change in various parameters of RV functions after CRT and covariates- age, QRS duration, and left ventricular ejection fraction (LVEF).

Results: Thirteen studies (N=1541) were selected for final analysis. CRT therapy led to statistically significant increases in TAPSE [1.21 (95% CI 0.55-1.86; p<0.001)], RV FAC [2.26 (95% CI 0.50-4.01; p<0.001)] and basal strain [2.82 (95% CI 0.59-5.05; p<0.001)] and statistically significant decreases in mean RV long axis diameter [-2.94 (95% CI -5.07- -0.82; p=0.005)] and short axis diameter [-1.39 (95% CI -2.10- -0.67; p=0.876)] after a mean follow up period of 9 months. However, after meta-regression analysis for age, QRS duration, and baseline LVEF as covariates, there was no significant improvement in any of the parameters of RV function after CRT.

Conclusion: There was a statistically significant improvement in TAPSE, RV basal strain, RV fractional area, RV long axis and short axis with CRT. However, improvement in these echocardiographic parameters of RV function after CRT was not independent of baseline clinical variables but statistically dependent on age, QRS duration and baseline LVEF.

KEYWORDS
right ventricular function, cardiac resynchronization therapy

1 | INTRODUCTION

Right ventricular (RV) function has been shown to an independent predictor of survival and plays an important role in risk stratification of heart failure (HF) patients.[1,2] RV dysfunction has been associated with adverse clinical outcomes in patients with HF and plays an important role in determining the response to medical therapy in patients with HF.[3]

Cardiac resynchronization therapy (CRT) has been shown to improve left ventricular (LV) ejection fraction (LVEF), decrease intraventricular mechanical dyssynchrony, and cause favorable LV remodeling in HF patients with markedly abnormal electrocardiographic QRS duration.[4,5] Improvement in LV function due to CRT results in significant improvement of quality of life and exercise tolerance and reduction in rate of rehospitalization and mortality.[6–8] Recently, studies have shown that CRT significantly improves RV size and function in patients with HF.[8–12] However, improvements in RV size and function post-CRT could be secondary to improvement in LV function. Possible confounding effects of age, QRS duration, and baseline LVEF were not evaluated in prior studies.[8–12]

In this study, we performed a meta-analysis and meta-regression analysis of published studies to evaluate the relationship of CRT on various echocardiographic parameters of RV function after adjusting for the above-mentioned potential confounders.

2 | METHODS

2.1 | Study design

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

2.2 | Data sources and search strategy

We systematically searched PubMed, CINAHL, Cochran Central, Scopus, and Web of Science databases for all studies that reported parameters of RV function before and after CRT implantation. All relevant combinations of following keywords related to cardiac resynchronization therapy were searched: RV function, tricuspid annular plane systolic excursion (TAPSE), RV diameters (RV short-axis and long-axis diameters), RV fractional area change (FAC), age, QRS duration, baseline LVEF, and pulmonary artery (PA) pressure. The search was conducted from the inception of these databases to May 31, 2016. No language or age restrictions were applied. Pertinent trials were also searched in http://www.clinicaltrials.gov and in the proceedings of major international cardiology meetings (American College of Cardiology, American Heart Association, European Society of Cardiology, and Heart Rhythm Society).

2.3 | Study selection

Studies were included in the meta-analysis if they met the following criteria: (1) a study on human subjects with participants of any age requiring CRT for any indication; and (2) studies reporting TAPSE, RV basal strain, RV long-axis diameter, RV short-axis diameter, or RV FAC as absolute number (with SDs) before and after CRT. Studies that did not provided absolute number for RV parameters before and after CRT therapy were excluded from the final analysis. Similarly, studies that did not report SD for parameters of RV function before and after CRT were also excluded.

2.4 | Data extraction

Two independent reviewers (AS, SG) screened the titles and abstracts for relevance. Discrepancies between reviewers were discussed until consensus was reached. The manuscripts of selected titles/abstracts were reviewed for inclusion and authors were contacted if additional data were needed. Using the above-mentioned selection criteria, these 2 reviewers independently determined the articles to be included and excluded, and data from the relevant articles were extracted using predefined extraction forms. Any disagreements in data extraction were discussed until consensus was reached.

2.5 | Data analysis

To analyze the data, the authors used MIX 2.0 Pro software (BiostatXL). A random-effects model with inverse-variance weighting was used to calculate pooled mean difference in RV measure and corresponding confidence interval (CI). Heterogeneity between studies was assessed using the Cochrane Q test and I^2 statistic, which denotes the percentage of total variation across studies that is a result of heterogeneity rather than chance. Heterogeneity was considered significant if the P value was <0.05. Publication bias was assessed by the Begg test and Egger regression test. The influence of individual studies was examined by removing each study one at a time to assess the degree to which meta-analysis estimate depends on a particular study (exclusion sensitivity analysis). Subsequently, meta-regression analysis for age, QRS duration, and baseline LVEF as covariate was performed to test the relationship between changes in various parameters of RV function after CRT.

2.6 | Study outlines and characteristics

A total of 13 studies were identified (N = 1541; see Supporting Information, Figure 1, in the online version of this article) that reported outcomes of interest.[8,9,14–24] A study by Campbell et al. could not be included in our analysis as the authors reported percentage change in echocardiographic parameters from baseline rather than providing absolute numbers for RV parameters before and after CRT therapy.[10] Similarly, a study by Damy and colleagues was not included in the final analysis as SD for parameters of RV function was not reported.[25] Sample size ranged from 16 to 738 subjects. Baseline characteristics of various studies and patient characteristics are summarized in Table 1. Publication bias was not detected by the Begg and Egger regression tests for any of the RV measures.

3 | RESULTS

3.1 | TAPSE

Eleven studies (N = 1422) with a mean patient age of 64.3 years reported TAPSE before and after CRT implantation, demonstrating that CRT led to a statistically significant increase in TAPSE (mean difference 1.32, 95% CI: 0.67 to 1.96, P < 0.001) after a median follow-up period of 6 months (interquartile range [IQR], 0.25–32 months; Figure 1, Table 2). There was significant heterogeneity across the studies (I^2 = 83%; P < 0.001). Sensitivity analysis demonstrated that pooled estimate did not change with exclusion of any one study for both effect size measures.

Meta-regression analysis showed significant association between age, QRS duration, LVEF, and PA pressure, and mean differences in TAPSE (Figure 1, Table 2).

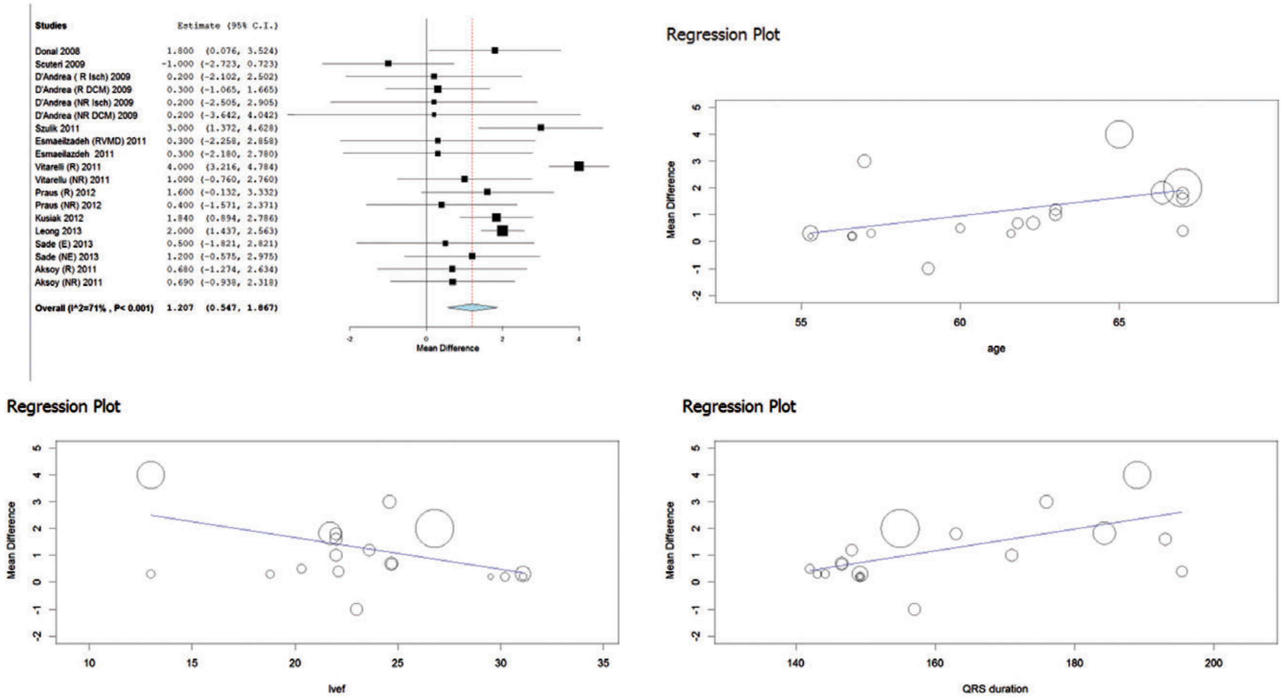

FIGURE 1 (A) Forest plot for change in TAPSE with CRT, followed by random-effects meta-regression analysis plots depicting the relationship between mean differences in TAPSE (on y-axis) and (B) age, (C) LVEF, and (D) QRS duration (on x-axis). Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was significant association between age (β = 0.137, *P* = 0.047), QRS duration (β = 0.041, *P* = 0.006), and LVEF (β = −0.118, *P* = 0.03) and mean differences in TAPSE. Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion

3.2 | RV basal strain

Five studies (N = 308) with a mean patient age of 62.9 years reported RV basal strain before and after CRT implantation. CRT led to a statistically significant increase in RV basal strain (mean difference 2.83, 95% CI: 0.68 to 4.97, *P* = 0.001) after a median follow-up period of 6 months (IQR, 0.25–32 months; Figure 2, Table 2). There was low heterogeneity across the studies (I^2 = 18%; *P* = 0.28). Sensitivity analysis demonstrated pooled estimate did not change with exclusion of any one study for both effect size measures. Meta-regression analysis showed significant association between age and RV basal strain change, but the results were not significant for QRS duration and LVEF (Figure 2, Table 2).

3.3 | RV fractional area change

Six studies (N = 1043) with a mean age of 65.1 years reported RV FAC before and after CRT implantation. CRT led to a statistically significant increase in RV FAC (mean difference 2.88, 95% CI: 0.94 to 4.83, *P* = 0.004) after a median follow-up period of 6 months (IQR, 0.25–18 months; Figure 3, Table 2). There was significant heterogeneity across the studies (I^2 = 63%; *P* = 0.001). Sensitivity analysis demonstrated pooled estimate did not change with exclusion of any one study for both effect size measures. Meta-regression analysis showed a significant association between QRS duration and mean differences in RV FAC. However, there was no significant impact of either age or LVEF on pooled estimate of RV FAC change (Figure 3, Table 2).

3.4 | RV long- and short-axis diameters

RV long-axis and short-axis diameters before and after CRT were reported in 4 studies (N = 270; mean age, 60.7 years) and 6 studies (N = 384; mean age, 62.4 years), respectively. CRT led to a statistically significant decrease in mean RV long-axis diameter (mean difference 2.95, 95% CI: −5.07 to −0.83, *P* = 0.01) and short-axis diameter (mean difference −1.39, 95% CI: −2.11 to −0.67, *P* < 0.001) after median follow-up periods of 6 months (IQR, 3–6 months) and 6 months (IQR, 3–15 months), respectively (Figures 4 and 5, Table 2). There was significant heterogeneity across the studies for RV long-axis diameter (I^2 = 66%; *P* = 0.004), whereas no heterogeneity was detected for RV short-axis diameter measurements (I^2 = 0%; *P* = 0.87). Sensitivity analysis demonstrated pooled estimate did not change with exclusion of any one study for both effect size measures. On meta-regression, no significant associations were found between age, QRS duration, or LVEF and mean differences in either RV short-axis or long-axis diameters (Figures 4 and 5, Table 2).

4 | DISCUSSION

These results, based on analysis of 1541 patients from 13 studies, demonstrate that CRT leads to improvements in TAPSE, RV basal strain, RV fractional area, and RV long-axis and short-axis diameters; however, the improvements in echocardiographic parameters of RV function after CRT were dependent on age, QRS duration, and baseline LVEF. Our results suggest that improvements in RV size

TABLE 1 Baseline study and patient characteristics

Study	Study Objective	Patient Population	Follow-up, mo	Imaging Modalities Used	RV Parameters Measured	LVEF, %	Mean Age, y	Male Sex, %	NYHA Class III/IV, %	Mean QRS Duration, ms	LBBB/RBBB, %	Ischemic, %
Bleeker et al. 2005	To evaluate RV remodeling after CRT	56 consecutive patients with severe HF scheduled for implantation of BVP were prospectively studied	6	Echo, TDI	Tricuspid valve annulus, RV short axis, RV long axis	19 ± 6	64	79	89/11	176 ± 30	—	52
Donal et al. 2008	To assess the early effects of CRT on RV function using myocardial strain analysis	50 patients with severe systolic HF selected for implantation of BVP were prospectively studied	3	Echo, TDI	TAPSE, RV strain, RV short axis, RV long axis	22 ± 6	67	75	68/32	163 ± 28	—	45
Scuteri et al. 2009	To evaluate whether baseline indexes of RV function and RV dimension affect response to CRT; to assess CRT response in patients with baseline severe RV dysfunction	44 consecutive patients with HF selected for implantation of BVP were prospectively studied	6	Echo, TDI	TAPSE, RV systolic PAP, RVEDA, RVESA, RV FAC	23 ± 5	59	81	—	157 ± 25	—	31
D'Andrea et al. 2009[a]	To analyze RV myocardial function in patients with either idiopathic or ischemic DCM without overt clinical signs of right HF by speckle tracking 2D strain; to assess possible different effects of CRT on RV myocardial strain	110 patients with either idiopathic (n = 60) or ischemic (n = 50) DCM and severe HF enrolled for implantation of a BVP were prospectively studied. Patient population was further divided into responder and nonresponder to CRT based on improvement in LVEF in both idiopathic and ischemic groups.	6	Echo, TDI	RV diameter, TAPSE, RV long axis and short axis, RV FAC, RV Tei strain, RV strain, RVEDA, RVESA	30.2 ± 5.2	57	52	82/18	149.2 ± 22.1	—	100
D'Andrea et al. 2009[b]						31.1 ± 3.1	55	55	82/19	149.2 ± 22.1	—	0
D'Andrea et al. 2009[c]						31.1 ± 3.2	57	52	82/18	149.2 ± 22.1	—	100
D'Andrea et al. 2009[d]						29.5 ± 5.1	55	55	82/18	149.2 ± 22.1	—	0
Aksoy et al. 2011[e]	To determine echo correlates of improvement in RV	54 consecutive patients with HF scheduled for CRT were prospectively studied.	6	Echo, TDI	RV FAC, TAPSE, RVEDD, RV strain, RVEDA, RVESA	24.68 ± 4	62	76	—	146.64 ± 25.94	89/11	64

(*Continues*)

TABLE 1 (Continued)

Study	Study Objective	Patient Population	Follow-up, mo	Imaging Modalities Used	RV Parameters Measured	LVEF, %	Mean Age, y	Male Sex, %	NYHA Class III/IV, %	Mean QRS Duration, ms	LBBB/RBBB, %	Ischemic, %
	systolic function after CRT	Patients were divided into responders and nonresponders to CRT based on % change in LVESV.										
Aksoy et al. 2011[f]						24.68 ± 5	62	87	–	146.64 ± 25.94	87/13	87
Szulik et al. 2011	To evaluate if baseline RV function and TDI-derived dyssynchrony could have incremental value over LV dyssynchrony measures for predicting CRT response	90 consecutive patients with chronic HF who fulfilled required criteria for CRT were retrospectively examined.	18	Echo, TDI	RVEDA, RVESA, RV FAC, TAPSE, RVSP, RV dyssynchrony	24.6 ± 7.6	57	62	64/36	176 ± 29	88/–	41
Esmaeilzadeh et al. 2011[g]	To evaluate the prevalence and severity of the RV dyssynchrony before and early after CRT via strain imaging	36 patients with severe LV systolic dysfunction receiving CRT were prospectively studied. The patients were further divided into 2 groups based on RVMD.	1 wk	Echo, TDI	RV size, TAPSE, RV FAC, RV strain, RVEDA, RVESA	18.8 ± 5.5	62	58	–	143.1 ± 19.5	53/6	48.3
Esmaeilzadeh et al. 2011[h]						19 ± 5.6	57	58	–	144.2 ± 14.8	53/7	50
Vitarelli et al. 2011[i]	To analyze the evolution of LV and RV parameters before and after CRT	81 patients with DCM were prospectively studied before and after CRT. Patients were further divided into responders and nonresponders to CRT based on percentage change in LVESV.	6	Echo, TDI, speckle tracking imaging	RVEF, TAPSE, RV FAC, RV Tei strain, RV strain, RVEDA, RVEDV	19 ± 11	65	64	–	189 ± 24	–	58
Vitarelli et al. 2011[j]						22 ± 8	63	68	–	171 ± 22	–	68
Praus et al. 2012[k]	To evaluate echocardiographic changes in clinical responders and	58 consecutive patients in whom a biventricular system (35 patients with CRT-D and 23 patients with	15	Echo	RV diameter, TAPSE	22.0 ± 5.4	67	–	–	193.0 ± 28.3	–	47

(*Continues*)

TABLE 1 (Continued)

Study	Study Objective	Patient Population	Follow-up, mo	Imaging Modalities Used	RV Parameters Measured	LVEF, %	Mean Age, y	Male Sex, %	NYHA Class III/IV, %	Mean QRS Duration, ms	LBBB/RBBB, %	Ischemic, %
	nonresponders to CRT	CRT only) were prospectively studied. The patients were divided to responders and nonresponders based on clinical response.										
Praus et al. 2012[l]						22.1 ± 6.9	67	—	—	195.4 ± 42.0	—	74
Kusiak et al. 2012	To evaluate the short-term effect of CRT on RV function	57 consecutive patients who underwent implantation of a BVP (CRT-P) or a defibrillator (CRT-D) for drug-refractory HF were prospectively studied.	3	Echo	RV size, TAPSE, RV FAC, RV strain, RVEDA, RVESA, RVSP, RV thickness	21.7 ± 4.81	66	95	—	184.23 ± 28.31	—	72
Leong et al. 2013	To assess the prognostic importance of RV function among CRT recipients; to characterize RV functional change following CRT and its determinants.	905 consecutive patients from the registry of CRT recipients at Leiden University Medical Center were prospectively studied.	6	Echo	TAPSE, RVSP	26 ± 8	67	78	68/9	155 ± 33	68/—	60
Sade et al. 2013[m]	To investigate the impact of RV function on the long-term outcomes of patients undergoing CRT	120 consecutive patients with HF undergoing CRT were prospectively studied. The patients were further divided into responders and nonresponders to CRT based on clinical events.	32	Echo, TDI	RV transverse diameter, RV systolic and diastolic areas, TAPSE, RV free wall strain	21 ± 5	60	82	—	142 ± 21	68/13	71
Sade et al. 2013[n]						24 ± 6	63	81	—	148 ± 22	72/5	53
Knappe et al. 2013	To assess if the benefits observed with CRT are due to the short-term effects of improvement in synchrony/contractile	63 patients enrolled in the MADIT-CRT trial after 1 year of CRT therapy underwent echocardiographic evaluation with CRT turned both on and off within minutes	12	Echo, speckle tracking imaging	RV FAC, RVEDA, RVESA	24 ± 5	64	81	0	162 ± 26	78	51

(*Continues*)

TABLE 1 (Continued)

Study	Study Objective	Patient Population	Follow-up, mo	Imaging Modalities Used	RV Parameters Measured	LVEF, %	Mean Age, y	Male Sex, %	NYHA Class III/IV, %	Mean QRS Duration, ms	LBBB/RBBB, %	Ischemic, %
	performance or are secondary to long-term improvement in ventricular structure and function by CRT											

Abbreviations: 6MWT, 6-min walk test; BVP, biventricular pacing/pacemaker; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DCM, dilated cardiomyopathy; echo, echocardiography; FAC, fractional area change; HF, heart failure; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; PAP, pulmonary artery pressure; RBBB, right bundle branch block; RV, right ventricular; RVEDA, right ventricular end-diastolic area; RVEDD, right ventricular end-diastolic diameter; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESA, right ventricular end-systolic area; RVMD, right ventricular mechanical dyssynchrony; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging.

[a] Responder ischemic DCM.

[b] Responder idiopathic DCM.

[c] Nonresponder ischemic DCM.

[d] Nonresponder idiopathic DCM.

[e] Responder (defined as decline in LVESV ≥10%).

[f] Nonresponder (defined as decline in LVESV <10%).

[g] Patients with regional RVMD.

[h] Patients without RVMD.

[i] Responders to CRT, according to the predefined criterion of a reduction in LVESV by >15%.

[j] Nonresponders to CRT, including the 2 patients who died before the 6-month follow-up.

[k] Responder (patients in whom quality of life, NYHA class, and/or 6MWT improved [improvement of ≥1 NYHA class, 6MWT by >10%] and who were neither in hospital for HF nor died for cardiac reasons were categorized as clinical responders).

[l] Nonresponder (patients who do not meet above criteria).

[m] Patient with events (death, heart transplantation, and assist device implantation).

[n] Patient without events (no death, heart transplantation, or assist device implantation).

TABLE 2 Results summary

		Meta Regression Analysis		
	Mean Difference (95% CI)	Age	QRS Duration	LVEF
TAPSE	1.32 (0.67 to 1.96), $P < 0.001$	β: 0.137, $P = 0.047$	β: 0.041, $P = 0.006$	β: −0.118, $P = 0.03$
RV basal strain	2.83 (0.68 to 4.97), $P = 0.001$	β: 0.664, $P = 0.04$	β: 0.156, $P = 0.577$	β: 0.144, $P = 0.15$
RV FAC	2.88 (0.94 to 4.83), $P = 0.004$	β: −0.044, $P = 0.84$	β: 0.139, $P = 0.019$	β: 0.035, $P = 0.87$
RV long-axis diameter	−2.95 (−5.07 to −0.83), $P = 0.01$	β: 0.043, $P = 0.86$	β: −0.134, $P = 0.185$	β: 0.097, $P = 0.684$
RV short-axis diameter	−1.39 (−2.11 to −0.67), $P < 0.001$	β: 0.098, $P = 0.201$	β: 0.019, $P = 0.31$	β: −0.092, $P = 0.299$

Abbreviations: CI, confidence interval; FAC, fractional area change; LVEF, left ventricular ejection fraction; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

and function after CRT were not independent of baseline clinical variables.

There have been conflicting reports on the effects of CRT on RV function. The most robust data on CRT currently available are from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial, which included 1820 patients with mild symptoms of HF (New York Heart Association class I–II).[10] The results from this trial showed that CRT was associated with an improvement in RV function as assessed by RV FAC.[10] Furthermore, patients with the best RV function at 1 year were reported to have lower event rates (defined as composite endpoint of all-cause mortality or a nonfatal HF event), and every 5-point increase in RV FAC was associated with a 22% reduction in event rates.[10] However, better clinical outcomes among patients with improved RV function were not independent of improvements in LV function.[10] In a study by Donal et al[9] using tissue Doppler imaging to assess RV function, improved RV contractility after CRT was observed. They reported an improvement in lateral tricuspid annular velocity, RV lateral wall basal and mid strain. These findings were persistent after a follow-up period of 3 months, although the same was not evident for other RV variables, such as TAPSE and RV diameters.[9] In another study, Bleeker et al[8] reported that CRT causes favorable RV remodeling within 6 months of follow-up in terms of improvement in RV size (diameters), tricuspid regurgitation, and PA pressures, which was more evident in patients with baseline RV dilation and LV dyssynchrony, suggesting the benefit of CRT even in patients with altered RV dimensions.[8] However, Scuteri and colleagues reported no significant improvements in RV dimensions and function with CRT therapy.[14] In another study, Boriani et al[26] showed no improvement in RV ejection fraction (RVEF) after 3 months following CRT with radionuclide angiography. Similarly, in the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, no significant increases in TAPSE were observed in the CRT group compared with the control group.[27] Furthermore, in post-hoc analysis of 688 patients from the Cardiac Resynchronization in Heart Failure (CARE-HF) study, no significant improvements in

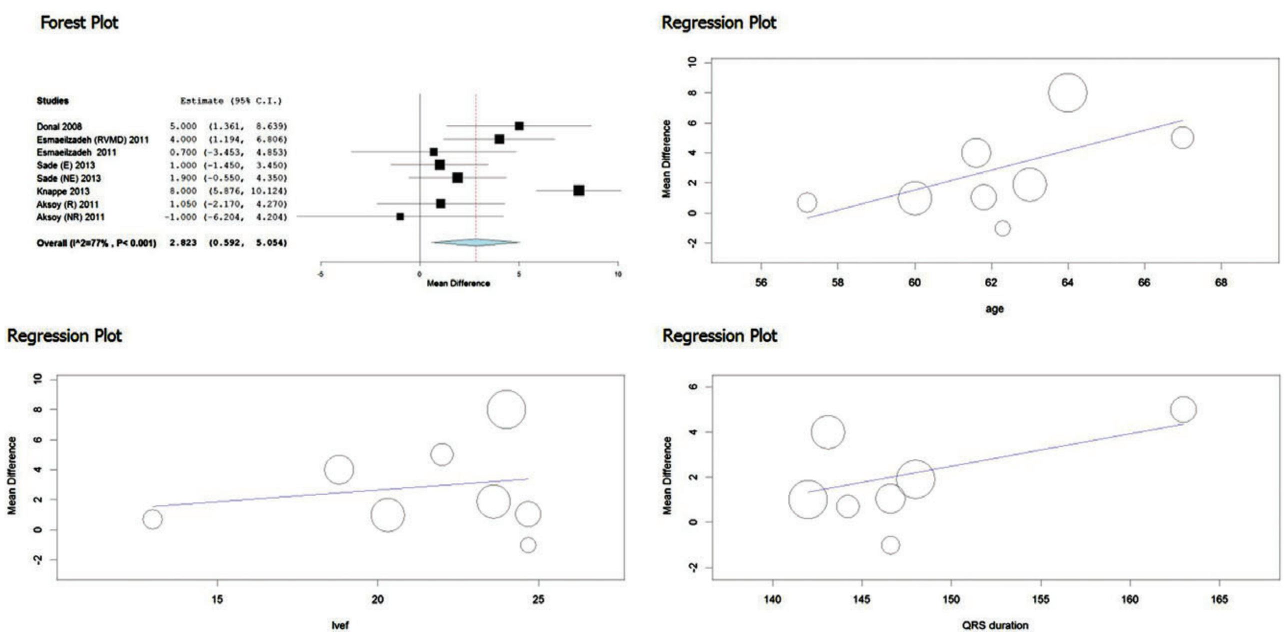

FIGURE 2 (A) Forest plot for change in RV basal strain with CRT, followed by random-effects meta-regression analysis plots depicting the relationship between mean differences in RV basal strain (on y-axis) and (B) age, (C) LVEF, and (D) QRS duration (on x-axis). Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was significant association between age and RV basal strain change (β = 0.664, $P = 0.04$), but the results were not significant for QRS duration (β = 0.156, $P = 0.577$) and LVEF (β = 0.144, $P = 0.15$). Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; RV, right ventricular

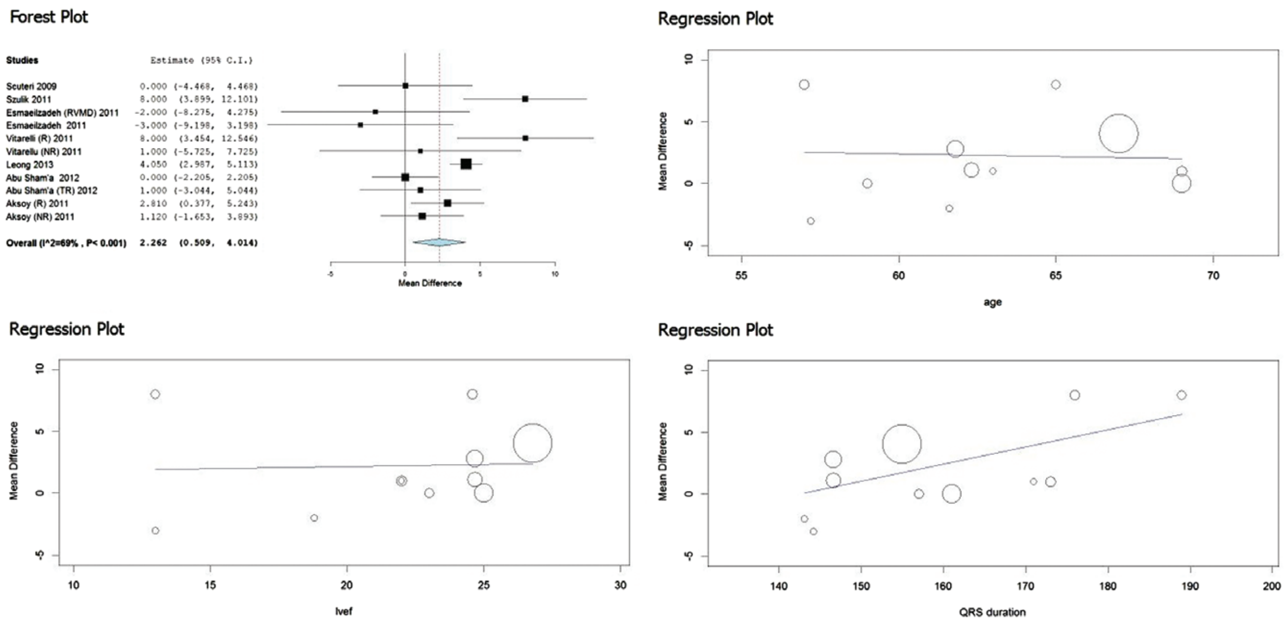

FIGURE 3 (A) Forest plot for mean difference in RV FAC with CRT, followed by random-effects meta-regression analysis plots depicting the relationship between mean difference in RV FAC (on y-axis) and (B) age, (C) LVEF, and (D) QRS duration (on x-axis). Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was significant association between QRS duration and mean differences in RV FAC (β = 0.139, *P* = 0.019), but the results were not significant for age (β = −0.044, *P* = 0.84) and LVEF (β = 0.035, *P* = 0.87). Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; FAC, fractional area change; LVEF, left ventricular ejection fraction; RV, right ventricular

TAPSE or RV dimensions were reported in patients who received CRT therapy.[25]

To our knowledge, this is the first meta-analysis to evaluate the impact of CRT therapy on various echocardiographic parameters of RV function, after adjusting for age, baseline QRS duration, and LVEF. We have reported outcomes of CRT on RV function in 1541 patients from 13 studies, with a mean follow-up period of almost 9 months. Due to the asymmetric shape and complex geometry of the RV, use of a single echocardiographic parameter might not be sufficient to comprehensively assess RV function. Therefore, in our meta-analysis we have used various echocardiographic parameters of RV function to analyze the effect of CRT on RV function. Most of the studies

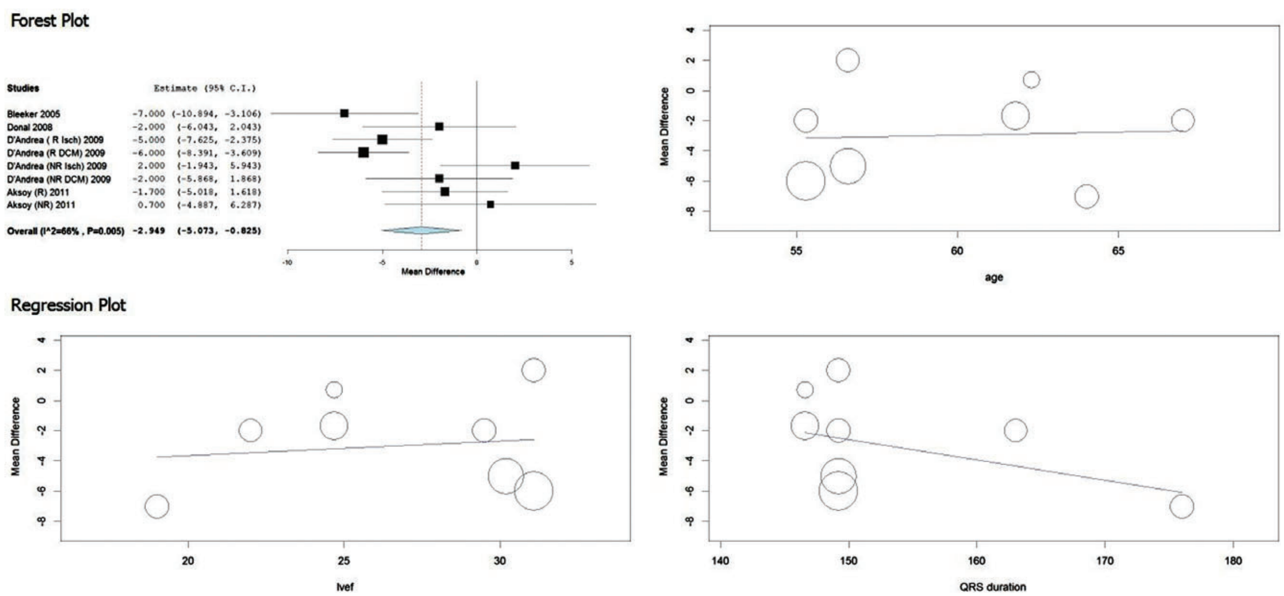

FIGURE 4 (A) Forest plot for mean difference in RV long-axis diameter with CRT, followed by random-effects meta-regression analysis plots depicting the relationship between mean difference in RV long-axis diameter (on y-axis) and (B) age, (C) LVEF, and (D) QRS duration (on x-axis). Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was no significant association between age, QRS duration, or LVEF and mean differences in RV long-axis diameters (β = 0.043, *P* = 0.86; β = −0.134, *P* = 0.185; and β = 0.097, *P* = 0.684, respectively). Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; RV, right ventricular

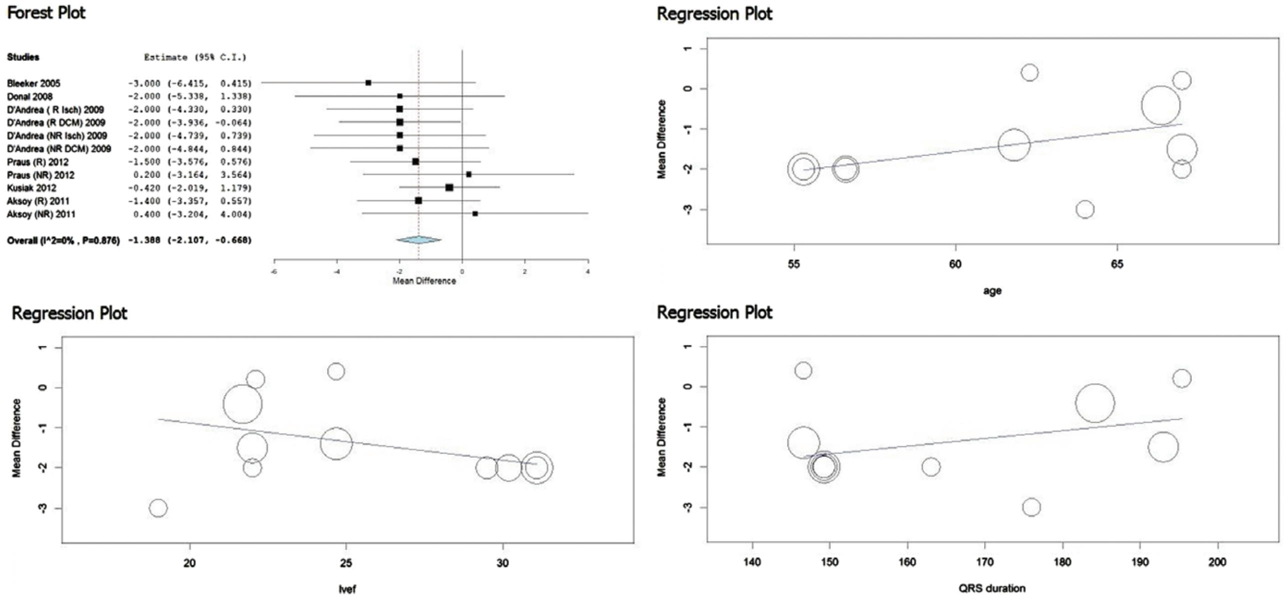

FIGURE 5 (A) Forest plot for mean difference in RV short-axis diameter with CRT, followed by random-effects meta-regression analysis plots depicting the relationship between mean difference in RV short-axis diameter (on y-axis) and (B) age, (C) LVEF, and (D) QRS duration (on x-axis). Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was no significant association between age, QRS duration, or LVEF and mean differences in RV short-axis diameters (β = 0.098, P = 0.201; β = 0.019, P = 0.31; and β = −0.092, P = 0.299, respectively). Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; RV, right ventricular

included in our study have used TAPSE as a measure of RV function, which is a relatively simple echocardiographic measure and represents RV longitudinal function and has shown to have a good correlation with more precise measures of RV systolic function, including radionuclide estimation of RVEF.[28] However, a major limitation of TAPSE is that it measures contribution of only the RV free wall to predict RV global systolic function.[29,30] A more global measure of RV systolic function is FAC, which has shown to correlate well with cardiac magnetic resonance imaging (CMR)-derived RVEF.[31] However, FAC is considered more a measure of RV response to afterload rather than contractility. Another echocardiographic method of quantifying RV systolic function is speckle tracking, which measures 2-dimensional RV strain and correlates with contractile function of RV. Speckle tracking echocardiography has been shown to more closely correlate with CMR-estimated RVEF, as compared with TAPSE.[32,33]

Prior studies have shown favorable LV remodeling and improvements in LV systolic function with CRT.[3] This leads to reduction in LV end-diastolic pressures, mitral regurgitation, and PA pressures, which subsequently decrease the RV afterload and could improve RV contractility.[34,35] The RV shares oblique fibers with the LV within the interventricular septum, which facilitates the augmentation of RV contraction with LV systolic contraction.[35] With declining LV function, there is reorientation of oblique septal fibers to a more transverse position as the LV becomes more spherical secondary to volume overload. This dramatically reduces the mechanical advantage of RV contractility by these oblique fibers.[35] CRT induces LV remodeling and thereby could lead to repositioning of these fibers and lead to improvements in RV function. The improvements observed in RV function after CRT could have been essentially due to improved LV function and not due to an independent effect of CRT on RV.

4.1 | Study limitations

There are several potential limitations to our meta-analysis. This analysis is based on published studies, and patient-level data were not available. Due to lack of patient-level data, it cannot be claimed conclusively that all patients included in the analysis received guideline-directed optimum medical therapy. Residual measured or unmeasured confounding may have impacted these findings. Our analysis includes several observational studies with relatively smaller sample size and short follow-up periods. This could lead to overestimation of effect and may influence the reported degree of RV remodeling. Further, evaluation of RV size and function in the studies used in our analysis was not done using advanced cardiac imaging modalities, such as CMR. Because the RV has a complex geometry, one echocardiographic measure might not accurately represent true RV size and function; therefore, we utilized multiple echocardiographic parameters to assess RV function. Furthermore, our results were consistent across all parameters of RV function, including TAPSE and FAC, which have been reported to correlate well with measures of RV function obtained by CMR.

5 | CONCLUSION

Results from current analysis suggest that improvements in echocardiographic parameters of RV function after CRT were not independent of baseline variables but rather were related to age, QRS duration, and baseline LVEF.

Conflicts of interest

The authors declare no potential conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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