Effect of cardiac resynchronization therapy on ventricular repolarization: A meta-analysis

Xu Duan, Wei Gao

Department of Cardiology, The First People's Hospital of Hangzhou; Hangzhou-China

Abstract

Objective: Cardiac resynchronization therapy (CRT) was thought to have a proarrhythmic effect on ventricular repolarization. But the results of previous studies were inconsistent. The aim of this study was to determine the effect of CRT on ventricular repolarization.
Methods: A meta-analysis of studies focused on the effect of CRT on ventricular repolarization in patients undergoing CRT was conducted. Endpoints including QT interval (QT), JT interval (JT), QT dispersion(QTD) and interval between the peak to end of T wave (Tp-e).
Results: A total of 14 studies were included in our meta-analysis. After pooling the data, no significant difference was observed in QT, JT and Tp-e between biventricular (BV) pacing and intrinsic ventricular rhythm. BV paced QTD was lower than intrinsic QTD, but the significance was ambiguous [mean difference (MD): -17.33, 95% CI -34.44 to -0.22, p=0.05]. Left ventricular (LV) paced Tp-e was significantly longer than intrinsic Tp-e (MD: 21.44, 95% CI 2.37 to 40.51, p=0.03). No significant difference was observed in QT, JT and QTD between LV pacing and intrinsic ventricular rhythm.
Conclusion: In patients undergoing CRT, BV pacing has no deteriorating effect on ventricular repolarization, but LV pacing has a prolonging effect on Tp-e. (*Anatol J Cardiol 2015; 15: 188-95*)

Keywords: cardiac resynchronization therapy, biventricular pacing, left ventricular pacing, ventricular repolarization, ventricular arrhythmia

Introduction

Cardiac resynchronization therapy (CRT) has been proved to be a therapeutic tool for selected group of patients with heart failure. In patients with heart failure and cardiac dysynchrony, CRT can improve haemodynamics, exercise capacity, quality of life and survival (1-3). Although CRT improves total survival of patients with heart failure, the risk of sudden death, which is mainly due to ventricular arrhythmia, is not decreased by CRT (3, 4). Some studies suggest that left ventricular epicardial pacing and biventricular pacing have deteriorating effect on ventricular repolarization, which may be proarrhythmic (5, 6). However, other studies have different results (7, 8). To determinate the effect of CRT on ventricular repolarization, we conducted a meta-analysis.

Methods

Search strategy

We searched for all published articles indexed in PubMed until June 30th 2013. The search terms were (CRT OR resynchro-

nization OR biventricular pacing OR left ventricular pacing) AND (repolarization OR QT OR JT OR TDR).

Eligibility

For this meta-analysis, the following inclusion criteria were adopted: 1) the study was self-control study; 2) the study subjects were patients undergoing cardiac resynchronization; 3) the study must focused both intrinsic ventricular rhythm and biventricular (BV) pacing, the left ventricular (LV) pacing was not compulsive; 4) means and standard deviations of at least one of endpoints of QT interval (QT), JT interval (JT), QT dispertion (QTD) and interval between the peak to end of T wave (Tp-e) were provided or could be calculated; 5) all the measurements were corrected for heart rate or the heart rate was constant in the study.

Data extraction

Data extraction was performed by 2 investigators (Duan and Gao) independently. A pre-tested data extraction form was used. The data extraction form included: general information,



Address for Correspondence: Dr. Xu Duan, MD, Department of Cardiology, The First People's Hospital of Hangzhou 261# Huansha Road, Hangzhou-*China* Phone: +86 571 87065701 Fax: +86 571 87914773 E-mail: duanxu410@yahoo.com.cn Accepted Date: 18.11.2013 Available Online Date: 26.02.2014 © Copyright 2015 by Turkish Society of Cardiology - Available online at www.anakarder.com DOI:10.5152/akd.2014.5255 study characteristics, information of participants, measuring method, data of endpoints and so on. In case of contradictory findings, the two investigators would be contacted for clarification.

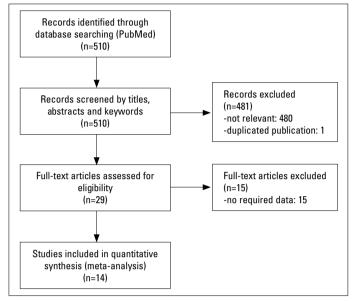


Figure 1. Flow chart showing the results of the search strategy

Statistical analysis

For all the interested data were continuous data, they were expressed as mean±standard deviation and an overall mean difference (MD) was calculated. Overall results were calculated based on fixed effect model if no heterogeneity was found among trials. Otherwise, random effects model was adopted.

Heterogeneity was tested by using the Z score and the chisquare statistic with significance set at p<0.10. Publication bias was accessed by visual inspection of funnel plot. Because of the small amount of included studies, meta-regression was not performed.

The analyses were done with the computer program RevMan Analyses in Review Manager 5.0.2 (2009, The Cochrane Collaboration).

Results

Search results

A total of 510 potentially eligible references were identified by electronic search. After screening by titles, abstracts and keywords, 480 references were excluded as irrelevant and 1 reference was excluded as duplicated publication. The rest 29 references were reviewed by full-text. 15 references were

	BV	paced Q			insic Q			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean		Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Anh 2008	438	51	19	470	36	19	7.1%	-32.00 [-60.07, -3.93]	
Chalil 2006	491.4	44.17	75	484.7	45.9	75	8.4%	6.70 [-7.72, 21.12]	
Dilaveris 2009	502.95	52.46	70	528.41	53.46	70	8.1%	-25.46 [-43.01, -7.91]	
Douglas 2012	460.7	42.3	52	483.8	41.4	52	8.2%	-23.10 [-39.19, -7.01]	
Harada 2006	509	44	14	486	50	14	6.3%	23.00 [-11.89, 57.89]	
Hina 2008(1)	546	43	18	569	52	18	6.7%	-23.00 [-54.17, 8.17]	
Hina 2008(2)	535	63	8	526	73	8	3.6%	9.00 [-57.82, 75.82]	
Huysduynen 2005	477	44	28	503	47	28	7.5%	-26.00 [-49.85, -2.15]	
_ellouche 2007(1)	518	57	48	498	39	48	7.9%	20.00 [0.46, 39.54]	
_ellouche 2007(2)	505	51	34	457	43	34	7.6%	48.00 [25.58, 70.42]	
Medina-Ravell 2003	535	38	29	468	38	29	7.9%	67.00 [47.44, 86.56]	
Prochnau 2011(1)	506	55	35	487	45	35	7.5%	19.00 [-4.54, 42.54]	
Prochnau 2011(2)	486	44	92	486	44	92	8.5%	0.00 [-12.72, 12.72]	
T	100 -0	10 -0	0	E00 67	67 26	9	4.7%	-28.89 [-80.93, 23.15]	
Turkoglu 2010	480.78	42.52	9	509.67	07.30	9	4.7 70	-20.09 [-00.93, 23.15]	
Turkoglu 2010 Total (95% CI)	480.78	42.52	9 531	509.67	07.30	5	100.0%	3.26 [-13.00, 19.51]	•
			531			531	100.0%	• • • • • • • • • • • • • • • • • • •	
Total (95% CI)	= 769.23; (Chi² = 98	531 3.98, df			531	100.0%	• • • • • • • • • • • • • • • • • • •	-100 -50 0 50 100 Eavours Intrinsic Eavours BV paced
Fotal (95% CI) Heterogeneity: Tau² =	= 769.23; (Chi² = 98	531 3.98, df			531	100.0%	• • • • • • • • • • • • • • • • • • •	+ + + + + + + + + + + + + + + + + + +
Fotal (95% CI) Heterogeneity: Tau² =	= 769.23; (Chi² = 98	531 3.98, df			531	100.0%	• • • • • • • • • • • • • • • • • • •	
Total (95% CI) Heterogeneity: Tau² = Fest for overall effect	= 769.23; (: Z = 0.39	Chi ² = 98 (P = 0.6 aced Q ¹	531 3.98, df 9) T	[:] = 13 (P Intri	< 0.000 nsic Q1	531 01); I ² :	100.0% = 87%	• • • • • • • • • • • • • • • • • • •	Favours Intrinsic Favours BV paced Mean Difference
Total (95% CI) Heterogeneity: Tau² = Fest for overall effect	= 769.23; (: Z = 0.39	Chi ² = 98 (P = 0.6 aced Q ¹	531 3.98, df 9)	[:] = 13 (P Intri	< 0.000 nsic Q1	531 01); I ² :	100.0%	3.26 [-13.00, 19.51]	Favours Intrinsic Favours BV paced Mean Difference
Total (95% CI) Heterogeneity: Tau² = Test for overall effect B	= 769.23; (: Z = 0.39 LV p	Chi ² = 98 (P = 0.6 aced Q ¹	531 3.98, df 9) T	[:] = 13 (P Intri	< 0.000 nsic Q1	531 01); I ² :	100.0% = 87%	3.26 [-13.00, 19.51] Mean Difference IV, Random, 95% Cl 5.00 [-13.52, 23.52]	Favours Intrinsic Favours BV paced Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect B Study or Subgroup	= 769.23; (: Z = 0.39 LV p <u>Mean</u>	Chi ² = 98 (P = 0.6 aced Q ¹ SD	531 3.98, df 9) T	= 13 (P Intri Mean	< 0.000 nsic Q1 SD	531 01); I ² :	100.0% = 87% Weight	3.26 [-13.00, 19.51] Mean Difference IV, Random, 95% Cl	Favours Intrinsic Favours BV paced Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect B Study or Subgroup Anh 2008	= 769.23; (: Z = 0.39 LV p <u>Mean</u> 475	Chi ² = 98 (P = 0.6 aced QT <u>SD</u> 20	531 3.98, df 9) T <u>Total</u> 19	^E = 13 (P Intri <u>Mean</u> 470	< 0.000 nsic Q1 <u>SD</u> 36	531 01); l ² :	100.0% = 87% <u>Weight</u> 21.4%	3.26 [-13.00, 19.51] Mean Difference IV, Random, 95% Cl 5.00 [-13.52, 23.52]	Favours Intrinsic Favours BV paced Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Budy or Subgroup Anh 2008 Harada 2006	= 769.23; (: Z = 0.39 <u>LV p</u> <u>Mean</u> 475 612	Chi ² = 98 (P = 0.6 aced QT <u>SD</u> 20 48	531 3.98, df 9) T <u>Total</u> 19 14	= 13 (P Intri <u>Mean</u> 470 486	< 0.000 nsic Q1 <u>SD</u> 36 50	531 01); l ² : <u>Total</u> 19 14	100.0% = 87% <u>Weight</u> 21.4% 20.4% 21.3%	3.26 [-13.00, 19.51] Mean Difference IV, Random, 95% Cl 5.00 [-13.52, 23.52] 126.00 [89.69, 162.31]	Favours Intrinsic Favours BV paced Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Budy or Subgroup Anh 2008 Harada 2006 Huysduynen 2005	= 769.23; (: Z = 0.39 <u>LV p</u> <u>Mean</u> 475 612 487	Chi ² = 98 (P = 0.6 acced QT 20 48 31 35	531 3.98, df 9) T Total 19 14 28 29	= 13 (P Intri Mean 470 486 503	< 0.000 nsic Q1 <u>SD</u> 36 50 47 38	531 01); i ² :	100.0% = 87% <u>Weight</u> 21.4% 20.4% 21.3%	3.26 [-13.00, 19.51] Mean Difference <u>IV, Random, 95% CI</u> 5.00 [-13.52, 23.52] 126.00 [89.69, 162.31] -16.00 [-36.85, 4.85]	Favours Intrinsic Favours BV paced Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect B Study or Subgroup Anh 2008 Harada 2006 Huysduynen 2005 Medina-Ravell 2003	= 769.23; (: Z = 0.39 <u>LV p</u> <u>Mean</u> 475 612 487 587	Chi ² = 98 (P = 0.6 acced QT 20 48 31 35	531 3.98, df 9) T Total 19 14 28 29	= 13 (P Intri <u>Mean</u> 470 486 503 468	< 0.000 nsic Q1 <u>SD</u> 36 50 47 38	531 01); l ² :	100.0% = 87% <u>Weight</u> 21.4% 20.4% 21.3% 21.4%	3.26 [-13.00, 19.51] Mean Difference IV. Random, 95% CI 5.00 [-13.52, 23.52] 126.00 [89.69, 162.31] -16.00 [-36.85, 4.85] 119.00 [100.20, 137.80]	Favours Intrinsic Favours BV paced Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Countries of the second Countries of t	= 769.23; (: Z = 0.39 <u>LV p</u> <u>Mean</u> 475 612 487 587 584.44	Chi ² = 98 (P = 0.6 acced Q1 20 48 31 35 120.17	531 3.98, df 9) r <u>Total</u> 19 14 28 29 9 99	Intri Mean 486 503 468 509.67	< 0.000 nsic Q1 <u>SD</u> 36 50 47 38 67.36	531 01); I ² :	100.0% = 87% 21.4% 20.4% 21.3% 21.4% 15.4% 100.0%	3.26 [-13.00, 19.51] Mean Difference IV. Random. 95% Cl 5.00 [-13.52, 23.52] 126.00 [89.69, 162.31] -16.00 [-36.85, 4.85] 119.00 [100.20, 137.80] 74.77 [-15.23, 164.77]	Favours Intrinsic Favours BV paced Mean Difference

Figure 2. (A) Forest plot comparing BV pacing with intrinsic ventricular rhythm on QT (ms). (B) Forest plot comparing LV pacing with intrinsic ventricular rhythm on QT (ms)

BV - biventricular; LV - left ventricular; QT - QT interval

Study	z	Participants characteristics	Study time	Study mode	V-V delay of BV	Available data	Correction formula
Douglas 2012	52	Patients undergoing CRT, with severe heart failure	79 days (17-161) after implantation	Intrinsic; BV pacing	NA	OT, Tp-e	Bazett's formula
Prochnau 2011	Subgroup with sVTA:35 Subgroup without sVTA:92	Patients undergoing CRT, with LVEF ≤35% and QRS ≥130ms on electrocardiograms or permenant right ventircular pacing	NA	Intrinsic; BV pacing	NA	QT	Bazett's formula
Türkoğlu 2010	6	Patients undergoing and responding to CRT	NA	Intrinsic; LV pacing; BV pacing	Oms	ОТ, ЈТ, Тр-е	NA
Dilaveris 2009	70	Patients undergoing CRT, with NYHA III-IV, QRS duration ≥120 ms and LVEF ≤30%;	Before implantation for data of intrinsic ventricular rhythm; 30 days implantation for data after of ventricular pacing	Intrinsic; BV pacing	LV+ 20~30 ms (on the basis of echocardiography)	QT	Fridericia's formula
Hina 2008	Subgroup of CRT responders:18; Subgroup of CRT nonresponders:8	Patients undergoing CRT, with NYHA III-IV and LVEF <35%	Before implantation for data of intrinsic ventricular rhythm; 3 month after implantation for data at ventricular pacing mode	Intrinsic; BV pacing	ИА	ατ,	Bazett's formula
Anh 2008	19	Patients undergoing CRT, with LVEF \leq 35% and QRS \geq 130 ms	After implantation	Intrinsic; LV pacing; BV pacing	NA	OT, Tp-e	At the rate of 110 bpm
Lellouche 2007	Subgroup of LBBB:48 Subgroup of normal QRS:34	Patients undergoing CRT, with NYHA III-IV , LVEF ≤35% and QRS >130 ms or QRS ≤130 ms with left intra-ventricular dyssynchrony	Before implantation for data of intrinsic ventricular rhythm; within 24 hours postimplantation for data at ventricular pacing mode	Intrinsic; BV pacing	ИА	OT	Bazett's formula
Chalil 2006	75	Patients undergoing CRT, with NYHA III-IV , QRS <120ms and LVEF <35%	Before implantation for data of intrinsic ventricular rhythm; mean 48 days after implantation for data at ventricular pacing mode	Intrinsic; BV pacing	LV +4ms or LV +30ms	QT	Bazett's formula
Harada 2006	14	Patients undergoing CRT, with NYHA III-IV, LVEDD 63±7 mm, LVEF 27±10% and DRS >120 ms	Before permanent pacemaker implantation	Intrinsic; LV pacing; BV pacing	Oms	ατ, Jτ, ατD, Tp-e	Bazett's formula
Santangelo 2006	50	Patients undergoing CRT, with NHYA III-IV,ORS>130 ms, LVEF <35% and LVEDD >55 mm	12 months after implantation	Intrinsic; LV pacing; BV pacing	NA	QTD, Tp-e	Bazett's formula
Huysduynen 2005	28	Patients undergoing CRT, with heart failure	2 days after implantation	Intrinsic; LV pacing; BV pacing	NA	0T, Tp-e	Bazett's formula
Berger 2005	25	Patients undergoing CRT, with NYHA II-III, LVEF 21±5% and QRS ≥130ms	1 or 2 days after pacemaker implantation and prior to active ventricular pacing	Intrinsic; LV pacing; BV pacing	NA	QTD	Bazett's formula
Boriani 2005	20	Patients undergoing CRT, with NYHA III-IV and QRS >120 ms	At implantation for data of intrinsic ventricular rhythm; 3 months after implantation for data at ventricular pacing mode	Intrinsic; BV pacing	0ms	Ţ	At the rate of 100 bpm
Medina-Ravell 2003	29	Patients undergoing CRT, with NYHA III-IV, LVEF 23±7%	24 hours after implantation; 1-2 weeks after implantation	Intrinsic; LV pacing; BV pacing	NA	OT	Bazett's formula
BV - biventricular; C sustained ventriculs	,RT - cardiac resynchroniz: ar tacharrhythmias; 0T - 01	ation; JT - JT interval; LV - left ventricular; LVEDD - le T interval; QTD - QT dispersion; Tp-e - interval betwe	BV - biventricular; CRT - cardiac resynchronization; JT - JT interval; LV = left ventricular; LVEDD - left ventricular end-cliastolic dimension; VEF - left ventricular ejection faction; NYHA - New York Heart Association functional classification; sVTA - sustained ventricular tacharrthythmias; OT - OT interval; OTD - OT dispersion; Tp-e - interval between the peak to end of T wave	ction faction; NYHA - New Yc	ork Heart Association functi	onal classificatio	n; sVTA -

	BV I	paced .	JT	Intr	insic J1	Г		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Boriani 2006	248.6	30	20	262.6	42.8	20	26.5%	-14.00 [-36.91, 8.91]	
Harada 2006	360	41	14	338	41	14	15.1%	22.00 [-8.37, 52.37]	
Hina 2008(1)	382	28	18	393	26	18	44.6%	-11.00 [-28.65, 6.65]	-8+
Hina 2008(2)	360	50	8	374	78	8	3.4%	-14.00 [-78.20, 50.20]	
Türkoğlu 2010	303.33	20.31	9	324.11	51.86	9	10.5%	-20.78 [-57.17, 15.61]	
Total (95% Cl)			69			69	100.0%	-7.95 [-19.74, 3.84]	•
Heterogeneity: Chi ² =	4.63, df =	4 (P = 0	0.33); l ^a	2 = 14%					-100 -50 0 50 100
Test for overall effect:	Z = 1.32	(P = 0.1)	9)						-100 -50 0 50 100 Favours Intrinsic Favours BV paced

Figure 3. Forest plot comparing BV pacing with intrinsic ventricular rhythm on JT (ms)
BV - biventricular; JT - JT interval

ł		BV na	aced Q	TD	Intri	nsic Q	тр		Mean Difference	Mean Difference
<u></u>	Study or Subgroup	Mean			Mean			Weight	IV, Random, 95% CI	
	Berger 2005	90	12	25	114	22	25	21.0%	-24.00 [-33.82, -14.18]	
	Harada 2006	57	23	14	50	25	14	18.2%	7.00 [-10.79, 24.79]	
	Hina 2008(1)	52	15	18	102	26	18	19.7%	-50.00 [-63.87, -36.13]	
	Hina 2008(2)	39	11	8	40	12	8	20.6%	-1.00 [-12.28, 10.28]	
	Santangelo 2006	73.93	19.4	50	91	36.7	50	20.5%	-17.07 [-28.58, -5.56]	
	Total (95% CI)			115			115	100.0%	-17.33 [-34.44, -0.22]	•
	Heterogeneity: Tau ² =	337.08: 0	Chi ² = 3	38.21.	df = 4 (F	o < 0.0	0001);	² = 90%		
	Test for overall effect:									
3	• •	Z = 1.99	(P = 0	.05)		nsic C	סדנ			Favours Intrinsic Favours BV paced
	Test for overall effect:	Z = 1.99	(P = 0) aced C	.05) 2TD		nsic C SD	-	Weight	Mean Difference	Favours Intrinsic Favours BV paced Mean Difference
	• •	Z = 1.99 LV pa	(P = 0) aced C	.05) 2TD	Intri Mean	SD	Total	<u>Weight</u> 35.9%	Mean Difference IV, Random, 95% CI	Favours Intrinsic Favours BV paced
	Test for overall effect: Study or Subgroup	Z = 1.99 LV pa Mean	(P = 0 aced C SD	05) TD Total	Intri <u>Mean</u> 114	SD 22	Total 25	35.9%	Mean Difference IV, Random, 95% CI	Favours Intrinsic Favours BV paced Mean Difference
	Test for overall effect: <u>Study or Subgroup</u> Berger 2005	Z = 1.99 LV pa <u>Mean</u> 100	(P = 0 aced C <u>SD</u> 15	.05) TD Total 25	Intri <u>Mean</u> 114 50	SD 22	Total 25 14	35.9% 32.2%	Mean Difference IV, Random, 95% CI -14.00 [-24.44, -3.56] 33.00 [11.73, 54.27]	Favours Intrinsic Favours BV paced
	Test for overall effect: <u>Study or Subgroup</u> Berger 2005 Harada 2006	Z = 1.99 LV pa <u>Mean</u> 100 83	(P = 0. aced C <u>SD</u> 15 32	.05) TD Total 25 14	Intri <u>Mean</u> 114 50	SD 22 25	Total 25 14	35.9% 32.2% 31.9%	Mean Difference IV, Random, 95% CI -14.00 [-24.44, -3.56] 33.00 [11.73, 54.27]	Favours Intrinsic Favours BV paced Mean Difference
	Test for overall effect: <u>Study or Subgroup</u> Berger 2005 Harada 2006 Santangelo 2006	Z = 1.99 LV pa <u>Mean</u> 100 83 116	(P = 0. aced C <u>SD</u> 15 32 71	.05) TD Total 25 14 50 89	Intri <u>Mean</u> 114 50 91	SD 22 25 36.7	Total 25 14 50 89	35.9% 32.2% 31.9% 100.0%	Mean Difference IV, Random, 95% CI -14.00 [-24.44, -3.56] 33.00 [11.73, 54.27] 25.00 [2.85, 47.15]	Favours Intrinsic Favours BV paced Mean Difference

Figure 4. (A) Forest plot comparing BV pacing with intrinsic ventricular rhythm on QTD (ms). (B) Forest plot comparing LV pacing with intrinsic ventricular rhythm on QTD (ms)

BV - biventricular; LV - left ventricular; QTD - QT dispersion

excluded because no required data was available. Finally, 14 references (5-18) were accorded with the inclusion criteria of this meta-analysis (Fig. 1 and Table 1). In 3 of the 14 references, the data of endpoints were provided by subgroups (6, 14, 17). In 2 of the 14 references, the data was expressed as mean and standard error, the standard deviation was calculated (11, 15). In 1 of the 14 references, the data of endpoints were provided by every patient, the means and standard deviations of endpoints were calculated (16).

QT interval

Intrinsic QT and BV paced QT were reported in 11 studies. After pooling the data, no apparent difference was observed between intrinsic QT and BV paced QT (MD: 3.26, 95% CI-13.00 to 19.51, p=0.69). The heterogeneity among studies in QT was significant (I²=87%, p<0.00001). LV paced QT was reported in 5 of the 11 studies. No apparent difference was observed between intrinsic QT and LV paced QT (MD: 60.40, 95% CI -4.93 to 125.74, p=0.07). The heterogeneity among studies in QT was significant (I^2 =97%, p<0.00001) (Fig. 2).

JT interval

Intrinsic JT and BV paced JT were reported in 4 studies. After pooling the data, no apparent difference was observed between intrinsic JT and BV paced JT(MD: -7.95, 95% CI -19.74 to 3.84, p=0.19) and no significant heterogeneity was found ($I^2=14\%$, p=0.33) (Fig. 3). Because LV paced JT was reported in only 2 of the 4 studies, pooled analysis was not referred for it.

QT dispersion

Intrinsic QTD and BV paced QTD were reported in 4 studies. After pooling the data, BV paced QTD was lower than intrinsic QTD, but the significance was ambiguous (MD:-17.33, 95% CI-34.44 to -0.22, p=0.05). The heterogeneity among studies in

ł		BV n	aced T	1-0	Intrin	sic Tp-			Mean Difference	Mean Difference
	Study or Subgroup	Mean		Total	Mean			Weight	IV. Random, 95% CI	
	Anh 2008	100	25	19	106	26	19	12.0%	-6.00 [-22.22, 10.22]	
	Douglas 2012	105.6	17.3	52	114.2	15.9	52	28.5%	-8.60 [-14.99, -2.21]	-
	Harada 2006	141	21	14	122	23	14	11.9%	19.00 [2.69, 35.31]	
	Huysduynen 2005	102	18	28	108	27	28	17.4%	-6.00 [-18.02, 6.02]	
	Santangelo 2006	93.16	15.6	50	101.55	19.08	50	27.5%	-8.39 [-15.22, -1.56]	-#-
	Turkoglu 2010	142	48.63	9	153.33	36.25	9	2.7%	-11.33 [-50.96, 28.30]	
	Total (95% CI)			172			172	100.0%	-4.56 [-11.36, 2.24]	•
	Heterogeneity: Tau ² =	31.65: C	hi² = 10	.16. df	= 5 (P =	0.07); l ²	= 51%			
	• •									-100 -50 0 50 100
	Test for overall effect:	Z = 1.32	(P = 0.1	19)						Favours Intrinsic Favours BV paced
3	Test for overall effect:		(P = 0. ⁻ aced T ₁		Intri	nsic Tp	-е		Mean Difference	Favours Intrinsic Favours BV paced Mean Difference
	Test for overall effect: Study or Subgroup		aced T			•	-e Total	Weight		Mean Difference
		LV pa	aced T	p-e		•	Total	<u>Weight</u> 23.0%		Mean Difference
	Study or Subgroup	LV pa Mean	aced T _I SD	p-e Total	<u>Mean</u> 106	SD	Total 19		IV, Random, 95% CI	Mean Difference
	<u>Study or Subgroup</u> Anh 2008	LV pa Mean 120	aced T _l <u>SD</u> 20	p-e <u>Total</u> 19	Mean 106 122	<u>SD</u> 26	Total 19	23.0%	IV, Random, 95% Cl 14.00 [-0.75, 28.75]	Mean Difference
	<u>Study or Subgroup</u> Anh 2008 Harada 2006	LV pa <u>Mean</u> 120 189	aced T _i <u>SD</u> 20 37	p-e <u>Total</u> 19 14	Mean 106 122 108	26 23 27	<u>Total</u> 19 14	23.0% 19.3%	IV, Random, 95% Cl 14.00 [-0.75, 28.75] 67.00 [44.18, 89.82]	Mean Difference
	<u>Study or Subgroup</u> Anh 2008 Harada 2006 Huysduynen 2005	LV pa <u>Mean</u> 120 189 106	aced T <u>SD</u> 20 37 21 26.1	p-e <u>Total</u> 19 14 28 50	Mean 106 122 108 101.55	5D 26 23 27 19.08	Total 19 14 28	23.0% 19.3% 23.9%	IV, Random, 95% Cl 14.00 [-0.75, 28.75] 67.00 [44.18, 89.82] -2.00 [-14.67, 10.67]	Mean Difference IV, Random, 95% CI
3	<u>Study or Subgroup</u> Anh 2008 Harada 2006 Huysduynen 2005 Santangelo 2006	LV pa <u>Mean</u> 120 189 106 114.71	aced T <u>SD</u> 20 37 21 26.1	p-e <u>Total</u> 19 14 28 50	Mean 106 122 108 101.55	5D 26 23 27 19.08	Total 19 14 28 50 9	23.0% 19.3% 23.9% 25.2%	IV, Random, 95% CI 14.00 [-0.75, 28.75] 67.00 [44.18, 89.82] -2.00 [-14.67, 10.67] 13.16 [4.20, 22.12] 28.34 [-25.02, 81.70]	Mean Difference IV, Random, 95% CI
	Study or Subgroup Anh 2008 Harada 2006 Huysduynen 2005 Santangelo 2006 Turkoglu 2010	LV pa <u>Mean</u> 120 189 106 114.71 181.67	aced T <u>SD</u> 20 37 21 26.1 73.19	p-e <u>Total</u> 19 14 28 50 9 120	Mean 106 122 108 101.55 153.33	5D 26 23 27 19.08 36.25	Total 19 14 28 50 9 120	23.0% 19.3% 23.9% 25.2% 8.6%	IV, Random, 95% CI 14.00 [-0.75, 28.75] 67.00 [44.18, 89.82] -2.00 [-14.67, 10.67] 13.16 [4.20, 22.12] 28.34 [-25.02, 81.70]	Mean Difference IV, Random, 95% CI

Figure 5. (A) Forest plot comparing BV pacing with intrinsic ventricular rhythm on Tp-e(ms). (B) Forest plot comparing LV pacing with intrinsic ventricular rhythm on Tp-e(ms)

BV - biventricular; LV - left ventricular; Tp-e - interval between the peak to end of T wave

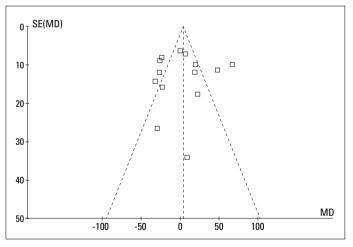


Figure 6. Funnel plot to assess systematic bias using BV paced QT ${\sf BV}$ - biventricular; QT - QT interval

QTD was significant (l^2 =90%, p<0.00001). LV paced QTD was reported in 3 of the 4 studies. No apparent difference was observed between intrinsic QTD and LV paced QTD (MD: 13.59, 95% CI-19.48 to 46.66, p=0.42). The heterogeneity among studies in QTD was significant (l^2 =90%, p<0.0001) (Fig. 4).

Тр-е

Intrinsic Tp-e and BV paced Tp-e were reported in 6 studies. After pooling the data, no apparent difference was observed between intrinsic Tp-e and BV paced Tp-e (MD: -4.56, 95% CI -11.36 to 2.24, p=0.19). The heterogeneity among studies in Tp-e was significant ($l^2=51\%$, p=0.07). LV paced Tp-e was reported in 5 of the 6 studies. After pooling the data, LV paced Tp-e was significantly longer than intrinsic Tp-e (MD: 21.44, 95% CI 2.37 to 40.51, p=0.03). The heterogeneity among studies in Tp-e was significant ($l^2=85\%$, p<0.0001) (Fig. 5).

Publication bias

Visual inspection of the funnel plot for QT did not show asymmetry, which indicated that significant publication bias was not likely (Fig. 6).

Discussion

In this meta-analysis, we found that BV pacing had no significant effect on QT, JT and Tp-e. A slightly decreased QTD was associated with BV pacing, but the significance was ambiguous. LV pacing had a prolonging effect on Tp-e but didn't significantly affect other parameters.

As a cornerstone of CRT, CARE-HF study proved that CRT could reduce the risk of all-caused death in patients with heart failure and cardiac dyssynchrony (3). But the risk of sudden death was not decreased by CRT in this study (3). A meta-analysis which included 2371 patients of 5 studies suggested that CRT alone reduced all-caused death predominantly by reducing worsening heart failure mortality but not affecting sudden death (4). Proarrhythmic effect of CRT was considered and was supported by some case reports of ventricular arrhythmia following the implantation of CRT (5, 19, 20). But other studies suggested

that CRT could decrease the incidence and inducibility of ventricular tachyarrhythmias (21, 22).

Medina-Ravell et al. (5) reported the potential proarrhythmic effect of CRT at the first time. In humans study and animal experiment, BV pacing and LV epicardial pacing was found to be associated with ventricular arrhythmia, including R-on-T extrasystoles and TdP. They attributed the potential proarrhythmic effect of CRT to the ventricular repolarization alteration caused by BV pacing and LV epicardial pacing, including prolongation of QT, JT and transmural dispersion of repolarization (TDR), which was defined as the Tp-e. These findings were verified by another experimental study reported by Fish et al. (23), which suggested that epicardial activation of left ventricular wall prolongs QT and TDR. However, results of following studies were inconsistent or even contradictory (7, 8, 14). Santangelo et al. (7) reported that LV pacing enhanced QTD and TDR, whereas BV pacing significantly reduced QTD and TDR. Anh et al. (8) reported that compared with RA pacing, BV pacing produced shorter QT. Hina et al.(14) reported that QTD and JT dispersion were significantly decreased after CRT in subgroup of CRT responders but no significant change in subgroup of CRT nonresponders. Another study of patients without structural heart disease suggested that RV pacing, LV pacing and BV pacing increased QT and Tp-e, but the effect of BV pacing was less than RV pacing and LV pacing (24).

QT is a traditional measurement of ventricular repolarization, prolonged QT has been proved to be a powerful predictor of all caused death and sudden cardiac death in patients with advanced heart failure (25). In patients with CRT, prolongation of QT induced by BV pacing has be proved to be related to sustained ventricular tachyarrhythmias (17). Some researchers considered JT to be a better measurement of ventricular repolarization than QT because it is independent of QRS duration (26, 27). In previous study, prolonged JT was suggested to be an independent risk factor of sudden cardiac death in patients with coronary artery disease (28). QTD, which is defined as the difference in QT interval between the different leads, is considered to be an indirect measurement of the inhomogeneity of myocardial repolarization (29, 30). Study of Chalil et al. (11) suggested that major arrhythmic events in patients undergoing CRT were related to pacing induced QTD increase. Our meta-analysis suggested that BV pacing and LV pacing had no deteriorating effect on QT, JT and QTD. On the contrary, a slightly decreased QTD was associated with BV pacing, although the significance was ambiguous.

Tp-e, which is considered as a measurement of TDR, was proved to be a predictor of ventricular arrhythmia superior to QT and QTD (31-33). In the study of Türkoğlu et al. (16) 2 patients with biventricular pacing-induced ventricular fibrillation were successfully treated by reprogramming of V-V delay resulting in shorter Tp-e. Our meta-analysis suggested that BV pacing didn't affect Tp-e, but LV pacing had a prolonging effect on Tp-e. Recent studies suggested that LV pacing alone may be noninferior or even superior to BV pacing with regard to echocardiographic responses (34-36). But the unfavourable effect of LV pacing on Tp-e should be taken in account when LV pacing alone is adopted in clinic.

Study limitations

There are limitations to this meta-analysis. Firstly, although the effect of CRT on the ventricular repolarization was reported to be time-dependent (37), the duration of BV pacing before or during study was different among studies. The results of different studies may be affected by the duration of CRT in various degrees. Secondly, although previous study suggested that programmed V-V delay had impact on QT, JT and Tp-e (16), it was different or not provided in our included studies. Thirdly, the intensity of pacing during our included studies was not available, although LV pacing intensity was proved to have a positive correlation with QT interval (38). Fourthly, although 14 studies were included in this meta-analysis, only 1 study provided all the four endpoints, more than half of the studies provided only 1 endpoint. Therefore, we did not perform meta-regression or subgroup analysis, although heterogeneity was found in QT, QTD, Tp-e. The heterogeneity may be attributed to the varied populations, methods and so on.

Conclusion

In patients undergoing CRT, BV pacing has no deteriorating effect on ventricular repolarization. The result suggests that CRT with BV pacing may be safe against ventricular arrhythmia, which needs to be verified by further study. LV pacing has a prolonging effect on Tp-e, which should be taken in account when LV pacing alone is adopted in clinic.

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Peer-review: Externally peer-reviewed.

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