The effect of right ventricle pacemaker lead position on diastolic function in patients with preserved left ventricle ejection fraction

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Abstract

Our aim was to analyze any changes during diastole in patients with normal left ventricular ejection fraction (LVEF), after pacemaker stimulation from the right ventricular outflow tract (RVOT) and right ventricular apex (RVA) lead position. This was a prospective, randomized, follow up study, which lasted for 12 months. *Our research included* 132 consecutive patients who were implanted with a permanent antibradycardiac pacemaker. Regarding the right ventricle lead position the patients were divided into two groups: The RVOT group -71 patients, with right ventricle outflow tract lead position and the RVA group - 61 patients, with right ventricle apex lead position. We measured LVEF and diastolic parameters: peak filling ratio and time to peak filling ratio obtained by radionuclide ventriculography (RNV). The LVEF and various diastolic parameters and left atrial diameter were obtained by echocardiography. Based on the values of deceleration time of early diastolic filling (DTE), and other diastolic parameters like left atrial diameter, all the patients were classified into three degrees of diastolic dysfunction. *Our results showed* that there was no group difference in distribution of gender, age, body mass index (BMI), VVI to DDD pacemakers implantation ratio, RNV parameters (LVEF, peak filling rate (PFR), time to PFR (TPFR)) and echocardiography parameters: LVEF and parameters of diastolic dysfunction. After 12 months of pacemaker stimulation, LVEF by RNV remained the same in the RVOT group 51.31±15.80% (P=0.75), and also in the RVA group 53.83±6.57%, (P=0.19). In the RVOT group the PFR was highly lower and this finding was significant (P=0.01), while TPFR was also significantly lower (P=0.03). By dividing the patients according to the degree of diastolic dysfunction we found that most patients in both groups at enrollment had a second degree diastolic dysfunction. In both groups diastolic dysfunction increased, the number of patients with third degree diastolic dysfunction increased, and the number of patients with second degree diastolic dysfunction decreased, however, the worsening of diastolic function was significant only in the RVOT group. *In conclusion,* pacemaker stimulation from RVOT, but not in RVA, leads to progression of diastolic dysfunction in patients with preserved LVEF. This negative effect of pacemaker stimulation from RVOT on diastolic parameters was confirmed by two independent methods, RNV and echocardiography.

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Introduction

Standard pacemaker lead position and thus stimulation from right ventricle apex (RVA), is followed by prolonging transseptal and intraventricular impulse conduction and at least doubling of QRS duration [1]. Pacemaker stimulation from the right ventricular outflow tract (RVOT) gives faster conduction, and enables activation from septum to the rest of myocardium which in turn gives less dissinchrony between walls of the left ventricle, and shorter QRS duration [2-4]. After 20 years, the results of multi centre randomized trials showed a benefit of using an alternative pacemaker stimulation site in patients with lower left ventricular ejection fraction (LVEF), but not in patients with normal LVEF [5]. The negative effect of pacemaker stimulation on LV diastolic function is well known [6, 7]. However, the influence on LV diastolic function has remained unclear in patients with lead position either in RVOT or RVA whose systolic function was not negatively affected by pacemaker stimulation during this period. Previous studies compared RVOT and RVA lead positions, either with echocardiography or radionuclide ventriculography (RNV), while in our study we used both echocardiography and RNV. We enhanced the precision of diastolic parameters assessment using the combination of two independent methods.

We have studied the difference of RVOT and RVA lead position, in pacemaker stimulation on the diastolic function in patients with normal LVEF.

Subjects and methods

This was a prospective, randomized study, which lasted for 12 months and included 132 consecutive patients who were implanted with permanent antibradycardiac pacemaker, in the Pacemaker Center-Medical Center Zaječar, Serbia during the years 2010-2011. This study was approved by the Ethical Committee of Zajeyar Health Center and by Medical Faculty of the University of Niš. All patients gave their informed consent for this study. The pacemakers used were: St. Jude Medical Verity ADx XL SR 5156 (USA), single chamber pacemaker (VVI), and Medtronic Sensia SEDR01 (USA) dual chamber pacemaker (DDD). Regarding the RV lead position the patients were divided into two groups:

The RVOT group of 71 patients, with RV outflow tract lead position and the RVA group of 61 patients, with RV apex lead position. In the RVOT group active fixation ventricle leads (St. Jude Medical Tendril 188TC/58) were used. In the RVA group, ventricle passive fixation leads (Medtronic 4074-58) were used. All patients with DDD pacemakers had a "J" passive fixation atrial lead Medtronic 4592-53.

Radionuclide ventriculography

The RNV exams were carried out in the Nuclear Medicine Service of Medical Center Zaječar and in the Center for Nuclear Medicine of Clinical Center Niš, Serbia. Red blood cells (RBC) were labeled using either in vivo technique, in Nuclear Medicine Service of Medical Center Zaječar and combined in vivo/vitro technique in Nuclear Medicine of Clinical Center Niš. For in vivo labeling, patients were intravenously (i.v.) injected with approximately 2.5mg stannous pyrophosphate for sensitizing RBC, 30min prior to the injection of 555-1110MBq of technetium-99m-pertechnetate ($^{99m}TcO^{-}_{4}$). For in vitro labeling, patients were i.v. injected with approximately 2.5mg stannous pyrophosphate for sensitizing RBC. Thirty minutes later, blood was withdrawn using sterile heparin coated syringe, 555-1110MBq of $^{99m}TcO^{-}_{4}$ was added into the syringe, which was incubated for 30min on 37°C. Then, the labeled blood was i.v. injected back to the patients. Acquisition started 10min later in supine position, using single headed Siemens Open Diacam gamma camera with high resolution parallel hole collimator, by gated single photon emission tomography (SPET) acquisition protocol first and immediately after, planar acquisition started in left anterior oblique position (LAO 45°) or in the best septal position. Gated SPET was performed by using circular, patient centered orbit, with an imaging arc of 180°, starting rotation clockwise from right anterior oblique (RAO 45°) to left posterior oblique (LPO 45°) position, by step and shoot in 32 positions, 30s/per position and using the R-R wave of the electrocardiogram (ECG) for gating, with 16 frames per R-R interval. Planar acquisition in LAO 45° or in the best septal position was done using R wave as a trigger, with 16 frames per R-R interval. The LVEF was calculated from the LV volumes counts using the formula:

$$EF = \frac{EDc - ESc}{EDc - BG}$$ (EDc: end diastolic counts, Esc: end systolic counts, BG: background counts).

Normal LVEF range was 50%-80%. Peak filling rate (PFR) represented peak velocity of LV filling. Reference value was 2.5 EDV/s, i.e. 2.5±0.2 EDV/s (EDV-end diastolic volume). Time to peak filling rate (TPFR) is the time of maximal filling velocity, representing the time interval from end systole to the point of LV peak filling. Reference value was smaller than 180ms i.e. 172±9ms [8].

Echocardiography

The LVEF and diastolic parameters were assessed by echocardiography (ECHO) in the Cardiology Department of Medical Center Zaječar, Serbia. The equipment was VVID 3 GE Medical Systems, USA. The diastolic parameters measured were: a) The peak velocity of early diastolic LV filling (E) with reference value 0.86±0.16m/s. b) Early diastolic filling deceleration time (DTE) with reference value 140-240ms. c) The speed of mitral ring (E'). 4. E/E' ratio was measured by tissue pulse Doppler. EmL is the speed of lateral mitral cusps movement, and its median value is over 10cm/s. Ems is the speed of septal mitral cusps movement, and its normal value is over 8cm/s. E/E' is the ratio of the peak velocity of early diastolic LV filling and the speed of mitral ring. Its norm value is less than 8, which refers to normal LV filling pressure, border value (gray zone) is 8-15, diastolic dysfunction is over 15 and points to increased LV filling pressure [9, 10].

Reference values for left atrial diameter are up to 4cm. Based on the values of measured diastolic parameters: DTE, E/E', left atrial diameter, all patients were classified into three degrees of diastolic dysfunction [11, 12] (Table 1).

We calculated LVEF by Teicholtz formula: $EF = \frac{EDV - ESV}{EDV}$ (a similar formula to the above mentioned, but without the background activity). Reference values of LVEF were 62±8%, with lower limit set at 54%.

Echocardiography and RNV were performed at the beginning of the follow-up period and at 12 months later.

Statistical analysis

All statistical analyses were performed in SPSS 12.0 (SPSS Inc., Chicago, Illinois). Results were presented as frequency, percent and mean±SD. The x^2 test was used to test differences between nominal variables. T test was used to test differences (independent or paired samples) between numerical variables with normal distributions while Mann-Whitney U test was used for variables with non-normal distributions or ordinal variables. Wilcoxon Signed Ranks test was used for testing differences of paired samples with non-normal distributions or ordinal variables. All P values less than 0.05 were considered significant.

Results

Group comparison

There were no differences between the two groups studied as for sex, age, body mass index (BMI), VVI to DDD pacemaker implantation ratio, RNV parameters (LVEF, PFR, TPFR) and ECHO for LVEF and diastolic dysfunction. The only difference between these groups was the QRS duration after pacemaker stimulation (Table 2).

Radionuclide ventriculography

EF

After 12 months of pacemaker stimulation, LVEF remained the same and also in the RVOT group 51.31±15.80% (P=0.75) and in the RVA group 53.83±6.57% (P=0.19).

PFR, TPFR

After 12 months of pacemaker stimulation PFR and TPFR

Table 1. *Patient classification based on echocardiography diastolic parameters, taken and adapted from references 11 and 12.*

Diastolic disfunction	Echocardiographic parameters
Without diastolic disfunction	DTE <250ms, E/ E` <8 i E`s >8cm/s Left atrial <4.5cm
I Degree Impaired LV relaxation	DTE >250ms, E/ E`<8, i E`s <8cm/s Left atrial >4.5cm
II Degree Left ventricle pseudonormalisation (Impaired relaxation with increased LV filling pressure)	DTE <200ms, E/E`8-14, for the mean E`<8cm/s Left atrial >4.5cm
III Degree Reversible left ventricle restriction	DTE<200ms, E/ E`>15, for the mean E`<8cm/s Left atrial >4.5cm

Table 2. *Comparison of RVA to RVOT group on study enrollment*

Baseline characteristics	RVA group N=61	RVOT group N=71	Test and statistic significance
Male	43 (70.50%)	46 (64.78%)	P=0.48 NS[a]
Female	18 (29.50%)	25 (35.22%)	
Age	72.72±9.40	72.69±8.66	P=0.98 NS[b]
BMI	26.47±4.48	27.09±4.33	P=0.42 NS[b]
QRSs (ms)	91.15±20.33	88.87±22.90	P=0.23 NS[b]
QRSp (ms)	151.34±35.05	126.34±21.53	P<0.001 HSS[b]
VVIR	26 (42.62%)	35 (49.29%)	P=0.44 NS[a]
DDDR	35(57.38%)	36 (50.71%)	
LVEF - SPET (%)	58.44±6.34	52.50±15.24	P=0.13 NS[b]
PFR (EDV/s)	2.57±1.51	2.89±1.34	P=0.11 NS[c]
TPFR (ms)	214.82±95.62	231.94±120.46	P=0.80 NS[c]
LVEF - echo (%)	59.16±10.43	59.55±11.40	P=0.85 NS[b]
Without diastolic dysfunction	3 (4.91%)	1 (6)	P=0,33 NS[c]
Degree I of diastolic dysfunction	4 (6.55%)	6 (8.45%)	
Degree II of diastolic dysfunction	39 (63.95%)	41 (57.76%)	
Degree III of diastolic dysfunction	15 (24.59%)	23 (32.39%)	

[a]Chi-square test [b]t test [c]Mann-Whitney U test
BMI: Body Mass Index, QRS: Duration in intrinsic rhythm [5], QRSp-QRS: Duration in pacemaker stimulation. NS: Non significant, HSS: Highly significant

were not significantly changed in the RVA group (Fig. 1, 2). In the RVOT group PFR was significantly lower, while TPFR was also significantly lower (Fig. 1, 2).

Echocardiography

After 12 months of pacemaker stimulation, LVEF remained the same: 57.77±10.86% (P=0.27) in the RVOT group and 60.96±10.56% (P=0.31) in the RVA group.

Analysis of the patients according to the degree of diastolic dysfunction showed that most patients from both groups had at enrollment a second degree diastolic dysfunction. After 12 months of pacemaker stimulation in both groups the number of patients with third degree diastolic dysfunction increased and those with second degree diastolic dysfunction decreased. However, the worsening of diastolic function was significant only in the RVOT group (Table 3).

Table 3. *The degree of diastolic dysfunction on enrollment and after 12 months of pacemaker stimulation, in RVA and RVOT groups.*

Diastolic dysfunction	RVA group N=61		Test and statistical significance	RVOT group N=71		Test and statistical significance
	Baseline	After 12 months		Baseline	After 12 months	
Without	3 (4.91%)	2 (3.92%)	P=0.20 NS[a]	1 (7)	1(8)	P=0.03 SS[a]
I degree	4 (6.55%)	4 (7.84%)		6 (8.45%)	3(5%)	
II degree	39 (63.95%)	30 (58.83%)		41 (57.76%)	29(48.34%)	
III degree	15 (24.59%)	15 (29.41%)		23 (32.39%)	27(45%)	
Sum	61	51		71	60	

[a]Wilcoxon Signed Ranks test

Discussion

The majority of published papers have followed the influence of pacemaker lead position on systolic LV function, and considerably fewer papers analyzed its influence on diastolic function. The influence of pacemaker stimulation on LV diastolic function was evaluated with invasive measurements, ECHO or RNV. Liberman et al (2006) followed the changes in LV relaxation in patients with normal and lower LVEF, in RVOT and RVA lead positions, and concluded that pacemaker stimulation from either of these positions worsens the hemodynamic characteristics of LV in patients with preserved and with lower EF [13]. Other researchers (2010) by also using invasive measurements found worsening of diastolic function in pacemaker stimulation from RVA [14].

Echocardiography evaluation showed that pacemaker stimulation from the apex was a strong predictor of worsening diastolic LV function [15, 16]. Fang F et al (2011) found that in patients with normal LVEF and preexisting diastolic dysfunction, RVA pacemaker stimulation leads to worsening of diastolic dysfunction and as a solution they proposed RVOT position of pacemaker lead [15]. Our patients had normal LVEF on enrollment, and most of the patients had a second degree diastolic dysfunction. After one year of pacemaker stimulation we found worsening of diastolic ECHO parameters in RVOT group, while the same remained unchanged in the RVA group. The LV dyssynchrony caused by RVA pacing slowed the LV relaxation process and prolonged the isovolumetric relaxation time, which led to the decreased E′. The delayed LV relaxation and the increased LV filling pressure resulted in left atria compensatory contraction [6, 17]. This is why the ECHO diastolic parameters and the left atrial volume are strong prognostic markers, and when worsening, even in asymptomatic patients gives us an undoubtful prognosis. Other researchers found that diastolic dysfunction appears within a month after RVA pacemaker stimulation [18]. The above mentioned studies followed the diastolic dysfunction only in patients with RVA pacemaker lead position.

Radionuclide ventriculography as a method for evaluation of systolic and diastolic left ventricle parameters in patients with pacemakers was intensively used during 1980's and 1990's, while it was replaced afterwards by ECHO. There are no recent papers with RNV as an evaluation method in patients with antibradycardiac pacemaker stimulation, as our PubMed search showed. On the other hand, ECHO is noninvasive, easily available, and feasible method. The downside of ECHO is the fact that diastolic function is evaluated only on the basis of the measurements during one heart cycle, while in RNV the same measurements are done in the course of several hundred cycles. In our study, diastolic function was evaluated with ECHO and RNV in both groups of patients.

At study enrollment, we found in both groups a diastolic dysfunction presented with prolonged filling time of the LV and preserved filling velocity, as measured by RNV. This dysfunction was not unexpected due to the age of the patients and the preexisting heart conditions which resulted in the pacemaker implantation. However, after 12 months of pacemaker stimulation, PFR and TPFR measured by RNV remained unchanged in the RVA group, while a drastic fall in filling velocity (P=0.01) and shortening of filling time (P=0.03) were observed in the RVOT group. Decreasing TPFR by pacemaker stimulation has been established in earlier papers, as a consequence of decreased relaxation, increased myocardial stiffness and end diastolic wall stress. Other researchers have also shown that by using animal models and

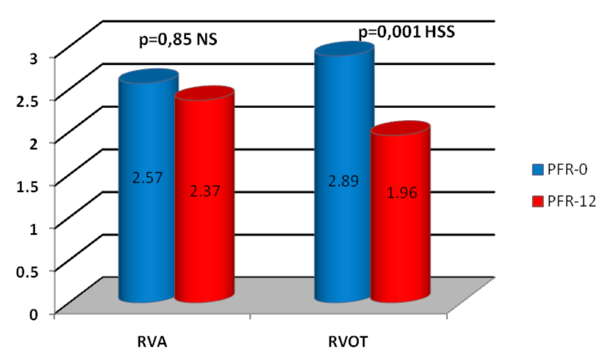

Figure 1. The values of RNV-PFR on the beginning and after 12 months of pacemaker stimulation in RVA (P=0.85 NS) and RVOT group (P=0.01 HSS).

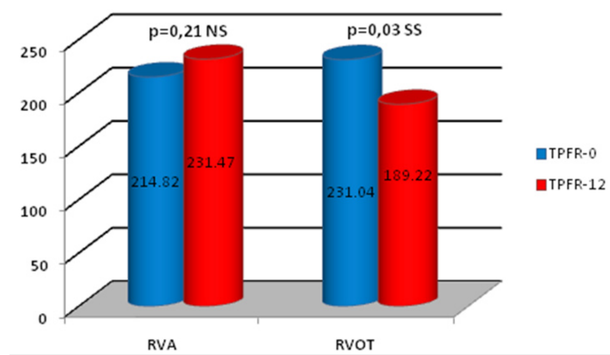

Figure 2. The values of RNV-TPFR on the beginning and after 12 months of pacemaker stimulation in RVA (P=0.21 NS) and RVOT group (P=0.03 SS).

rapid pacing could induce systolic and diastolic dysfunction [19]. Others have also found decreased TPFR in patients with lone atrial fibrillation and normal LVEF. This fact is explained with left ventricular filling disturbance caused by loss of atrial contribution [20].

The same trend of diastolic function parameters changes were observed by ECHO. Patients in the RVA group did not show greater diastolic dysfunction, while those in the RVOT group did show a decrease in the second degree dysfunction. These patients also showed increase in the degree of diastolic dysfunction. After using both methods, RNV and ECHO in measuring diastolic parameters, we estimated the comparable efficacy and reliability of these methods in measuring the above mentioned diastolic parameters.

In conclusion, one year of pacemaker stimulation from RVOT, but not from RVA, led to progression of diastolic dysfunction in patients with normal LVEF as confirmed by two independent methods, RNV and echocardiography. RNV and echocardiography were equally valuable and reliable in measuring diastolic parameters compared to each other.

The authors declare that they have no conflicts of interest.

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