Hemodynamic effect of atrioventricular and interventricular dyssynchrony in patients with biventricular pacing: Implications for the pacemaker syndrome

Mollazadeh R., Mohimi L., Zeighami M., Fazelifar A., Haghjoo M.

Cardiac Electrophysiology Research Center, Rajaie Cardiovascular Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Address for correspondence: *Dr. Majid Haghjoo, Cardiac Electrophysiology Research Center, Rajaie Cardiovascular Medical Center, Mellat Park, Vali-E-Asr Avenue, Tehran 1996911151, Iran.*
E-mail: majid.haghjoo@gmail.com

ABSTRACT

Background/Objectives: Pacemaker syndrome was mainly described as the sequel of atrioventricular (AV) dyssynchrony. The role of interventricular (VV) dyssynchrony has not been studied yet. The aims of this study were to noninvasively assess the hemodynamic effects of different ventricular pacing sites with and without AV and VV dyssynchrony and to observe the patients for clinical symptoms of the pacemaker syndrome during the AV sequential and ventricular-only pacing modes. **Materials and Methods:** Between March 2009 and February 2010, 40 patients (28 men; mean age, 61 ± 15 years) with biventricular (BiV) device were enrolled. Mean systolic and diastolic blood pressures (BP) of 5 beats were measured 5 minutes after each mode change using fingertip plethysmography. The patients were also observed for the occurrence of symptoms suggestive of the pacemaker syndrome, including dyspnea, palpitations, dizziness, presyncope, and syncope. **Results:** There was no difference in mean systolic BP among different ventricular-only pacing modes (all P = NS). However, mean systolic BP was significantly higher in AV sequential biventricular pacing (DDD-BiV) compared with ventricular-only pacing modes (all $P<0.05$). In addition, there was no difference in terms of pacemaker syndrome-related symptoms following mode change from DDD-BiV to DDD-RV or DDD-LV (all $P>0.05$). **Conclusions:** The present study showed that the non-AV sequential BiV and LV pacing may have no significant benefit compared with RV pacing in terms of systolic blood pressure. However, there was marked hemodynamic improvement following mode change to AV sequential BiV pacing. This study may have important implications for pathogenesis of pacemaker syndrome.

Key words: Atrioventricular synchrony, interventricular dyssynchrony, pacemaker syndrome

INTRODUCTION

Original description of pacemaker syndrome was done for the first time by Mitsui *et al.* in 1969 as a collection of symptoms associated with right ventricular (RV) pacing.[1] Since its first description, several definitions have been proposed for the pacemaker syndrome. The Mode Selection Trial (MOST) investigators defined the pacemaker syndrome as occurring if either one of two different criteria was met: The first criterion was new or worsened dyspnea, orthopnea, rales, elevated jugular venous pressure, and edema with ventriculoatrial conduction during ventricular pacing. The second criteria was symptoms of dizziness, weakness, presyncope, or syncope, and a >20 mmHg reduction of systolic blood pressure when the patient had VVIR pacing compared with atrial pacing or normal sinus

Access this article online

Quick Response Code:

Website: www.jcdronline.com

DOI: 10.4103/0975-3583.98892

rhythm.[2] These symptoms lead to significant decrease in quality of life, and sometimes surgical intervention was required to change the pacing mode from VVIR to DDDR.

Despite the significant progress, understanding of the cause of pacemaker syndrome is still under investigation. Role of atrioventricular (AV) synchrony in the emergence of this syndrome has been carefully addressed, but the role of RV-left ventricle (LV) dyssynchrony has not been studied yet.[3,4] There are speculations that the pacemaker syndrome may be etiologically related to interventricular (VV) dyssynchrony imposed by the high percentage of ventricular pacing commonly seen in the DDDR pacing.[4] This data shortage is mainly related to fact that standard antibradycardia pacing only allowed for univentricular RV pacing. Consequently, we enrolled a cohort of the patients with biventricular pacing to permit univentricular pacing from RV and LV, AV sequential and ventricular-only BiV pacing, and no pacing (sinus rhythm). Utility of beat-to-beat finger plethysmography for hemodynamic assessment of different pacing modes has been demonstrated previously.[3] Therefore, we designed a study to noninvasively assess the hemodynamic effects of different ventricular pacing sites with and without AV and VV dyssynchrony using beat-to-beat finger plethysmography and to observe the patients for clinical symptoms of the pacemaker syndrome during the different AV sequential and ventricular-only pacing modes.

MATERIALS AND METHODS

Study population

Between March 2009 and February 2010, a total of 40 patients (28 men, mean age, 61 ± 15 years) with cardiac resynchronization therapy (CRT) device were enrolled in this cross-sectional study. The resynchronization devices consist of 31 biventricular defibrillators (CRT-D) and 9 biventricular pacemakers (CRT-P). The patients with pacemaker dependency, atrial fibrillation, and recent heart failure decompensation were excluded. The study protocol was approved by the local Ethics Committee, and all patients gave written consent prior to the study.

Hemodynamic study protocol

After attaching the plethysmography probe to patient's finger, systolic and diastolic blood pressures (BP) were recorded in different pacing modes, namely, right ventricle pacing (VVI-RV), left ventricular pacing (VVI-LV), biventricular pacing (VVI-BiV), biventricular sequential pacing (DDD-BiV), and sinus rhythm (ODO). Average of five beats' blood pressure (BP) in each mode was accepted for comparison. Five minutes was allowed between each mode change to ensure that the effect of previous pacing mode on measured BP had vanished.[5] Patients' symptoms were recorded simultaneously (palpitation, dyspnea, chest pain, dizziness, presyncope, and syncope).

Statistical analysis

The data were recorded in SPSS (Chicago, IL, USA) ver. 16 software package. The continuous variables are presented as means + SD. The Student t-test was used to compare the data between the two groups with a normal distribution. Otherwise, a nonparametric Mann-Whitney U test was employed. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Hemodynamic data in different pacing modes

Hemodynamic data in different pacing modes are depicted in Figures 1 and 2. Paired comparisons of systolic BP in VVI-RV, VVI-LV, and VVI-BiV did not show any difference between them [Table 1]. Systolic BP in DDD-BiV mode is similar to sinus rhythm (ODO mode); however, the former had a significantly higher systolic BP than ventricular-only (VVI-RV, VVI-LV, and VVI-BiV) modes [Figure 1]. The diastolic BP was comparable in different ventricular-only modes [Table 1] and there were no significant differences between the AV sequential biventricular and any of the ventricular-only modes [Figure 2].

Clinical symptoms in different pacing modes

None of the patients developed syncope, presyncope, or dizziness after mode change. Mode change from DDD-BiV to VVI-RV was associated with palpitations and dyspnea in 22.5% of the patients. Similarly, 22.5% of the patients experienced palpitations and dyspnea after DDD-BiV to VVI-LV mode change. DDD-BiV to VVI-BiV resulted in palpitations and dyspnea in 12.5% of the patients. However, incidence of palpitations and dyspnea was similar between the mode changes from DDD-BiV to all VVI modes [Table 2]. Importantly,

Table 1: Comparison of hemodynamic data between different ventricular-only pacing modes

	VVI-RV	VVI-LV	*P*-value	VVI-RV	VVI-BiV	*P*-value	VVI-LV	VVI-BiV	*P*-value
Systolic BP (mmHg)	112 ± 26	111.5 ± 23	0.76	112 ± 26	101 ± 19	0.56	111.5 ± 23	101 ± 19	0.50
Diastolic BP (mmHg)	81 ± 22	80 ± 18	0.25	81 ± 22	72 ± 19	0.29	80 ± 18	72 ± 19	0.91

Values are mean ± SD. VVI-RV = Ventricular-only pacing from RV; VVI-LV = Ventricular-only pacing from LV; VVI-BiV = non-AV sequential biventricular pacing

Table 2: Comparison of symptoms suggestive of pacemaker syndrome in different pacing modes

	DDD-BiV/ VVI-RV	DDD-BiV/ VVI-LV	*P*-value	DDD-BiV/ VVI-RV	DDD-BiV/ VVI-BiV	*P*-value	DDD-BiV/ VVI-LV	DDD-BiV/ VVI-BiV	*P*-value
Palpitation	9 (22.5)	9 (22.5)	0.65	9 (22.5)	5 (12.5)	0.57	9 (22.5)	5 (12.5)	0.65
Dyspnea	9 (22.5)	9 (22.5)	0.65	9 (22.5)	5 (12.5)	0.57	9 (22.5)	5 (12.5)	0.65

Values are n (%) DDD-BiV = AV sequential biventricular pacing; VVI-RV = Ventricular-only pacing from right ventricle; VVI-LV = Ventricular-only pacing from left ventricle; VVI-BiV = non-AV sequential biventricular pacing

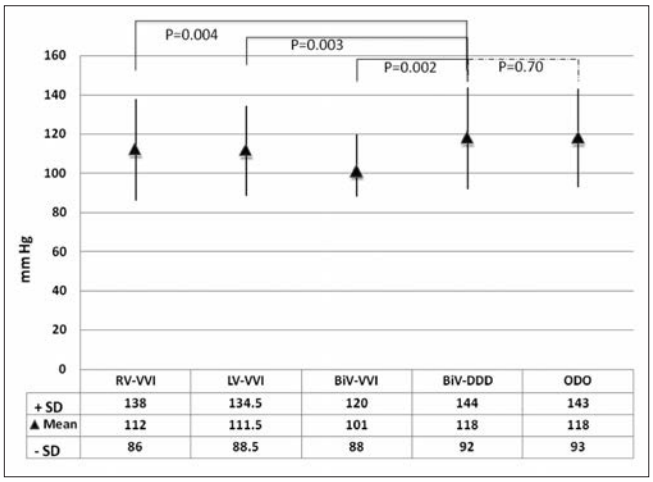

Figure 1: Paired comparisons of the systolic blood pressure between the atrioventricular sequential biventricular pacing (DDD-BiV) and ventricular-only pacing modes (VVI-RV, VVI-LV, and VVI-BiV). Note that systolic blood pressure is higher in DDD-BiV pacing mode compared with any of ventricular-only pacing modes. In addition, systolic blood pressure is comparable between the DDD-BiV and sinus rhythm

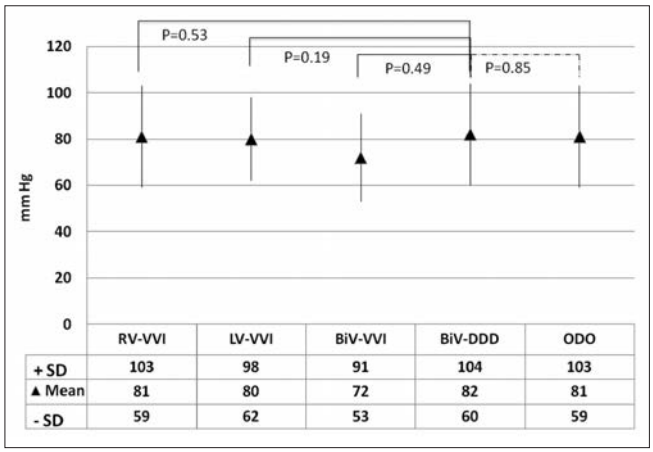

Figure 2: Paired comparisons of the diastolic blood pressure between the atrioventricular sequential biventricular pacing (DDD-BiV) and ventricular-only pacing modes (VVI-RV, VVI-LV, and VVI-BiV). There is no difference in the diastolic blood pressure between the DDD-BiV and ventricular-only pacing modes. In addition, diastolic blood pressure is similar between the DDD-BiV and sinus rhythm

palpitations and dyspnea did not occur after turning the CRT devices off.

DISCUSSION

Major findings of the current study are as follows: (1) Non-AV sequential biventricular pacing, univentricular RV pacing, and univentricular LV pacing produced similar systolic and diastolic BPs; (2) AV sequential biventricular pacing and sinus rhythm had similar hemodynamic profile and produced higher systolic BP than ventricular-only pacing modes; (3) mode downgrading from AV sequential biventricular (DDD-BiV) to all ventricular-only modes (VVI-RV, VVI-LV, and VVI-BiV) were associated with similar rate of palpitations and dyspnea, but mode change from DDD-BiV to ODO was not associated with development of new symptoms.

To the best of our knowledge, this is the first quantitative study performed in different pacing modes to evaluate for AV and VV dyssynchrony in patients with biventricular device. Similar to our study, Varma *et al.* showed no hemodynamic benefit for BiV and LV pacing compared with RV pacing.[5] Previously, it was shown that in patients having dual-chamber pacemaker, mode change from DDD to VVI leads to systolic BP decline with no significant change in diastolic BP, which is related to symptomatic intolerance of VVI pacing and may have potential utility as an aid to diagnosis or as a predictor of pacemaker syndrome.[3]

In our study, diastolic BP was similar in different pacing modes; this is in accordance with prior quantitative studies. [3] Diastolic blood pressure is not directly linked to cardiac output and ventricular systolic function, but on the contrary it is derived from systemic vascular resistance, peripheral run-off, and heart rate.[6] Besides the decisive role for

AV dyssynchrony in the emergence of pacemaker syndrome since early reports of VVI-RV pacing,[1] another role for interventricular dyssynchrony caused by RV pacing was raised. [4,7] Since the first nomination of "cardiac synchronization" by Cazeau *et al.*[8] in 1994 for placement of four epicardial leads on all four cardiac chambers, role of AV synchrony and optimization was not less than V-V synchrony. [9] It is hypothesized that RV pacing with or without AV synchrony induces a nonphysiologic contraction similar to that caused by left bundle branch block. This dyssynchrony leads to disturbed LV diastolic filling, reduction of cardiac output, and increase in mitral regurgitation.[10-12] Our analysis showed that decrease in systolic BP accompanied by dyspnea and palpitation (as an index of pacemaker syndrome) is related to loss of AV synchrony rather than site of ventricular pacing (RV, LV or BiV). Farmer *et al.* believed that the majority of the symptoms of pacemaker syndrome are likely attributable to the reduction in ejection fraction and cardiac output.[4] Increase in mitral regurgitation associated with right ventricular pacing is guilty for pacemaker syndrome, and if BiV pacing is performed, pacemaker syndrome is less likely. This is in contradiction with our results. We observed that with mode change from DDD-BiV to ODO (when device was turned off), no new symptom or change in blood pressure was observed. Considering the design of our study (quantitative assay accompanied by reproduction of symptoms, high fidelity measurement with fingertip plethysmography), we believe that pacemaker syndrome is derived mainly from AV dyssynchrony rather than VV dyssynchrony.

Limitations

This study was an acute hemodynamic study; real value of these findings should be tested in a long-term study. This study is also limited by the fact that we did not evaluate the role of different RV pacing sites (mid septal, low septal, or apical) on the hemodynamic data and the clinical symptoms.

CONCLUSIONS AND CLINICAL IMPLICATIONS

The present acute hemodynamic study showed that location of ventricular pacing and VV dyssynchrony may have no important role in the pathogenesis of the pacemaker syndrome. This study also confirmed the fundamental role of AV synchrony in preventing the pacemaker syndrome.

REFERENCES

1. Mitsui T, Hori M, Suma K, Wanibuchi Y, Saigusa M. The "pacemaking syndrome" [abstract]. In: Jacobs JE, editor. Proceedings of the eighth annual international conference on medical and biological engineering. Vol. 29. Chicago: Association for the Advancement of Medical Instrumentation; 1969. p. 3.
2. Link MS, Hellkamp AS, Estes NA III, Orav EJ, Ellenbogen KA, Ibrahim B,*et al.*; MOST Study Investigators. High incidence of pacemaker syndrome in patients with sinus node dysfunction treated with ventricular based pacing in the Mode Selection Trial (MOST). J Am Coll Cardiol 2004;43:2066-71.
3. Channon KM, Hargreaves MR, Gardner M, Ormerod OJM. Noninvasive Beat-to-Beat Arterial Blood Pressure Measurement during VVI and DDD Pacing: Relationship to Symptomatic Benefit from DDD Pacing. Pacing Clin Electrophysiol 1997;20(1 Pt 1):25-33.
4. Farmer DM, Estes NA III, Link MS. New Concepts in Pacemaker Syndrome. Indian Pacing Electrophysiol J 2004;4:195-200.
5. Varma C, O'Callaghan P, Rowland E, Mahon NG, Mckenna W, Camm AJ, *et al.* Comparison between biventricular pacing and single site pacing in patients with poor ventricular function: a hemodynamic study. Pacing Clin Electrophysiol 2003;26(2 Pt 1):551-8.
6. Daniels SR, Kimball TR, Khoury P, Witt S, Morrison J. Correlates of the Hemodynamic determinants of Blood Pressure. Hypertension 1996;28:37-41.
7. Zile MR, Blaustein AS, Shimizu G, Gaasch WH. Right ventricular pacing reduces the rate of left ventricular relaxation and filling. J Am Coll Cardiol 1987;10:702-9.
8. Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L, *et al.* Four chamber pacing in dilated cardiomyopathy. Pacing Clin Electrophysiol 1994;17(11 Pt 2):1974-9.
9. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P,*et al.* Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Circulation 1999;99:2993-3001.
10. Rosenqvist M, Isaaz K, Botvinick EH, Dae MW, Cockrell J, Abbott JA, *et al.* Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. Am J Cardiol 1991;67:148-56.
11. Burkhoff D, Oikawa RY, Sagawa K. Influence of pacing site on canine left ventricular contraction. Am J Physiol 1986;251 (2 Pt 2):H428-35.
12. Mark JB, Chetham PM. Ventricular pacing can induce hemodynamically significant mitral valve regurgitation. Anesthesiology 1991; 74:375-7.

How to cite this article: Mollazadeh R, Mohimi L, Zeighami M, Fazelifar A, Haghjoo M. Hemodynamic effect of atrioventricular and interventricular dyssynchrony in patients with biventricular pacing: Implications for the pacemaker syndrome. J Cardiovasc Dis Res 2012;3:200-3.

Source of Support: Nil, **Conflict of Interest:** None declared.