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Implications for the pacemaker syndrome: The hemodynamic impact of atrioventricular and interventricular dyssynchrony in patients with biventricular pacing

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ABSTRACT

Das Pacemaker-Syndrom wurde hauptsächlich als Folge einer atrioventrikulären (AV) Dyssynchronie beschrieben. Es wurde noch keine Untersuchung der Funktion der Interventrikulären (VV) Dyssynchronie durchgeführt. Das Ziel dieser Studie war es, noninvasiv die hemodynamischen Auswirkungen verschiedener ventrikularer Pacing-Sites mit und ohne AV- und VV-Dyssynchrony zu bewerten und Patienten auf clinical symptoms of the pacemaker syndrome während der AV-sequentiellen und ventrikular-only Pacing-Modi zu beobachten. Material und Verfahren: Zwischen März 2009 und Februar 2010 wurden 40 Patienten (28 Männer) behandelt. They were enrolled with a biventricular (BiV) device (average age, 61 ± 15 years). 5 Minuten nach jedem Wechsel der Mode wurden die mittleren systolicen und diastolicen Blutdruckwerte (BP) bei fünf Beaten mittels fingertipplethysmografie gemessen. Patienten wurden auch auf das Auftreten von Symptomen überwacht. Zeichen des Herzschrittmachersyndroms, einschließlich Atemnot, Herzrasen, Verwirrung, Presyncope und Syncope. Result: In different ventricular-only pacing modes there was no difference in mean systolic BP (all P = NS). However, when compared to ventricular-only pacing modes, mean systolic BP was significantly higher in AV sequential biventricular pacing (DDD-BiV). Furthermore, following mode change from DDD-BiV to DDD-RV or DDD-LV, no difference in pacemaker syndrome-related symptoms was observed (all P>0.05). Ergebnisse: In Bezug auf systolic blood pressure may the non-AV sequential BiV and LV pacing have no significant advantage compared to RV pacing. However, following the mode change to AV sequential BiV pacing, there was marked hemodynamic improvement. Dieser

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 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 pacingmodes.

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 enrolledin 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 EthicsCommittee, and all patients gave written consent priorto 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

Die Daten wurden im Softwarepaket SPSS (Chicago, IL, USA) Version 16 gespeichert. Die kontinuierlichen Variablen werden als Mittel plus SD dargestellt. Die Daten der beiden Gruppen mit einer normalen Verteilung wurden mithilfe des Student-t-Tests verglichen. Alternatively, a nonparametric Mann-Whitney U test was used. Es wurde festgestellt, dass eine Werte von P kleiner als 0.05 statistisch signifikant war.

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 (ODOmode); 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

Following a mode change, none of the patients experienced syncope, presyncope, or dizziness. In 22.5% of the patients, palpitations and dyspnea were associated with the mode change from DDD-BiV to VVI-RV. Similarly, after DDD-BiV to VVI-LV mode change, 22.5% of the patients experienced palpitations and dyspnea. In 12.5 % of the patients, DDD-BiV to VVI-BiV caused palpitations and dyspnea. However, the mode changes from DDD-BiV to all VVI modes had a similar incidence of palpitations and dyspnea [Table 2]. Insbesondere,

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

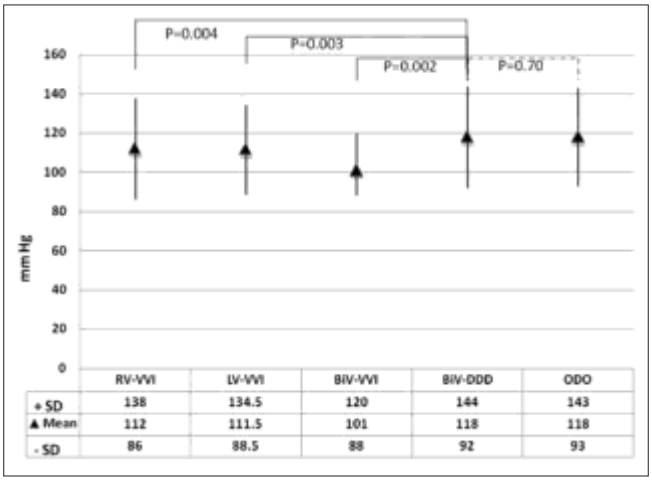

Figure 1: Paired comparisons of the systolic blood pressure between the atrioventricular sequential biventricular pacing (DDD-BiV) and ventricular-only pacing modes (VVI-RV, VVI-LV, and VVI-BiV). Note that systolic blood pressure is higher in DDD-BiV pacing mode compared with any of ventricular-only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

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.

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). Thereis no difference in the diastolic blood pressure between the DDD-BiVand ventricular-only pacing modes. In addition, diastolic blood pressure is similar between the DDD-BiV and sinus rhythm

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 apredictor 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 withoutAV synchrony induces a nonphysiologic contractionsimilar to that caused by left bundle branch block. Thisdyssynchrony 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 byreproduction of symptoms, high fidelity measurement with fingertip plethysmography), we believe that pacemaker syndrome is derived mainly from AV dyssynchrony rather than VV dyssynchrony.

Limitations

Diese Untersuchung war eine kurzfristige hemodynamische Untersuchung; die tatsächliche Bedeutung dieser Ergebnisse sollte in einer langfristigen Untersuchung getestet werden. In addition, this study is limited because we did not investigate the impact of various RV pacing sites (mid-septal, low-septal, or apical) on hemodynamic data and clinical symptoms.

CONCLUSIONS AND CLINICAL IMPLICATIONS

According to the current acute hemodynamic study, the location of ventricular pacing and VV dyssynchrony may not play a significant role in the pathogenesis of the

pacemaker syndrome. This study also confirmed the fundamental role of AV synchrony in preventing the pacemaker syndrome.

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