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

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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 dispersion (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,
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.

**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 1. Flow chart showing the results of the search strategy](image)

![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)](image)

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

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| 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 permanent right ventricular pacing | NA                                               | Intrinsic; BV pacing | NA              | QT              | Bazett’s formula   |
| Türküoğlu 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: 16; 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 LVEF ≤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, Tp-e     | Bazett’s formula   |
| Santangelo 2006 | 50   | Patients undergoing CRT, with NYHA III-IV, QRS >130 ms, LVEF <35% and LVEDD >55 mm          | 12 months after implantation                     | Intrinsic; LV pacing; BV pacing | NA              | QT, 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 fraction; NYHA - New York Heart Association functional classification; sVTA - sustained ventricular tachyarrhythmias; QT - QT interval; QTD - QT dispersion; Tp-e - interval between the peak to end of T wave
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) (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 (I²=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
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 been 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 Türküoğlu 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 echocardio-

graphic 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.

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