

# COMPARISON OF VENTRICULAR DYSSYNCHRONY ACCORDING TO THE POSITION OF RIGHT VENTRICULAR PACING ELECTRODE: A MULTI-CENTER PROSPECTIVE ECHOCARDIOGRAPHIC STUDY

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**BACKGROUND:** Conventional pacemaker implantation induces left ventricular (LV) dyssynchrony, which might affect the LV function. We sought to evaluate the impact of different right ventricular (RV) pacing sites on the LV dyssynchrony and performance.

**METHODS:** Comprehensive echocardiographic evaluation including the atrio-ventricular, inter- and intra-ventricular dyssynchrony based on M-mode, conventional Doppler and tissue Doppler imaging (TDI) was done before and immediately after (< 7 days) pacemaker implantation. For the LV performance, LV ejection fraction, longitudinal peak systolic velocity at the mitral annulus (S') annular or mean longitudinal velocity of the 6 basal segments (Sm) were used. These results were compared with those of 15 age matched controls.

**RESULTS:** A total of 79 patients (48 females, mean age  $63 \pm 12$  years) underwent RV pacing at the apex ( $n = 45$ , group I) or the septum ( $n = 34$ , group II). After pacemaker implantation, the QRS duration was significantly increased in both groups, but the change was greater in group I ( $57.1 \pm 28.3$  versus  $32.8 \pm 40.5$  msec). Both the S' and Sm were lower in pacing groups than those in controls and Sm was significantly higher in group II ( $4.2 \pm 1.0$  versus  $4.9 \pm 1.3$  m/sec) than group I despite a similar LV ejection fraction. The aortic pre-ejection time and septal to posterior wall motion delay in patients with pacemaker were longer compared to normal controls, but there were no significant differences. Both the TDI velocity and strain analysis showed no difference of the dyssynchrony indices between the two groups, despite a higher tendency of Doppler strain dyssynchrony indices in the RV apical pacing group compared to those of the control.

**CONCLUSION:** Despite the marked increase of the QRS duration after pacing, M-mode, Doppler and TDI failed to demonstrate any difference according to the pacing sites. The long-term effect of the longitudinal contraction being less affected and a smaller increase of the QRS duration in the RV septal pacing group needs to be confirmed in a longitudinal follow-up study.

**KEY WORDS:** Pacemaker · Dyssynchrony · Echocardiography.

## INTRODUCTION

Right ventricular (RV) apical pacing allows for safe and sta-

ble long term pacing. However, RV apical pacing inevitably induces non-physiologic left ventricular (LV) activation with

• Received: July 5, 2010 • Revised: October 26, 2010 • Accepted: October 29, 2010

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alteration of the intraventricular contraction sequence, which delays LV activation.<sup>1)</sup> This delay is accompanied with LV dyssynchrony, and the development of LV dyssynchrony was reported to be associated with deterioration of heart failure symptoms and the systolic LV dysfunction.<sup>2)</sup> To overcome this potential limitation, other pacing sites including the RV outflow tract, the interventricular septum, and the his bundle have been tried.<sup>3)</sup> However, contradictory results have been reported in the literature<sup>4,5)</sup> and the impact of different RV pacing sites on LV dyssynchrony has not been seriously investigated. In this study, we sought to evaluate the acute changes of LV dyssynchrony according to the RV pacing sites.

## METHODS

### STUDY POPULATIONS

This study is a multicenter, prospective observational study. The study population consisted of the patients who needed permanent pacemaker implantation for sick sinus syndrome (SSS) or high degree atrio-ventricular (AV) block. Of these, we excluded the patients who had a temporary or permanent pacemaker prior to the study, and those with poor image quality, significant mitral or aortic steno-insufficiency, underlying left bundle branch block, or advanced LV systolic dysfunction (ejection fraction < 40%). Seventy nine patients with pacemaker implantation and 15 age-matched healthy controls were included.

### PACEMAKER IMPLANTATION

Pacemaker leads were inserted through the subclavian vein using standard implantation techniques. The RV leads were positioned in the RV apex (n = 45) or interventricular septum (n = 34) under fluoroscopic guidance. The decision for the lead positioning was determined at the electrophysiologists' discretion.

### ECHOCARDIOGRAPHY

All the patients underwent comprehensive echocardiographic evaluation before and after (< 7 days) pacemaker implantation. All the images were obtained with a standard ultrasound machine (Vivid 7, GE Vingmed, Horton, Norway) with a 2.5 MHz probe. Standard techniques were used to obtain M-mode, two-dimensional, and Doppler measurement in accordance with the American Society of Echocardiography guidelines. The tissue Doppler derived peak systole (S') were measured at the septal mitral annulus. The averaged peak systolic tissue velocity (Sm) was also calculated from 6 basal segments. S' and Sm were considered to represent the LV longitudinal function. The LV end-systolic, end-diastolic volume, and ejection fraction were calculated by the Simpson's methods from the apical four and two chamber views.

### ASSESSMENT DYSSYNCHRONY

Digital loops with one cycle of fundamental 2D image and

three cycles of the color coded tissue Doppler imaging (TDI) were acquired from a parasternal short axis view at the mid-papillary and three apical views for off-line analysis of LV dyssynchrony using Echopac (BT07, GE, Vingmed). All the images were transferred to one center and analyzed by one observer (GY Cho), who was blinded to the clinical data and the other echocardiographic information.

### ATRIO-VENTRICULAR DYSSYNCHRONY

A delay in the LV ejection can be reflected in the LV filling time, which is measured by the mitral inflow velocity. The atrio-ventricular dyssynchrony was measured as the LV filling time as the ratio of the RR interval.<sup>6)</sup>

### INTER-VENTRICULAR DYSSYNCHRONY

Using pulsed-wave Doppler, we measured the difference between the pre-ejection intervals from the QRS onset to the beginning of ventricular ejection at the right and left ventricular outflow tract.<sup>7)</sup>

### INTRA-VENTRICULAR DYSSYNCHRONY

A) M-mode echocardiography: The septal to posterior wall motion delay (SPWMD) was assessed using M-mode echocardiography at the parasternal window.<sup>8)</sup> The interval between the maximal thickening of the septum and posterior wall was calculated.

B) Conventional Doppler imaging technique: We measured the pre-ejection interval from the QRS onset to the beginning of ventricular ejection at the LV outflow tract by using pulsed-wave Doppler for the assessment of global intra-ventricular dyssynchrony.

C) Tissue Doppler imaging technique: The peak myocardial velocity during the ejection phase and the time to the peak myocardial velocity (Ts) were measured with reference to the QRS complex. If the peak velocity could not be defined because of the noise signal or flat velocity contour, then the sample volume (12 × 6 mm) was gradually moved to the apex or base until clear signal intensity could be obtained. Intra-ventricular dyssynchrony was assessed by measuring the difference of Ts between the basal septum and basal lateral segment (Ts-SL)<sup>9)</sup> or by measuring the standard deviation of Ts of 12 basal and mid segments (Ts-SD).<sup>10)</sup> For strain analysis, the longitudinal strain curves were obtained from 12 basal and mid segments. The region of interest with a 12 × 6 mm oval shaped was placed in the middle of the respective segments from the three apical views and maintained same position during the cardiac cycle by manually tracking to avoid blood or pericardial contamination. The minimal frame rate was 130 frames per second. The time to peak strain (Te) with reference to the QRS complex were measured. The time difference of Te between basal septum and basal lateral segment (Te-SL) or standard deviation in time to peak strain among the 12 segments (Te-SD) was obtained for the strain derived dyssynchrony.<sup>11)</sup>

The timing of events, such as aortic valve opening and closure, was obtained from color-coded M-mode of anterior mitral valve from the apical windows.<sup>12)</sup>

D) 2D speckle strain: Radial strain using speckle tracking was assessed on LV short axis at the mid-papillary muscle level (frame rate varied from 60 to 80 frames per second). Endocardium was traced manually at the end-systolic frame. The traced endocardium was automatically divided into 6 segments. The strain curves for each segment were constructed. We measured the time to peak radial strain of each segment. The absolute time interval of peak strain between anteroseptum and posterior segment was calculated.<sup>13)</sup> In addition, the time interval between the earliest and latest segment (maximal temporal difference) was also measured.

### STATISTICAL METHODS

Data are presented as the mean  $\pm$  standard deviation for continuous variables and as proportion for the categorical variables. The mean values of continuous variable were compared by t-test or ANNOVA, and the differences in the prevalence between the groups were compared via  $\chi^2$ -test. All the analyses were performed with SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) and  $p < 0.05$  was considered to be statistically significant.

### RESULTS

The baseline characteristics and echocardiographic measurements are summarized in Table 1. Age, pre-pacing QRS duration and LV ejection fraction were comparable between the

two groups (Table 1). After pacemaker implantation, LV volume and ejection fraction did not significantly change. The QRS duration was significantly increased in both groups after pacing, but the difference between the pre- and post-pacing QRS duration was significantly higher in apical pacing group ( $57.1 \pm 28.3$  versus  $32.8 \pm 40.5$  msec).

The echocardiographic variables immediately after pacemaker implantation are demonstrated in Table 2. The patients with RV apical pacing showed a lower  $S'$  ( $5.3 \pm 1.3$  versus  $5.7 \pm 1.5$  cm/sec) and  $S_m$  ( $4.2 \pm 1.0$  versus  $4.9 \pm 1.3$  cm/sec) than those with septal pacing. Aortic pre-ejection time and SPWMD in patients with a pacemaker were longer compared to those of normal controls, but there was no significant difference. Both TDI velocity and strain analysis showed no difference of dyssynchrony indices between the two groups, despite that there was a higher tendency of Doppler strain dyssynchrony indices in RV apical pacing group compared with those of the control ( $p = 0.063$  for Te-SL and  $p = 0.026$  for Te-SD).

### DISCUSSION

In this study, we demonstrated that both septal and apical pacing produce LV dyssynchrony, but septal pacing is superior to RV apical pacing in terms of LV longitudinal function. However, there was no significant difference in LV dyssynchrony between septal and apical pacing.

### PACING AND LV DYSFUNCTION

In the past several years, there has been increasing recognition of the deleterious clinical effects of RV apical pacing,

**Table 1.** Baseline characteristics

Variables	Apical pacing	Septal pacing	Control
Number	45	34	15
Age, years	65.7 $\pm$ 11.7	61.7 $\pm$ 12.8	62.8 $\pm$ 7.4
Male gender, n (%)	12 (26.7%)	20 (58.8%)*	8 (53.3%)*
Ischemic heart disease	11.1%	2.9%	
Hypertension	64.4%	44.1%	
Diabetes mellitus	24.4%	29.4%	
BMI (kg/m <sup>2</sup> )	24.4 $\pm$ 3.1	24.5 $\pm$ 3.9	
QRS duration, msec			
Pre-pacemaker	104.3 $\pm$ 22.6	115.3 $\pm$ 25.3	93.1 $\pm$ 9.2
Post-pacemaker	163.4 $\pm$ 18.7	152.8 $\pm$ 26.3	
Difference	57.1 $\pm$ 28.3	32.8 $\pm$ 40.5*	
Underling disease, n			
SSS/AV block	19 / 26	10 / 24	
Pre-pacemaker left ventricular volume, mL			
End-systolic	37.7 $\pm$ 16.3	43.5 $\pm$ 20.5	25.7 $\pm$ 4.7
End-diastolic	84.7 $\pm$ 27.9	107.2 $\pm$ 37.0	69.6 $\pm$ 15.1
Ejection fraction, %	60.0 $\pm$ 8.0	62.2 $\pm$ 8.1	63.5 $\pm$ 4.3
Post-pacemaker left ventricular volume, mL			
End-systolic	37.9 $\pm$ 21.0	39.5 $\pm$ 15.8	
End-diastolic	88.7 $\pm$ 33.3	99.6 $\pm$ 28.2	
Ejection fraction, %	57.5 $\pm$ 8.9	62.5 $\pm$ 7.8	

\* $p < 0.05$  versus the apical pacing group. AV: atrio-ventricular, BMI: body mass index, SSS: sick sinus syndrome

**Table 2.** Echocardiographic variables after pacemaker implantation

Variables	Apical pacing	Septal pacing	Control
S', cm/sec	5.3 ± 1.3	5.7 ± 1.5*	6.6 ± 1.4*
Sm, cm/sec	4.2 ± 1.0	4.9 ± 1.3*	5.6 ± 0.9*
Interventricular dyssynchrony, msec	27.0 ± 24.1	30.7 ± 23.0 <sup>†</sup>	13.6 ± 9.8
Aortic pre-ejection time, msec	115.7 ± 31.9 <sup>†</sup>	112.4 ± 29.8 <sup>†</sup>	79.3 ± 14.7
AV filling (%)	53.3 ± 7.4	48.6 ± 7.9	43.6 ± 4.6
SPWMD, msec	79.8 ± 40.9 <sup>†</sup>	96.3 ± 38.1 <sup>†</sup>	46.7 ± 21.3
TDI velocity			
Ts-SL, msec	49.1 ± 39.7	58.8 ± 41.5	35.3 ± 36.2
Ts-SD, msec	36.5 ± 16.1	38.6 ± 14.6	33.3 ± 11.9
TDI Doppler			
Te-SL, msec	83.4 ± 70.7	66.2 ± 45.9	44.7 ± 42.7
Te-SD, msec	63.8 ± 18.6	60.2 ± 17.3	55.3 ± 8.4

\**p* < 0.05 versus apical pacing, <sup>†</sup>*p* < 0.05 versus the control. SPWMD: septal to posterior wall motion delay, S': systolic annular tissue velocity, Sm: averaged value of the peak systolic tissue velocity in the 6 basal segments, Ts: time to the peak systolic velocity with reference to the QRS complex, Te: time to the peak strain with reference to the QRS complex, SL: time difference between the basal septum and lateral segment, SD: standard deviation of the time difference in 12 basal and mid segments

both in patients with pacemakers and in those with ICDs. In patients with a permanent pacemaker, every 1% incremental of RV pacing increases the risk of atrial fibrillation by 1% and the risk of heart failure hospitalization by 5.4%.<sup>14)</sup> Several studies have reported that RV apical pacing is associated with regional perfusion defects,<sup>15)</sup> adverse LV remodeling,<sup>16)</sup> a decrease in LV ejection fraction,<sup>17-19)</sup> and heart failure.<sup>2)</sup> More recently, several studies have reported that dyssynchronous LV contraction results from RV apical pacing.<sup>2)20)21)</sup>

The DAVID (Dual Chamber with VVI Implantable Defibrillator) trial suggested that RV apical pacing was associated with an increased risk of death and hospitalization for heart failure in patients with an implantable defibrillator.<sup>22)</sup> In that study, a higher cumulative percent of ventricular pacing was manifest in a significantly prolonged QRS duration at 6 months after pacemaker implantation and therefore, RV pacing might produce electrical dyssynchrony. Dual-chamber minimal ventricular pacing, as compared with conventional dual-chamber pacing, reduces ventricular desynchronization and moderately reduces the risk of persistent atrial fibrillation in patients with sinus node disease.<sup>23)</sup> The cumulative percent of ventricular pacing is associated with heart failure hospitalization and atrial fibrillation.<sup>14)22)</sup> Furthermore, in the patients with SSS, DDD pacing but not AAI pacing induces significant LV desynchronization and reduction of LV ejection fraction.<sup>24)</sup> Therefore, unnecessary RV pacing induces dyssynchronous LV contraction, which results in deterioration of LV systolic function and therefore, it can induce clinical heart failure. In our study, a dramatic increase of the QRS duration and SPWMD immediately after pacemaker implantation was demonstrated, and this suggests the potential detrimental long-term effect on the LV performance. Although the LV EF did not change immediately after implantation, the development of heart failure might depend on the pacing duration and so longer clinical observation is warranted.

By speckle tracking analysis, more than 50% of the patients showed dyssynchrony after RV pacing, which results in deteriorated LV systolic function and a worsened NYHA functional class.<sup>21)</sup> The development of LV dyssynchrony after permanent pacing is an important mechanism of LV function deterioration.<sup>25)</sup> Therefore, an alternative pacing mode or alternative pacing sites have been tested in order to prevent LV dyssynchrony and hemodynamic deterioration. Several studies have showed that either RV outflow tract (RVOT) pacing<sup>26-28)</sup> or RV septal pacing<sup>29)30)</sup> might have an advantage over classic RV apical pacing, but controversial results have also been reported.<sup>4)</sup> We could not demonstrate any significant difference of the LV dyssynchrony indices between the RV apical and septal pacing. According to the PROSPECT trial, no single echocardiographic measure of dyssynchrony may be recommended because of the poor reproducibility and moderate sensitivity of cardiac resynchronization therapy response.<sup>31)</sup> In this study, we used various kinds of mechanical dyssynchrony parameters. However, none of the echocardiographic measures of dyssynchrony showed a significant difference according to the pacing site.

One interesting finding of our study is that RV septal pacing showed better longitudinal systolic movement than did RV apical pacing. Although the resting LV EF was similar between the groups, this difference might affect the long-term LV performance, which should be tested by another study.

**STUDY LIMITATIONS**

The LV mechanical function and dyssynchrony could be evaluated by a recently introduced speckle-tracking imaging technique, which might provide other indices including LV twist and 2-dimensional radial strain.<sup>32)</sup> Using this relatively new technique, it might be interesting to test whether LV mechanical function or dyssynchrony indices show significant difference according to the different pacing sites. Finally, al-

though longitudinal function was better in the septal pacing group, we could not rule out the possibility that the difference of age and sex between two groups might affect our results.

#### • Acknowledgements

This work was supported by a research grant from the Korean Society of Echocardiography 2007.

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