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Endocardial biventricular pacing for chronic heart failure patients: Effect on transmural dispersion of repolarization

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Abstract

Background and Aim: Conventional epicardial cardiac resynchronization therapy (CRT) can cause fatal arrhythmia associated with increased transmural dispersion of repolarization (TDR). It is unknown whether endocardial biventricular pacing in various locations will decrease TDR and hence the occurrence of fatal arrhythmia. This study aimed to find out the most effective location of endocardial biventricular pacing resulting in the shortest homogenous TDR.

Methods: A before-and-after study on adult chronic heart failure (CHF) patients undergoing endocardial biventricular pacing in several defined locations. The changes in TDR from baseline were compared among various pacing locations.

Results: Fourteen subjects were included with age ranged 36-74 years old, of which 10 were males. Location revealed the highest post biventricular pacing TDR (113.4 (SD 13.8) ms) was the outlet septum of right ventricle in combination with lateral wall of left ventricle (RVOTseptum-LVlateral) while the lowest one (106.1 (SD 11.6) ms) was of the right ventricular apex and posterolateral left ventricle (RVapex-LVposterolateral). Two CRT locations resulted in the most homogenous TDR, that is the right ventricular apex - left ventricular lateral wall (RVapex-LVlateral, mean difference −9.43; 95% CI (−19.72;0.87) ms, $P = 0.07$) and right ventricular apex - left ventricle posterolateral wall (RVapex-LVposterolateral, mean difference −6.85; 95% CI (−13.93;0.22) ms, $P = 0.056$).

Conclusion: Endocardial biventricular pacing on right ventricular apex and left ventricular lateral/posterolateral walls results in the most homogenous TDR.

KEYWORDS

arrhythmia, cardiac resynchronization therapy, chronic heart failure, endocardial biventricular pacing, transmural dispersion of repolarization

1 | INTRODUCTION

In epidemiological study, 25% of the chronic heart failure (CHF) are accompanied by intraventricular conduction disturbance, mainly left bundle branch block (LBBB) which is an independent risk factor for cardiac death.[1] LBBB causes dyssynchrony of right and left ventricular contraction resulting in hemodynamic alterations, such as decreased cardiac output and mitral regurgitation.[2] Therefore, symptomatic heart failure patients with reduced ejection fraction (HF*r*EF) with prolonged QRS duration is indicated for cardiac resynchronization therapy (CRT) based on various international guideline.[3] CRT reduces mortality and HF hospitalizations in selected patients with left ventricular (LV) systolic dysfunction and prolonged QRS duration.[4]

However, the mortality in patients receiving CRT remain high (3-year mortality of 24.7% in CRT recipients vs 38.1% in the control population).[5] Conventional CRT (epicardial biventricular pacing or LV pacing) could cause fatal arrhythmia in the form of polymorphic ventricular tachycardia which is associated with increased transmural repolarization dispersion (TDR).[6] In experimental study, epicardial pacing proved to prolong TDR significantly compared to mid-myocardial pacing.[7]

Transmural repolarization dispersion occurs because the myocardium possesses three types of cells with different electrophysiological properties (epicardial, endocardial, and M-cells) found in the inner sub endocardial layer, causing myocardial electrical heterogeneity.[8,9] An animal study found that LV septal pacing resulted in transmyocardial activation mimicking normal sinus rhythm rather than the epicardial LV or biventricular pacing.[8] These findings lead to the idea of performing endocardial CRT which has been shown to be effective for electrical resynchronization.[8] A study demonstrated that endocardial biventricular pacing decreases TDR significantly compared to the conventional epicardial pacing.[8] However that study only investigated single RV location (RV apex). It is unknown whether endocardial biventricular pacing in various locations of left and RV will decrease TDR as well. This study aimed to find out the most effective location of endocardial biventricular pacing resulting in the shortest homogenous TDR.

2 | METHODS

This one group before-and-after study was performed at the Cardiology Clinic Department of Internal Medicine and at the Integrated Cardiovascular Service Cipto Mangunkusumo Hospital (CMH) Jakarta from February 2010 to October 2010. Ethical clearance was obtained from the Ethics Committee of Faculty of Medicine Universitas Indonesia.

We included patients according to the following criteria: (a) 18 years old/older; (b) diagnosed with heart failure (HF) NYHA class III/IV despite optimal medications accompanied by QRS duration > 120 ms, LBBB on surface ECG, LV dilatation with ejection fraction (EF) <35% or QRS duration > 200 ms after apical RV pacing; (c) planned to undergo one of the following procedures: right heart study, electrophysiology study, coronary angiography, permanent pacemaker implantation, or biventricular cardiac pacing. We excluded patients with hemodynamic instability, ventricular tachycardia, or acute coronary syndrome. Informed consent was obtained from all participants.

We calculated the minimum sample size using the formula for estimating mean difference of paired samples. We performed a pilot study on the first five subjects of which we obtained standard deviation of the mean difference in TDR (SD 18). We also determined 15 as the minimal value of mean difference in TDR to be considered clinically significant. Using those values, 0.05 significance level, and 80% power, we found that the minimum number of subjects required was 12.

The endocardial biventricular pacing at various location was the primary intervention of this study. At the beginning of the procedure (Figure 1), we inserted temporary pacemaker (TPM) lead and a mapping catheter through femoral vein and artery. The pacing procedure was performed using a TPM lead (*Pacel bipolar pacing*, *St Jude Medical*) or a decapolar catheter for electrophysiology (EP) study (*Biosense Webster*). Pacing was conducted using EP system (*EP Tracer 70*, *Netherlands*).

We determined biventricular pacing location based on fluoroscopy image, 12-lead ECG and coronary sinus road map which was obtained by left coronary artery angiography at 40° left anterior oblique (LAO) and 30° right anterior oblique (RAO) projections.[8] Following determination of pacing locations, we paced each location sequentially with interval ≤ 80 ms between both ventricles (V-V delay).[8] To empirically ensure that pacing was performed

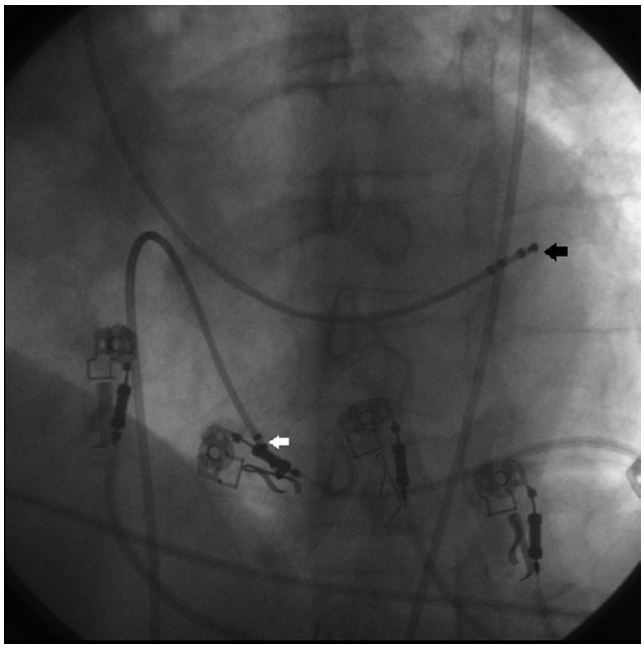

FIGURE 1 Simultaneous pacing at apex of right ventricle (white arrow) and lateral left ventricular wall (black arrow)

sequentially, we applied surface ECG and intra-cardiac electrogram (EGM) with the speed of 150 mm/s. Sequential pacing was fulfilled if the difference between transseptal time (TT) and the summation of left ventricular conduction time (LVCT) plus biventricular time (BT) [TT-(LVCT + BT)] was ≤+80 ms or ≤−80 ms in each location. The pacing output was set twice above the threshold with a rate of 10% above subject's intrinsic baseline rate. The pacing procedure was performed until surface ECG recording for each location was complete.

The primary outcome of this study was TDR which was measured as the Tpeak-Tend interval (the interval between the peak of T-wave and the point where the end of T-wave crossed the isoelectric line)[9] as shown in Figure 2. We calculated the mean of TDR measured from several leads (I, aVF, V1, and V5) and excluded biphasic or flat T from the measurement. This measurement was performed by two experienced EP technicians blinded to each other.

Data were described using mean (standard deviation), median (range), or proportion as appropriate. Normality of data was evaluated using histogram and Shapiro-Wilk test. The mean difference of TDR among various pacing locations was evaluated using paired t-test. A value of $P < 0.05$ was considered as statistically significant.

3 | RESULTS

During the study period, 14 subjects were recruited with ages ranging from 36-74 years old, of which 10 were males. All subjects present with NYHA III/IV HF despite maximal medical treatment and were indicated for RV lead monitoring or coronary angiography. The baseline characteristics are described in Table 1. Two of 14 patients had ventricular pacing rhythm after previous univentricular pacemaker implantation at RV. All patients showed LBBB on ECG. We observed alteration in QRS duration before and after treatment (145.2 (SD 25.07) to 133.6 (SD 26) ms, $P < 0.001$).

The baseline TDR before intervention was 99.2 (SD 14.2) ms. We found that postpacing TDR among various locations were different. The highest postpacing TDR (113.4 (SD 13.8) ms) location was the outlet septum of right ventricle and lateral wall of left ventricle (RVOTseptum - LVlateral) while the lowest one (106.1 (SD 11.6) ms) was the right ventricular apex and posterolateral left ventricle (RVapex - LVposterolateral). Two CRT locations resulted in the most homogenous TDR, that is, the right ventricular apex-left ventricular lateral wall (RVapex-LVlateral) and right ventricular apex - left ventricle posterolateral wall (RVapex-LVposterolateral) as described in Table 2.

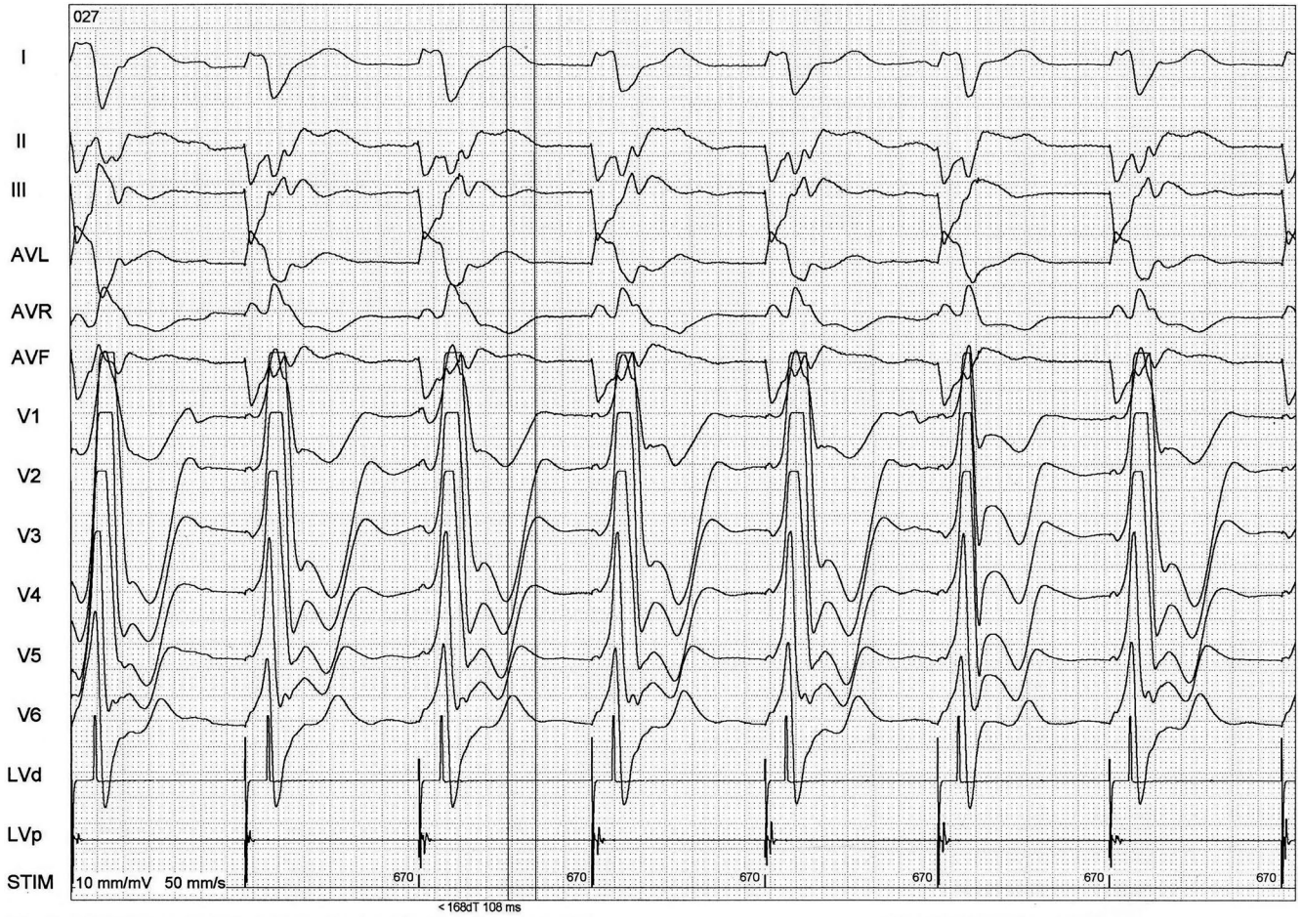

FIGURE 2 Measurement of Tpeak-Tend interval (108 ms) at lead I obtained from pacing location at RV apex and LV posterolateral wall

TABLE 1 The baseline characteristics of subjects

Variable	Values (n = 14)
Age (year)	53.5 ± 10.2
Echocardiography	
Ejection fraction (%)	23.7 ± 5.2
Diastolic final dimension (mm)	69.29 ± 9.9
Ischemic cardiomyopathy	9 (66.7)
NYHA grading	
III	11 (79)
IV	3 (21)
QRS complex duration (milliseconds)	153.2 ± 22.1
Basic rhythm	
Normal sinus	12 (85)
Racing ventricles	2 (15)
Weight (kg)	59.3 ± 12.2

Values are shown in mean ± SD or n (%).

In subgroup analysis on patients with ischemic HF, the mean of baseline TDR was 95.0 (SD 15.1) ms. In this group, the highest TDR (109.0 (SD 14.2) ms) pacing was the RVOT septum and left ventricular lateral wall (RVOTseptum-LVlateral), while the lowest one (101.7 (SD 11.0) ms) was of the right ventricular apex and left ventricular posterolateral wall (RVapex-LVposterolateral). In nonischemic group, the mean baseline TDR was 106.8 (SD 9.4) ms. The highest (121.2 (SD 9.6) ms) and lowest TDR (114.0 (SD 8.7) ms) were obtained from the RVOTspetum-LVlateral and RVapex-LVposterolateral pacing, respectively.

The baseline TDR in subjects with EF ≤ 20% was higher than those with EF ≥ 20% although not statistically significant. In subjects with EF ≤ 20%, the shortest TDR (103.2 (SD 17.4) ms) and longest TDR (115.8 (SD 16.4) ms) were obtained from pacing at RVOTseptum-LVposterolateral and RVOTseptum-LVlateral, respectively, but are not statistically different from the baseline TDR. In subjects with EF ≥ 20%, highest TDR (113.3 (SD 10.7) ms) was also obtained from the RVOTseptum-LVposterolateral pacing while the shortest one (106.0 (SD 13.9) ms) was RVapex-LVposterolateral. Both were also not statistically different from the baseline TDR.

Patients with QRS complex duration ≤ 150 ms had shorter baseline TDR (97.2 (SD 14.6) ms) compared to those with QRS complex duration > 150 ms (104.3 (SD 13.5) ms). However, both groups similarly demonstrated shortest and highest postpacing TDRs in RVapex-LVposterolateral and RVOTseptum-LVlateral, respectively.

TABLE 2 Baseline TDR values and postendocardial biventricular pacing TDR values of six different locations

TDR	Values (n= 14)
Baseline	99.2 ± 14.2
RVapex-LVposterolateral	106.1 ± 11.6
RVapex-LVlateral	108.6 ± 11.1
RVseptum-LVposterolateral	109.9 ± 12.4
RVseptum-LVlateral	110.2 ± 13.1
RVOTsept-LVposterolateral	109.7 ± 13.8
RVOTsept-LVlateral	113.4 ± 13.8

Abbreviations: TDR, transmural repolarization dispersion; RV, right ventricle; LV, left ventricle; RVOT, right ventricle outflow tract.
Values are shown in mean ± SD or n (%).

4 | DISCUSSION

Epicardial LV lead placement of CRT has become a routine procedure to improve symptoms and reduce mortality in selected HF patients.[10] To our knowledge, this was the first study on CHF patients evaluating the effect of endocardial biventricular pacing on various locations of the heart on TDR homogeneity. The work on endocardial CRT actually started in 1998.[11] Previous studies have looked at the effect of endocardial CRT on TDR but only in single or limited locations.[12]

This study did not reveal different baseline TDR among patients with CHF. This was in line with the results of studies about RV and LV activation pattern in patients with LBBB. In LBBB, activation starts homogenously at RV endocardium before spreads transseptally to the left causing LV endocardial breakthrough, mostly in septal and superior basal area.[13] In HF accompanied by LBBB, the endocardial activation was normal or only slightly prolonged on evaluation with noncontact mapping system.[14]

We found that pacing locations revealing most homogenous TDR compared to baseline were the RVapex-LVlateral and the RVapex-LVposterolateral. In CHF with LBBB, mechanical and electrical activation dyssynchrony occurs resulting in electrical remodeling mostly in areas with slowest activation such as LV lateral wall.[15,16] At the same time, these areas are also most responsive to CRT.[17] In addition to that, in LBBB, RV apex was the last area to be electrically activated.[18,19] This supports the hypothesis that pacing on LV lateral wall and RV apex will reduce electrical and mechanical dyssynchrony and decrease TDR. Our findings were similar with previous studies,[12,18] which could be explained by two things: (a) Pacing at LV lateral wall will induce significant electrical remodeling that decreases TDR; (b) Pacing at those location may result in reverse structural remodeling associated with decreased repolarization heterogeneity. The *Reverse Remodeling and the Risk of Ventricular Tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy)* study showed that patients with severe LV dysfunction had reverse remodeling that strongly associated with decreased risk of life-threatening arrhythmia.[20]

Our study found that pacing RV apex in combination with LV posterolateral wall resulted in the second most homogenous TDR. A previous study did not find the similar result probably because the study measured TDR by using only surface ECG.[12] However, our findings are supported by some previous works showing that posterior area is one of the areas which is activated the last.[21-23]

Our finding that endocardial pacing resulted in decreased TDR was not in agreement with some previous works.[12] This difference

might be explained by the differences in methods and timing of measuring TDR. We measured TDR at I, aVF, V1, and V5 leads using electrocardiographic imaging (ECGI), while previous studies utilized only 12-lead ECG.[12] The previous study also measured the TDR on follow-up with surface ECG,[12] which might results in different precordial lead placement compared to the baseline examination.

We found no difference between baseline and postpacing TDRs in patients with poor LV function (EF < 20%). The locations with the most homogenous TDR in this group are the RVOT septum and LV posterolateral wall which are different compared to the group with better LV function (EF > 20%). However, a previous study found that EF value did not correlate with LV heterogeneity, but the TDR was mostly influenced by the amount of scar tissue.[24] The difference in locations giving the most homogenous TDR could be explained by several things: (a) In this study all subjects with EF < 20% had ischemic HF in whom the electrical substrate modification is limited by the presence of slow conduction zone due to ischemia or scar;[24] (b) The distance between pacing location and the myocardium scar;[25] (c) Coronary sinus or RV apex pacing can shift the line of block during intrinsic rhythm which may influence the resynchronization effect of biventricular pacing on the TDR. In this study, we found that among patients with EF > 20%, the TDRs were more heterogeneous although this finding was not statistically significant.

Previous studies showed that QRS duration is a predictor of CRT responsiveness and the occurrence of adverse clinical events.[25,26] We found that patients with QRS duration ≥ 150 ms tends to have more heterogeneous baseline and postpacing TDR compared to those with QRS duration of < 150 ms.

Our study has several limitations. First, not all patients meeting the inclusion criteria underwent the study procedure due to unstable hemodynamic or comorbidities hampering intervention using contrast agent. Second, the sample size determination used standard deviation from the pilot study and educated guess of effect size. This might result in inaccurate estimation since there has not been any study evaluating how large TDR difference that correlates with arrhythmia. Third, we used different electrodes and pacing equipment between left and right ventricles which could cause different sequential pacing rate. However, we set a limit for the QRS duration difference so that it did not differ more than 80 ms (the maximal tolerable V-V delay in conventional pacing) between each ventricular and simultaneous pacings.[11] We also had limitation in determining the pacing location in LV by only using indirect venogram and surface ECG. Moreover, in patients with very large ventricular dimension, pacing location and procedure were not easily confirmed. The other limitation of this study is the status of atrioventricular (AV) conduction of the subject was not differentiated as it may contribute to TDR value.

5 | CONCLUSION

Endocardial biventricular pacing on RV apex and LV lateral/posterolateral walls results in the most homogenous TDR while pacing on RV outflow tract septum and LV lateral walls cause the largest TDR.

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CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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