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 resynchronization 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

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.

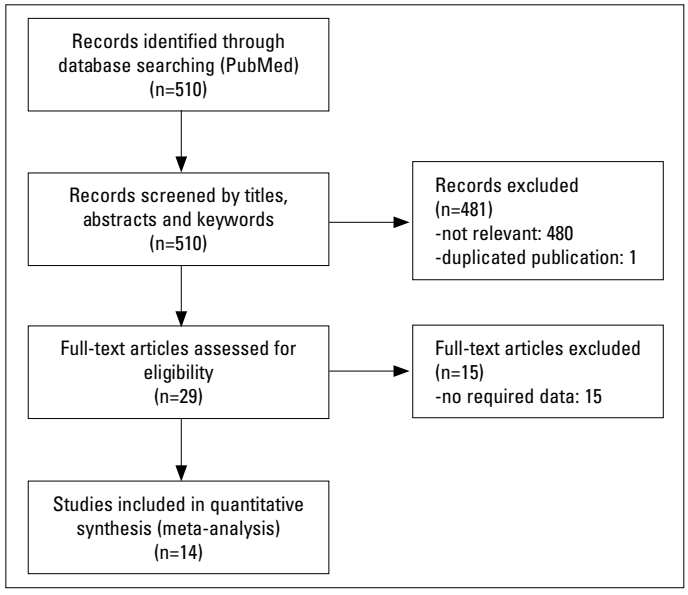

Figure 1. Flow chart showing the results of the search strategy

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 chi-square 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

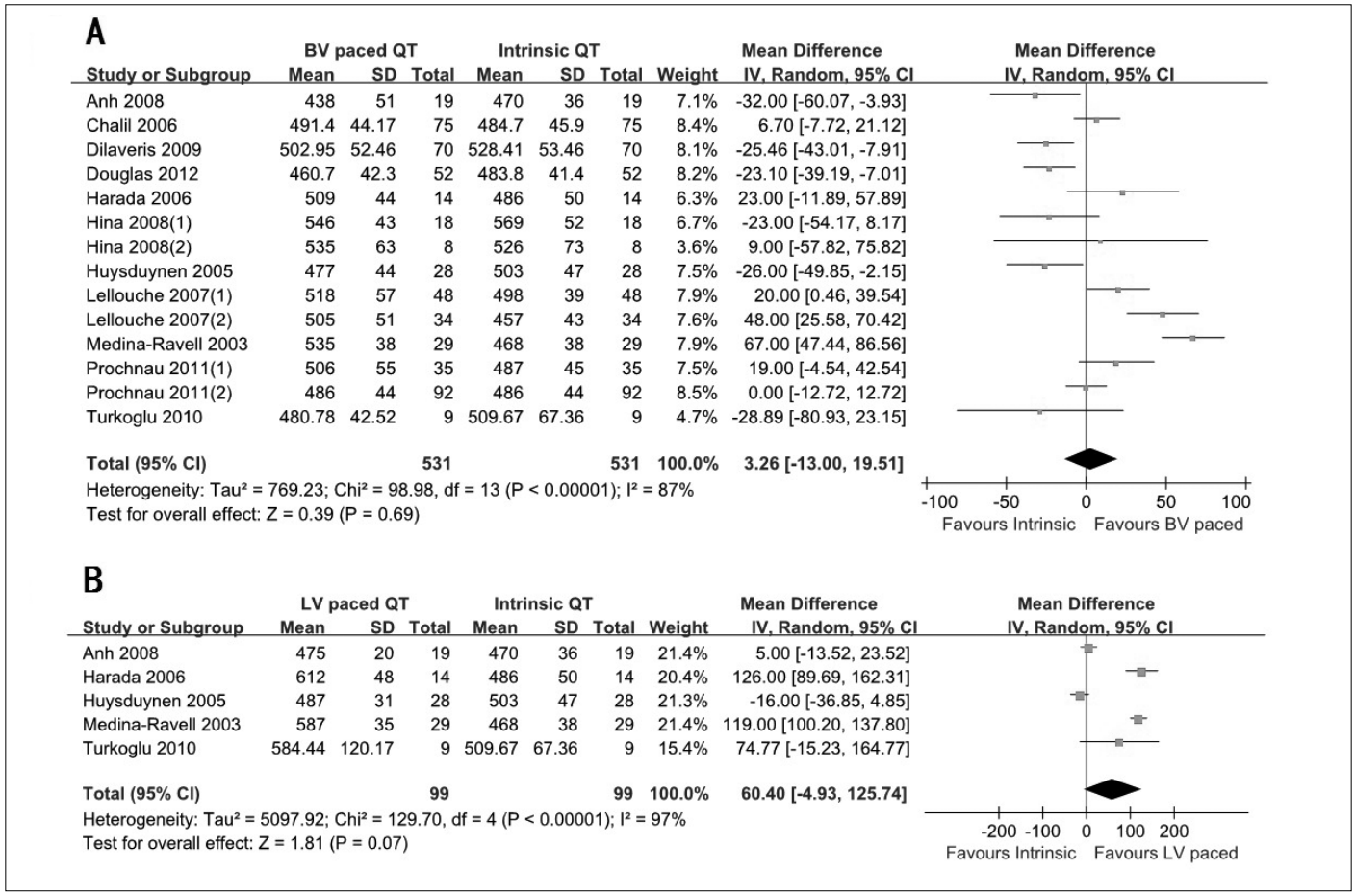

Figure 2. (A) Forest plot comparing BV pacing with intrinsic ventricular rhythm on QT (ms). (B) Forest plot comparing LV pacing with intrinsic ventricular rhythm on QT (ms)

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

Table 1. Individual study characteristics

Study	N	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	QT, 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	9	Patients undergoing and responding to CRT	NA	Intrinsic; LV pacing; BV pacing	0ms	QT, JT, Tp-e	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	NA	QT, JT, QTD	Bazett's formula
Anh 2008	19	Patients undergoing CRT, with LVEF ≤35% and QRS ≥130 ms	After implantation	Intrinsic; LV pacing; BV pacing	NA	QT, 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	NA	QT	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 QRS >120 ms	Before permanent pacemaker implantation	Intrinsic; LV pacing; BV pacing	0ms	QT, JT, QTD, Tp-e	Bazett's formula
Santangelo 2006	50	Patients undergoing CRT, with NHYA III-IV,QRS>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	QT, 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	JT	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	QT	Bazett's formula

BV - biventricular; CRT - cardiac resynchronization; JT - JT interval; LV - left ventricular; LVEDD - left ventricular end-diastolic dimension; VEF - left ventricular ejection faction; NYHA - New York Heart Association functional classification; sVTA - sustained ventricular tacharrhythmias; QT - QT interval; QTD - QT dispersion; Tp-e - interval between the peak to end of T wave

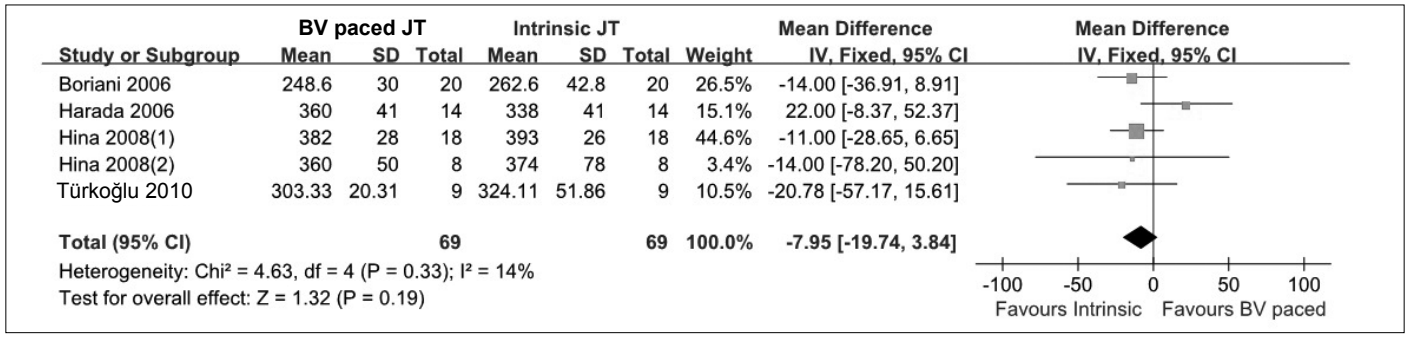

Figure 3. Forest plot comparing BV pacing with intrinsic ventricular rhythm on JT (ms)
BV - biventricular; JT - JT interval

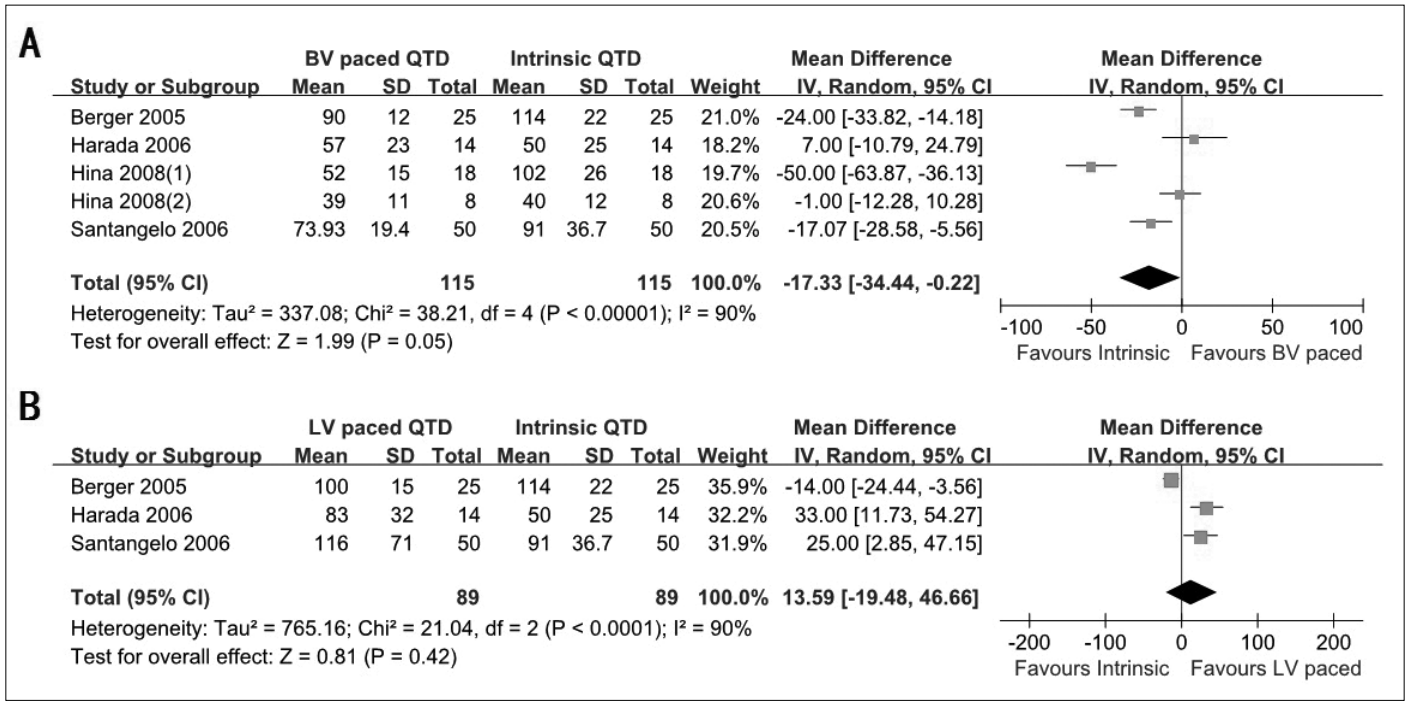

Figure 4. (A) Forest plot comparing BV pacing with intrinsic ventricular rhythm on QTD (ms). (B) Forest plot comparing LV pacing with intrinsic ventricular rhythm on QTD (ms)
BV - biventricular; LV - left ventricular; QTD - QT dispersion

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 (I^2=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

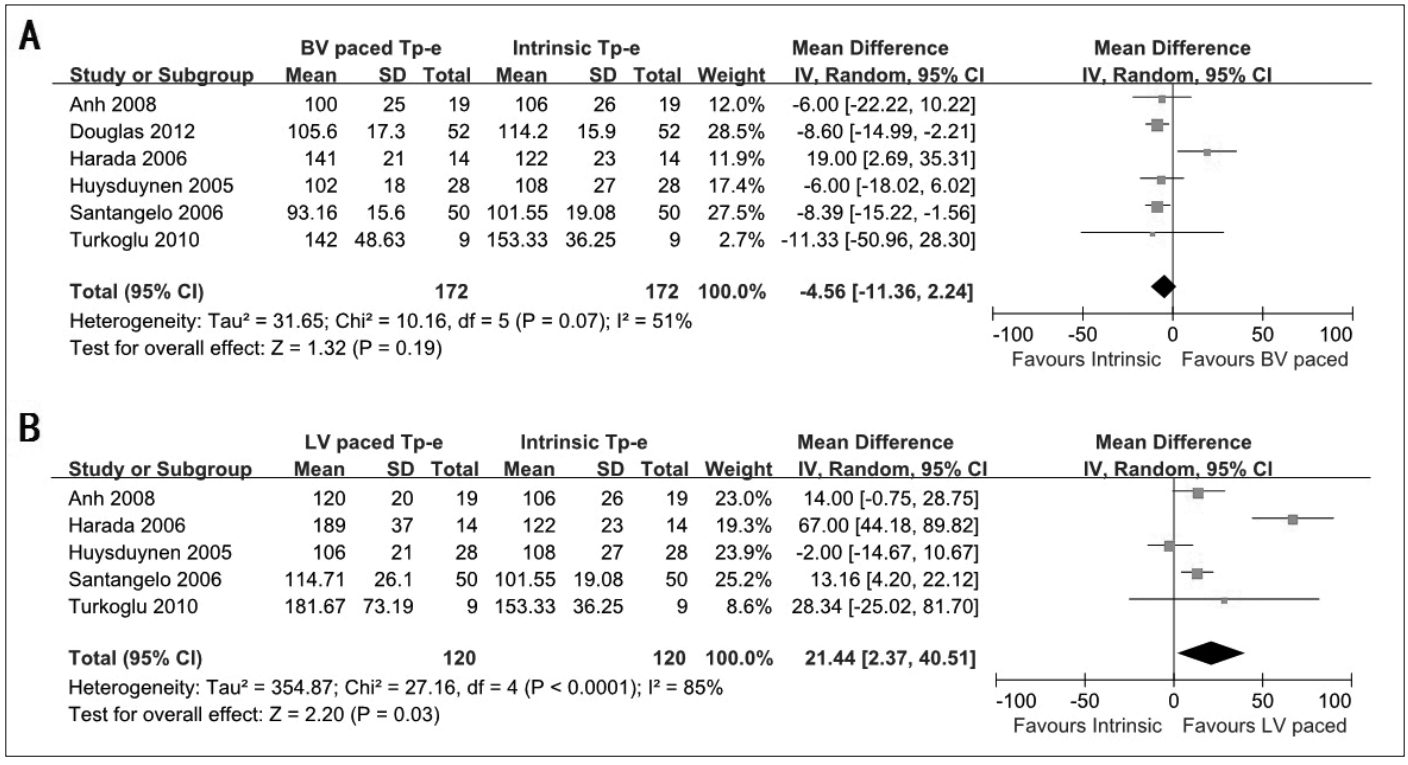

Figure 5. (A) Forest plot comparing BV pacing with intrinsic ventricular rhythm on Tp-e(ms). (B) Forest plot comparing LV pacing with intrinsic ventricular rhythm on Tp-e(ms)
BV - biventricular; LV - left ventricular; Tp-e - interval between the peak to end of T wave

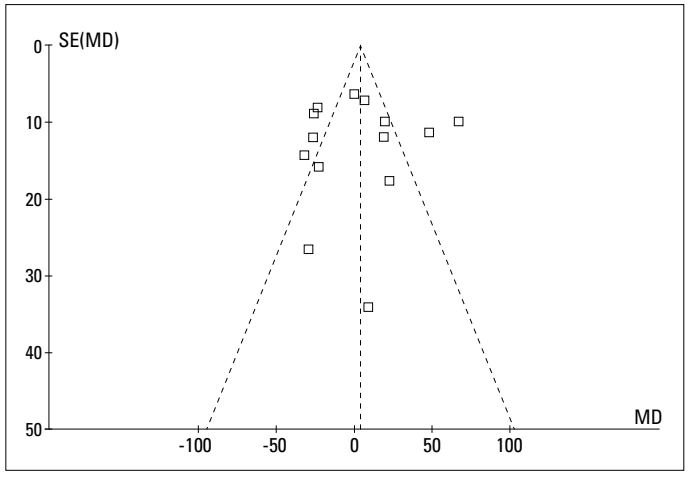

Figure 6. Funnel plot to assess systematic bias using BV paced QT
BV - biventricular; QT - QT interval

QTD was significant (I^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 (I^2=90%, p<0.0001) (Fig. 4).

Tp-e

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 (I^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 (I^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.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

References

1. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003; 42: 1454-9. [CrossRef]
2. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 2003; 289: 2685-94. [CrossRef]
3. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352: 1539-49. [CrossRef]
4. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ. Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials. Eur Heart J 2006; 27: 2682-8. [CrossRef]

5. Medina-Ravell VA, Lankipalli RS, Yan GX, Antzelevitch C, Medina-Malpica NA, Medina-Malpica OA, et al. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization: does resynchronization therapy pose a risk for patients predisposed to long QT or torsade de pointes? Circulation 2003; 107: 740-6. [CrossRef]
6. Lellouche N, De Diego C, Akopyan G, Boyle NG, Mahajan A, Cesario DA, et al. Changes and predictive value of dispersion of repolarization parameters for appropriate therapy in patients with biventricular implantable cardioverter-defibrillators. Heart Rhythm 2007; 4: 1274-83. [CrossRef]
7. Santangelo L, Russo V, Ammendola E, Cavallaro C, Vecchione F, Garofalo S, et al. Biventricular pacing and heterogeneity of ventricular repolarization in heart failure patients. Heart Int 2006; 2: 27. [CrossRef]
8. Anh D, Srivatsa U, Bui HM, Vasconcellos S, Narayan SM. Biventricular pacing attenuates T-wave alternans and T-wave amplitude compared to other pacing modes. Pacing Clin Electrophysiol 2008; 31: 714-21. [CrossRef]
9. van Huysduynen BH, Swenne CA, Bax JJ, Bleeker GB, Draisma HH, van Erven L, et al. Dispersion of repolarization in cardiac resynchronization therapy. Heart Rhythm 2005; 2: 1286-93. [CrossRef]
10. Berger T, Hanser F, Hintringer F, Poelzl G, Fischer G, Modre R, et al. Effects of cardiac resynchronization therapy on ventricular repolarization in patients with congestive heart failure. J Cardiovasc Electrophysiol 2005; 16: 611-7. [CrossRef]
11. Chalil S, Yousef ZR, Muyhaldeen SA, Smith RE, Jordan P, Gibbs CR, et al. Pacing-induced increase in QT dispersion predicts sudden cardiac death following cardiac resynchronization therapy. J Am Coll Cardiol 2006; 47: 2486-92. [CrossRef]
12. Harada M, Osaka T, Yokoyama E, Takemoto Y, Ito A, Kodama I. Biventricular pacing has an advantage over left ventricular epicardial pacing alone to minimize proarrhythmic perturbation of repolarization. J Cardiovasc Electrophysiol 2006; 17: 151-6. [CrossRef]
13. Boriani G, Biffi M, Martignani C, Ziacchi M, Saporito D, Grigioni F, et al. Electrocardiographic remodeling during cardiac resynchronization therapy. Int J Cardiol 2006; 108: 165-70. [CrossRef]
14. Hina K, Kawamura H, Murakami T, Yamamoto K, Yamaji H, Murakami M, et al. Association of corrected QT dispersion with symptoms improvement in patients receiving cardiac resynchronization therapy. Heart Vessels 2008; 23: 325-33. [CrossRef]
15. Dilaveris P, Giannopoulos G, Synetos A, Aggeli C, Raftopoulos L, Arsenos P, et al. Effect of biventricular pacing on ventricular repolarization and functional indices in patients with heart failure: lack of association with arrhythmic events. Europace 2009; 11: 741-50. [CrossRef]
16. Türkoğlu C, Aliyev F, Çeliker C, Cetin G, Alıcı G, Uzunhasan I, et al. Optimization of repolarization during biventricular pacing: a new target in patients with biventricular devices? Ann Noninvasive Electrocardiol 2010; 15: 36-42. [CrossRef]
17. Prochnau D, Kuehnert H, Figulla HR, Surber R. QRS duration and QTc interval are predictors of risk for ventricular arrhythmias during cardiac resynchronization therapy. Acta Cardiol 2011; 66: 415-20.
18. Douglas RA, Samesima N, Filho MM, Pedrosa AA, Nishioka SA, Pastore CA. Global and regional ventricular repolarization study by body surface potential mapping in patients with left bundle-branch block and heart failure undergoing cardiac resynchronization therapy. Ann Noninvasive Electrocardiol 2012; 17: 123-9. [CrossRef]
19. Di Cori A, Bongiorni MG, Arena G, Soldati E, Giannola G, Zucchelli G, et al. New-onset ventricular tachycardia after cardiac resynchronization therapy. J Interv Card Electrophysiol 2005; 12: 231-5. [CrossRef]
20. Mykytsey A, Maheshwari P, Dhar G, Razminia M, Zheutlin T, Wang T, et al. Ventricular tachycardia induced by biventricular pacing in patient with severe ischemic cardiomyopathy. J Cardiovasc Electrophysiol 2005; 16: 655-8. [CrossRef]
21. Higgins SL, Yong P, Sheck D, McDaniel M, Bollinger F, Vadecha M, et al. Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy. Ventak CHF Investigators. J Am Coll Cardiol 2000; 36: 824-7. [CrossRef]
22. Kies P, Bax JJ, Molhoek SG, Bleeker GB, Zeppenfeld K, Bootsma M, et al. Effect of cardiac resynchronization therapy on inducibility of ventricular tachyarrhythmias in cardiac arrest survivors with either ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 2005; 95: 1111-4. [CrossRef]
23. Fish JM, Di Diego JM, Nesterenko V, Antzelevitch C. Epicardial activation of left ventricular wall prolongs QT interval and transmural dispersion of repolarization: implications for biventricular pacing. Circulation 2004; 109: 2136-42. [CrossRef]
24. Fuenmayor AJ, Delgado ME. Ventricular repolarization during uni and biventricular pacing in normal subjects. Int J Cardiol 2013; 165: 72-5. [CrossRef]
25. Vrtovec B, Delgado R, Zewail A, Thomas CD, Richartz BM, Radovancevic B. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. Circulation 2003; 107: 1764-9. [CrossRef]
26. Das G. QT interval and repolarization time in patients with intraventricular conduction delay. J Electrocardiol 1990; 23: 49-52. [CrossRef]
27. Spodick DH. Reduction of QT-interval imprecision and variance by measuring the JT interval. Am J Cardiol 1992; 70: 103. [CrossRef]
28. Teodorescu C, Reinier K, Uy-Evanado A, Navarro J, Mariani R, Gunson K, et al. Prolonged QRS duration on the resting ECG is associated with sudden death risk in coronary disease, independent of prolonged ventricular repolarization. Heart Rhythm 2011; 8: 1562-7. [CrossRef]
29. Statters DJ, Malik M, Ward DE, Camm AJ. QT dispersion: problems of methodology and clinical significance. J Cardiovasc Electrophysiol 1994; 5: 672-85. [CrossRef]
30. Zabel M, Portnoy S, Franz MR. Electrocardiographic indexes of dispersion of ventricular repolarization: an isolated heart validation study. J Am Coll Cardiol 1995; 25: 746-52. [CrossRef]
31. Shimizu M, Ino H, Okeie K, Yamaguchi M, Nagata M, Hayashi K, et al. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. Clin Cardiol 2002; 25: 335-9. [CrossRef]
32. Watanabe N, Kobayashi Y, Tanno K, Miyoshi F, Asano T, Kawamura M, et al. Transmural dispersion of repolarization and ventricular tachyarrhythmias. J Electrocardiol 2004; 37: 191-200. [CrossRef]
33. Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. Clin Sci (Lond) 2003; 105: 671-6. [CrossRef]
34. Gasparini M, Bocchiardo M, Lunati M, Ravazzi PA, Santini M, Zardini M, et al. Comparison of 1-year effects of left ventricular and biventricular pacing in patients with heart failure who have ventricular arrhythmias and left bundle-branch block: the Bi vs Left

Ventricular Pacing: an International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias (BELIEVE) multicenter prospective randomized pilot study. Am Heart J 2006; 152: 155 e1-7.
35. Thibault B, Ducharme A, Harel F, White M, O'Meara E, Guertin MC, et al. Left ventricular versus simultaneous biventricular pacing in patients with heart failure and a QRS complex >/=120 milliseconds. Circulation 2011; 124: 2874-81. [CrossRef]
36. Boriani G, Kranig W, Donal E, Calo L, Casella M, Delarche N, et al. A randomized double-blind comparison of biventricular versus left ventricular stimulation for cardiac resynchronization therapy: the Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients (B-LEFT HF) trial. Am Heart J 2010; 159: 1052-8 e1.
37. Itoh M, Yoshida A, Fukuzawa K, Kiuchi K, Imamura K, Fujiwara R, et al. Time-dependent effect of cardiac resynchronization therapy on ventricular repolarization and ventricular arrhythmias. Europace 2013; 15: 1798-804. [CrossRef]
38. Theis C, Bavikati VV, Langberg JJ, Lloyd MS. The relationship of bipolar left ventricular pacing stimulus intensity to cardiac depolarization and repolarization in humans with cardiac resynchronization devices. J Cardiovasc Electrophysiol 2009; 20: 645-9. [CrossRef]