ORIGINAL ARTICLE

Potential Prevention of Pacing-Induced Heart Failure Using Simple Pacemaker Programming Algorithm

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Introduction: Right ventricular pacing (RVP) causes ventricular desynchronization and may lead to the development of heart failure (HF). Prolongation of atrioventricular delay (AVD) in DDDR pacemakers reduces unnecessary RV stimulation. The aim of the study was to verify the influence of RVP reduction on HF symptoms.

Methods: The study comprised 31 patients (17 men, mean age: 71.6 ± 8 yrs) with DDDR pacemaker implanted due to sinus node dysfunction (SND). At baseline, 28 patients did not present any symptoms of HF. Three patients were in NYHA class II. Patients were randomized either to 150 ms AVD or to minimizing right ventricular pacing (MRVP). Crossing over to the alternate mode took place after 4 months. Cardiopulmonary exercise test (CPX), echocardiography (ECHO) and BNP measurements were done before pacemaker implantation, after 4 and 8 months.

Results: The percentage of RVP was significantly higher in 150 ms AVD than in MRVP: 81.7 ± 22.6 versus $14.2 \pm 20.5\%$, $P < 0.0001$. Patients with 150 ms mode had worse CPX parameters than those with MRVP mode: peak oxygen uptake was 14.2 ± 4.3 versus 19.9 ± 6.3 ml/kg per min, $P = 0.0001$, higher BNP concentrations: 72.3 ± 48.3 versus 49.4 ± 43.9 pg/ml, $P = 0.001$ and worse left ventricle [LV] function: ejection fraction: 53.2 ± 6.7 versus $57.3 \pm 5.5\%$, $P < 0.0001$; LV diastolic diameter: 4.86 ± 0.52 versus 4.66 ± 0.5 cm, $P < 0.01$.

Conclusion: Predominant RVP in patients without symptoms of HF at baseline may be responsible for worse performance in cardiopulmonary exercise test, higher BNP concentrations and impairment of LV function. Specific DDDR pacemaker programming promotes intrinsic AV conduction and may prevent the development of pacing-induced HF.

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pacing; sinus node dysfunction; cardiopulmonary exercise; BNP; echocardiography

Sinus node dysfunction (SND), first described by Wenckebach in 1923 and as a clinical syndrome in 1968, involves a broad spectrum of sinus node function abnormalities.¹ It may manifest itself with

sinus bradycardia, chronotropic incompetence, paroxysmal sinus arrest, or in coincidence with paroxysmal atrial fibrillation (AF), known as tachycardia-bradycardia syndrome. The clinical

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manifestations of SND include recurrent syncope due to sinus pause or sinus bradycardia, or inappropriate heart rate response to physical activities, mostly submaximal.²

Although the incidence of sudden cardiac death in SND is very low and pacemaker therapy does not improve the survival rate, it is the treatment of choice, as it eliminates most of clinical manifestations of SND. The optimal pacing mode in SND is still not established, especially in the light of data suggesting deleterious effects of right ventricular pacing (RVP).³⁻⁶

DAVID trial and subanalysis of MADIT II revealed an increase in combined end point of death or hospitalization for heart failure (HF) and worsening of HF in patients with reduced ejection fraction (EF) receiving ICD therapy. The results are attributed to increased burden of ventricular pacing.^{7,8}

Results of these trials demonstrate the necessity of minimizing RVP by preserving physiological activation sequence and seeking alternative places for ventricular pacing. One of the methods leading to ventricular pacing reduction is the prolongation of atrioventricular delay (AV delay) and searching for intrinsic AV conduction. This study was designed to test the hypothesis that specific DDDR pacemaker programming may influence patients' exercise tolerance, echocardiographic parameters of cardiac function and BNP concentrations.

METHODS

The study was conducted from January 1, 2006 until December 31, 2007. The study population was recruited from consecutive patients with SND hospitalized in the Institute of Cardiology. The patients were over 18 years old, all had indications for cardiac pacemaker implantation. They signed an informed consent to participate in the study. Bioethical Committee approval was issued on October 31, 2005. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Inclusion Criteria

Patients with diagnosed SND (including tachycardia-bradycardia syndrome) with implanted DDDR pacemaker.

Exclusion Criteria

Chronic HF in NYHA class III or IV, PR prolongation of more than 300 ms, atrioventricular block of 2nd or 3rd degree, chronic AF, history of unstable angina, coronary revascularization <3 months from randomization, EF <45%, uncontrolled arterial hypertension.

Study design

The study was designed as a prospective, randomized, single-blinded, cross-over clinical trial. Clinical baseline characteristics were assessed at enrolment. Before pacemaker implantation, patients underwent BNP measurements, echocardiographic examinations, and a cardiopulmonary exercise tests (CPX) with expired gas analysis. All patients had a DDDR pacemaker implanted with ventricular lead in a standard apical position. Apical pacing was defined basing on intraoperative chest x-ray images. Medtronic, Biotronik and St. Jude Medical pacemakers were used. One day after implantation a person unaware of the study protocol randomized patients using sealed envelopes. Subjects were randomized to either Group 1 with short AV delay (150 ms AVD mode) or Group 2 with a minimizing RVP program: longer AV delay (250 ms) with intrinsic AV search hysteresis, the basic interval was lengthened after detection of intrinsic activity. We used repetitive hysteresis mode, in which the hysteresis interval is repeated for a programmable number of cycles. This programming mode was called MRVP. All patients had programmed mode switch on. After 4 months BNP measurements, CPX, and echocardiographic examinations were performed in every patient. Patients were crossed over to the alternate pacing mode for another 4 months. At study completion, all tests (BNP, ECHO, CPX) were repeated. The percentage of ventricular paced beats and the number of mode switches were assessed telemetrically at the end of each period. After the study completion, pacemakers were programmed to the MRVP to promote intrinsic conduction.

BNP measurements

Blood samples were obtained by direct venipuncture of one of forearm veins, after the patients

had remained in supine position for 15 min. Blood samples were collected in tubes with potassium EDTA. They were centrifuged at 3000 rpm to separate plasma. Samples were frozen (-25°C). Afterwards samples were defrosted and plasma BNP concentrations were measured with an immunoradiometric assay using commercial kits (Roche Diagnostics, Mannheim, Germany).

Cardiopulmonary exercise test

Symptom limited cardiopulmonary stress tests were performed using a Marquette treadmill device (Case 15, Marquette Electronics, Milwaukee, WI, USA) and breath-to-breath respiratory gas analysis was carried out with Vmax 29c equipment (Sensor Medics, Yorba Linda, CA, USA). The standardized modified Bruce exercise protocol was applied. An exercise test was not stopped until maximal patient's exertion or maximal heart rate, or dangerous ventricular arrhythmia occurred. Patients were encouraged to reach their maximal exertion level. The following parameters were monitored during CPX:

- Heart rate, arterial blood pressure, ST segment changes.
- Peak oxygen uptake (peak VO_2 , ml/kg per min, l/min).
- Peak VO_2 as percentage of normalized VO_2 in given population.
- Peak carbon dioxide exhalation (peak VCO_2 , l/min).
- Oxygen pulse (O_2 pulse, ml/heart rate).
- Maximal minute ventilation (VE , l/min).
- Breathing reserve (BR): maximal voluntary ventilation/maximal exertional ventilation $\times 100\%$.
- Heart rate reserve (HRR): maximal HR/peak exertional HR $\times 100\%$.
- Anaerobic threshold level (ml/kg per min).
- Maximal CO_2 equivalent: VE/VCO_2 max.
- VE/VCO_2 slope and VE/VO_2 slope.
- Subjective dyspnea level (according to Borg scale from 1 to 5, where 5 is maximal dyspnoea).

Exertion level was assessed subjectively by patients in Borg scale (6–20, where 6: no exertion, 20: maximal exertion).

Echocardiography

Conventional M-mode, two-dimensional and Doppler echocardiography was performed using a commercially available Sonos 5500 machine (Philips Medical Systems, Andover, MA, USA). Measurements were obtained from parasternal long- and short-axis views and apical four- and two-chamber views. M-mode was used to obtain LV and RV end-diastolic diameters (LVdD and RVdD), left atrium dimension and interventricular septum thickness. LV end systolic and diastolic volumes (LVESV, LVEDV) and EF were estimated using Simpson's biplane method. The pulsed-wave Doppler transmitral velocity profile was performed to calculate transmitral peak early (E) and late diastolic velocities (A), the deceleration time and the E/A ratio. Pulmonary artery pressure and acceleration time were also measured. Three consecutive measurements were averaged for each parameter. Examinations were performed by an experienced cardiologist unaware of the clinical data.

Statistical analysis

The Shapiro-Wilk test was performed to assess the normality of continuous variables. Normally distributed continuous data were expressed as mean $\pm$ standard deviation. For these variables, means between two categories were compared with the 2-tailed paired t-test. Because the hypothesis for normal distribution of BNP had to be rejected (Shapiro-Wilk), we preferred a non-parametric statistical analysis to test this parameter further. The Wilcoxon rank-sum test was applied for statistical testing of BNP between baseline, 150 ms AVD and MRVP categories. These data were presented as medians and inter-quartile range. Spearman's rank correlation method was used as a nonparametric measure of association for correlations between BNP and echocardiographic or ergospirometric data. Logistic regression analysis was performed to identify the factors responsible for differences between groups.

All statistical analyses were performed with SAS software version 9.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The study group consisted of 31 patients with SND. Mean age was 71.6 ± 8 years; 17 patients (55%) were male. Arterial hypertension was diagnosed in 15 patients (48%), eight patients had arterial hypertension and coronary artery disease. Four of these patients (13%) had myocardial infarction, one patient was treated with coronary artery bypass- grafts and three of them with primary angioplasty. Other concomitant diseases included hyperlipidemia in ten (32%) patients, diabetes mellitus in four patients (13%), mild aortic stenosis in one, and thyroid insufficiency in two patients. Four patients had left His bundle branch block with mean QRS duration 138 ± 15 ms. Mean QRS duration in the whole group was 105 ± 21 , $P = 0.0002$. Three patients (9.7%) had chronic HF in NYHA class II diagnosed. The remaining 28 patients were in the functional NYHA class I. Nine patients (29%) in 150 ms AVD group developed symptoms of HF in NYHA II class ($P = 0.002$) and four patients (12.9%) deteriorated to NYHA II/III ($P = 0.1$). Two patients developed persistent AF at the end of follow-up, both of them were at this point in 150 ms AV delay group. These patients had their pacemakers reprogrammed. The first patient had unsuccessful electrical cardioversion, second patient did not agree to cardioversion and was left with AF. Their results were included in the statistical analysis on the intention-to-treat basis. All other patients completed the study per protocol. The telemetrically assessed percent of ventricular paced beats (% VP) was $81.7 \pm 22.6\%$ in the 150 ms AVD mode and $14.2 \pm 20.5\%$ in MRVP mode ($P < 0.0001$).

The analysis revealed significant differences in CPX parameters between the both pacing modes and in comparison with baseline parameters (Table 1). Peak oxygen uptake (peak VO_2) in 150 ms AVD mode was lower than baseline peak VO_2 : 14.2 ± 4.3 versus 17 ± 4.5 ml/kg per min, $P = < 0.001$ (Fig. 1). Peak VO_2 in MRVP mode was significantly higher than in 150 ms AVD mode ($P = 0.0001$) and baseline ($P < 0.05$). Median values of peak VO_2 were 16.6 ml/kg per min at baseline, 14.0 in 150 ms AVD mode and 19.2 in MRVP mode. Maximal reached heart rate was statistically higher in MRVP compared to 150 ms AVD. Seven patients at baseline and in MRVP and three in 150 ms AVD group reached heart rate $> 130/\text{min}$, which was set as maximal tracking rate.

Patients with MRVP mode of pacing reached anaerobic threshold (AT) later than those in 150 ms AVD mode ($P < 0.0005$). Patients with 150 ms AVD mode had AT level lower than at their baseline values ($P < 0.001$). There was a positive correlation between $\text{VE}/\text{VCO}_{2\text{max}}$ level and percent of paced beats in MRVP mode ($r = 0.46$, $P = 0.0133$).

Exercise time was longer in MRVP mode in comparison with those at baseline and 150 ms AVD mode ($P < 0.0001$). Exercise time in 150 ms AVD mode was shorter than that at baseline ($P < 0.01$). Patients assessed their exertion level as lower in MRVP mode than at baseline or 150 ms AVD mode: 13.7 ± 1.6 versus 14.5 ± 1.6 versus 15.1 ± 1.2 , $P < 0.001$, $P < 0.0001$, respectively.

Left ventricle diastolic diameter (LVdD) was significantly larger in patients with 150 ms AVD in comparison with MRVP ($P < 0.01$). Other echocardiographic parameters are listed in Table 2. There was a significant decrease of left ventricle EF in 150 ms AVD mode group when compared to MRVP mode ($P < 0.0001$) and baseline EF, ($P < 0.001$) (Fig. 2). In the study group, 25 patients (81%) had E/A wave ratio below 1 in baseline echocardiography, which may be due to mild diastolic dysfunction. In 150 ms AVD group, another 3 patients developed echocardiographic signs of diastolic dysfunction. In MRVP group, only 19 patients (61%) had signs of diastolic dysfunction, $P = 0.076$. Echocardiographic measurements, CPX and BNP results were statistically not different in groups with and without diastolic dysfunction. Finally, it was not proved, that diastolic dysfunction was related to LV dysfunction in patients with predominant right apical pacing in 150 ms AVD group. Patients in 150 ms AVD mode had E wave lower than at baseline, $P = 0.04$ and than in MRVP mode, $P < 0.01$. There were no differences in A wave velocity and E/A ratio.

QRS duration in 150 ms AVD group was 36 ms longer than at baseline ($P < 0.001$), there were no differences in QRS duration in MRVP group (Table 3). Paced QRS duration correlated negatively with LV EF in 150 ms AVD group ($r = -0.32$, $P = 0.0752$), and with maximum heart rate in MRVP group. Neither peak VO_2 nor BNP level were dependent on QRS duration.

Mean BNP concentration was significantly higher in 150 ms AVD mode when compared to mean baseline value ($P < 0.0001$), and it was significantly higher than in patients with MRVP mode ($P = 0.001$) (Table 4). Mean BNP

Table 1. Results of Cardiopulmonary Exercise Test in All Groups (Mean Values)

Parameter	Baseline	150 ms AVD	MRVP			
	1	2	3	1 vs 2	1 vs 3	2 vs 3
Exercise time (s)	283 ± 163	225 ± 147	397 ± 164	P<0.01	P<0.0001	P<0.0001
Maximal HR reached	120 ± 23	112 ± 18	122 ± 19	NS	NS	P=0.0051
Peak VO ₂ (ml/kg per min)	17 ± 4.5	14.2 ± 4.3	19.9 ± 6.3	P<0.001	P<0.05	P=0.0001
VE/VCO _{2max}	42.1 ± 8.6	47.3 ± 12.8	40.3 ± 5.7	P<0.05	NS	P<0.01
VE/VCO _{2slope}	31.7 ± 4	35 ± 6.1	32.6 ± 4.9	P<0.001	NS	P<0.05
VE/VO ₂	32.4 ± 5.7	34.1 ± 6.7	33.6 ± 6.7	NS	NS	NS
AT (ml/kg per min)	14.5 ± 3.4	11.8 ± 2.7	16.0 ± 4.2	P<0.001	NS	P<0.0005
HR recovery (s)	320 ± 138	330 ± 94	218 ± 93	NS	P<0.0005	P<0.0001
ABP recovery (s)	275 ± 106	323 ± 91	234 ± 76	P<0.05	P<0.0005	P<0.0001
Borg scale	14.5 ± 1.6	15.1 ± 1.2	13.7 ± 1.6	NS	P<0.001	P<0.0001
%VP	–	85.5 ± 18.8	15.8 ± 22.8			P<0.0001

HR = heart rate; peak VO₂ = value of peak oxygen uptake; VE/VCO_{2max} = maximal value of carbon dioxide ventilatory equivalent; VE/VCO_{2slope} = slope value of carbon dioxide ventilatory equivalent; VE/VO₂ = value of oxygen ventilatory equivalent; AT = anaerobic threshold; 150 ms AVD = group of patients with AV delay of 150 ms; MRVP = minimizing ventricular pacing group; ABP = arterial blood pressure; %VP = percentage of ventricular pacing; NS = not significant.

Figure 1. Peak oxygen uptake in all study groups.

concentration did not change significantly in patients with MRVP mode versus baseline. There were significant positive correlations between BNP concentrations and VE/VCO_{2max}: $r = 0.4$, $P = 0.02$, VE/VCO_{2slope}: $r = 0.6$, $P < 0.0001$ and VE/VO_{2slope}: $r = 0.66$, $P < 0.0001$ in 150 ms AVD mode. There were no significant correlations between BNP concentration and CPX parameters at baseline and MRVP mode of pacing.

DISCUSSION

The optimal mode of pacing in sinus node disease is not established. First reports favored AAIR

over VVIR pacing.^{3–6} Despite that AAIR pacing was not widely implemented in SND because of concerns about patients' safety during unexpected atrioventricular block and possible ventricular bradycardia in paroxysmal AF.⁹ According to ESC guidelines (2007): "Regarding the choice of AAIR or DDD pacemaker implantation, we should take into consideration that although DDD is more expensive, there is a possibility, albeit small (~1% of annual incidence), of the future development of AV block."¹⁰ The definite proof of superiority of DDDR over AAIR pacing in sick sinus syndrome was provided by DANPACE investigators.¹¹ In this study, the patients randomized to single-lead

Table 2. Echocardiographic Parameters

	Baseline	150 ms AVD	MRVP			
	1	2	3	1 vs 2	1 vs 3	2 vs 3
LVdD (cm)	4.90 ± 0.58	4.86 ± 0.52	4.66 ± 0.50	NS	P<0.05	P<0.01
LVsD (cm)	3.06 ± 0.51	3.13 ± 0.53	2.95 ± 0.51	NS	NS	NS
LVEdV (cm)	116 ± 28	117 ± 26	102 ± 25	NS	P<0.01	P<0.05
LVEsV (cm)	39 ± 16	40 ± 15	34 ± 13	NS	P<0.05	P<0.05
RVdD (cm)	3.03 ± 0.77	3.11 ± 0.65	3.13 ± 0.58	NS	NS	NS
LA (cm)	4.15 ± 0.54	4.15 ± 0.51	4.08 ± 0.46	NS	NS	NS
RA (cm)	3.90 ± 0.65	4.11 ± 0.63	3.77 ± 0.54	NS	NS	P<0.05
EF (%)	56.3 ± 6.6	53.2 ± 6.7	57.3 ± 5.5	P<0.001	NS	P<0.0001
PA max(mmHg)	24.0 ± 9.0	26.8 ± 8.5	22.6 ± 8.0	NS	NS	P<0.05
PA mean(mmHg)	16.9 ± 6.5	19.1 ± 6.5	16.0 ± 6.1	NS	NS	P<0.05
Acceleration time (ms)	103 ± 17	86 ± 18	107 ± 27	P<0.0001	NS	P=0.0002
E	80.1 ± 23.1	67.8 ± 26.6	81.1 ± 18.6	P<0.05	NS	P<0.01
A	90.9 ± 20.7	80.1 ± 22.6	82.9 ± 15.9	NS	NS	NS
E/A	0.9 ± 0.25	0.87 ± 0.28	1.01 ± 0.27	NS	NS	NS
Deceleration time (ms)	231 ± 23	243 ± 28	223 ± 19	NS	NS	NS

Abbreviations: LVdD = left ventricle diastolic diameter; LVsD = left ventricle systolic diameter; LVEdV = left ventricle end-diastolic volume; LVEsV = left ventricle end-systolic volume; RVdD = right ventricle diastolic diameter; LA = left atrium; RA = right atrium; EF = ejection fraction; PA max = maximal pressure in pulmonary artery; PA mean = mean pressure in pulmonary artery; E = E wave; A = A wave; E/A = E wave/A wave ratio; NS = not significant. Bold type indicates statistical significance.

Figure 2. Ejection fraction in all study groups.

pacing had a 27% higher risk of developing AF and double the risk of need of a second operation to upgrade their pacemaker compared with the patients treated with dual-chamber pacing.

Over the years, DDD pacing became the treatment of choice in SND, though there is strong evidence of deleterious effects of RVP. Some of them are: asymmetric hypertrophy,^{12,13} left atrium dilatation^{14,15} and reduction of EF.¹⁶ The cause of this is the asynchronous ventricular activation sequence, which resembles left bundle branch block (LBBB). LBBB is known to be a predictor of worse outcome in patients with systolic

HF.^{17,18} In the Mode Selection Trial (MOST), the risk for HF hospitalization and AF increased with the percentage of cumulative ventricular pacing (%VP).¹⁹ The only clinical advantage over VVIR pacing was the reduction of AF rate (MOST, CTOPP) and HF symptoms (MOST), but there was no reduction in mortality when compared to VVIR.^{19,20} Other trials revealed an increase in combined endpoint of death or hospitalization for HF and worsening of HF in patients with reduced EF receiving ICD therapy: DAVID study⁷ and subanalysis of MADIT II.⁸ The DAVID trial included patients with ICD and no indications

Table 3. QRS Duration and Morphology

	Baseline	150 ms AVD	MRVP	P Value
QRS duration in all patients (ms)	105 ± 21	141 ± 27	106 ± 23	Baseline vs 150 ms AVD : P<0.0001; 150 ms AVD vs MRVP : P<0.0001
Patients without conduction disturbances (n=27)	100 ± 17	138 ± 27	102 ± 20	Baseline vs 150 ms AVD : P<0.0001; 150 ms AVD vs MRVP : P<0.0001
Patients with conduction disturbances (n=4)	138 ± 15	160 ± 24	137 ± 15	Baseline vs 150ms P=NS; 150ms vs 250ms: P=NS
QRS in 27 vs 4 pts	0.0002	NS	0.0019	

Table 4. QRS Duration, Exercise Capacity, EF and BNP in Groups with and without Conduction Disturbances

	Patients without Conduction Disturbances (n=27)	Patients with Conduction Disturbances (n=4)	P Value
Baseline			
QRS (ms)	100 ± 17	138 ± 15	0.0002
VO ₂ (ml/kg per min)	17.0 ± 4.4	16.8 ± 6.1	NS
EF (%)	57 ± 4	51 ± 9	0.0164
BNP (pg/ml)	37 ± 26	39 ± 35	NS
150 ms AVD			
QRS	138 ± 27	160 ± 24	NS
VO ₂	14.5 ± 3.9	12.4 ± 6.8	NS
EF	54 ± 5	47 ± 13	NS (0.0578)
BNP	69 ± 50	96 ± 26	NS
MRVP			
QRS	102 ± 20	137 ± 15	0.0019
EF	58 ± 4	51 ± 12	0.0174
VO ₂	20.3 ± 6.4	17.0 ± 5.1	NS
BNP	50.5 ± 46.7	42.3 ± 17.8	NS

150 ms AVD = group of patients with AV delay is 150 ms; MRVP = minimizing ventricular pacing group; EF = ejection fraction; VO₂ = peak oxygen uptake; BNP = brain natriuretic peptide concentration; NS = not significant.

for antibradycardia pacing. Group of rate-response DDDR pacing at 70/min had higher rates of death or first hospitalization for HF than the group of VVI backup pacing at 40/min. These results are attributed to ventricular pacing and AV desynchronization.

To avoid unnecessary ventricular pacing, pacemakers are programmed using specific algorithms. One of the methods is programming a long atrioventricular delay (AVD), which promotes native conduction. Another possibility is using an atrioventricular search hysteresis (AVSH) algorithm. AVSH searches for intrinsic conduction and extends AVD up to 100% of the initial value. This algorithm promotes native conduction and reduces ventricular pacing. INTRINSIC RV trial proved that patients in DDDR pacing mode and AVSH algorithm have lower rate of mortality or hospitalizations than patients in VVI pacing mode.²⁰ Another useful protocol, which helps

to reduce RVP is Managed Ventricular Pacing which provides AAIR pacing with ventricular monitoring and DDDR during AV block and finally reduces cumulative percentage of ventricular pacing compared to standard DDDR.²¹

However, these pacemakers were not available at this time in our hospital. That is why we tried to develop our own method of programming aimed to minimize RVP. The present prospective, randomized, single-blinded, cross-over clinical study focuses on the short term effects and markers of left ventricular dysfunction which are a potential harbinger of HF. This study confirmed results of other observations, that predominant ventricular stimulation may produce symptoms of HF.^{20,21} In contrast to that, minimizing RVP may reduce symptoms of pacemaker induced HF.

In this study, patients were randomized either to short AVD (150 ms) or longer (250 ms) AVD with AVSH, which we called minimizing RVP

Table 5. Comparison of Groups with 150 ms AVD as First Stimulation Mode and MRVP as First Stimulation Mode

	First Stimulation Mode	Baseline	150 ms AVD	MRVP	Baseline vs 150 ms AVD	Baseline vs MRVP	150 ms AVD vs MRVP
QRS (ms)	150 ms	103.6 ± 21.7	142.1 ± 29.4	102.9 ± 21.6	0.0005	0.5830	0.0003
	MRVP	105.3 ± 21.0	139.7 ± 26.3	108.8 ± 24.2	<0.0001	0.1635	0.0002
	P	0.8242	0.8092	0.4797			
HR (beats/min)	150 ms	124.9 ± 25.6	114.6 ± 12.8	125.6 ± 17.4	0.1290	0.9181	0.1061
	MRVP	116.3 ± 20.2	110.1 ± 20.9	118.5 ± 20.3	0.2611	0.5879	0.0069
	P	0.3017	0.4858	0.3096			
EF (%)	150 ms	55.0 ± 4.6	53.7 ± 6.8	57.4 ± 5.0	0.3877	0.1060	0.0362
	MRVP	57.4 ± 5.3	52.8 ± 6.9	57.2 ± 6.1	<0.0001	0.7468	<0.0001
	P	0.2034	0.7097	0.9299			
VO ₂ (ml/kg per min)	150 ms	17.7 ± 4.7	14.7 ± 4.9	21.4 ± 7.1	0.0122	0.0714	0.0061
	MRVP	16.4 ± 4.5	13.8 ± 3.9	18.7 ± 5.5	0.280	0.0851	0.0087
	P	0.4260	0.5783	0.2320			
AT (ml/kg per min)	150 ms	14.8 ± 3.7	12.2 ± 2.8	16.7 ± 4.7	0.0220	0.2554	0.0069
	MRVP	14.1 ± 3.2	11.7 ± 2.8	15.4 ± 3.7	0.0347	0.1704	0.0068
	P	0.7366	0.8799	0.5543			
BNP (pg/ml)	150 ms	33.0[17.0 ;58.0]	65.5[39.0 ;96.0]	38.5[28.0 ;72.0]	0.0024	0.1937	0.0166
	MRVP	25.0[17.0 ;49.0]	53.0[38.0 ;85.0]	26.0[20.0 ;54.0]	0.0038	0.2744	0.0174
	P	0.6940	0.4109	0.1469			

Abbreviations: 150 ms AVD = group of patients with AV delay is 150 ms; MRVP = minimizing ventricular pacing group; EF = ejection fraction; HR = heart rate; VO₂ = peak oxygen uptake; AT = anaerobic threshold; BNP = brain natriuretic peptide concentration; P = statistical significance.

algorithm (MRVP). Poorer CPX results, higher BNP concentrations and lower EF in patients with 150 ms AVD may be explained by prevalence of RVP (mean%VP = 85.5%) in this group. MRVP led to a reduction in RV pacing to 15.8%. Patients with MRVP mode of pacing had better CPX results than at baseline and versus 150 ms AVD mode: peak VO₂, ventilatory parameters and anaerobic threshold. Exercise time was longer, heart rate and arterial pressure recovery better. Apart from that, subjective exertion level was lower in MRVP patients than in 150 ms AVD and at baseline. Better results of CPX in MRVP mode of pacing in comparison with those at baseline may result from the "second exercise test phenomenon." Patients' performance was better in the second test at the same conditions, because they were acquainted with the treadmill and expired gas analysis system and felt safer. Worse results in 150 ms AVD mode group can only be explained by objective reasons, because the same proportion of patients performed their CPX as a second exercise: randomization and then cross-over.

We performed the additional analysis comparing the group who had 4 months of prior 150 ms AVD to the group who were initially programmed

to MRVP (Table 5). There were no differences at the baseline in the both groups. All the analyzed parameters changed significantly in favor of MRVP, not depending on the first stimulation mode. This subanalysis proves, that RV pacing induced LV dysfunction is entirely reversible even after the 4 month period. We do not know how long it takes for these processes to become irreversible. It is unknown when patients with predominant RV pacing start to develop HF symptoms. The peak VO₂ level of 14.2 ml/kg/min (mean in 150 ms AVD) is classified as moderate anaerobic failure in the Weber scale. In DAVID and MADIT studies, it took less than one year for the HF symptoms induced by ventricular pacing to appear.

In the substudy of MOST, the relative risk for HF increased in a linear relationship with cumulative percentage of RVP.²² The risk also depended on the paced QRS duration.²³ The MOST study population was relatively healthy: less than 25% had prior myocardial infarct, PCI or CABG.

All MADIT II patients had myocardial infarction and severely reduced LVEF.²⁴ It turned out that the patients with cumulative percentage of RVP over 50% of total time had a two-fold higher risk of new or worsened HF and more frequently

needed ICD interventions.¹⁰ ICD recipients are more exposed to deleterious effects of RV pacing. It is particularly important in the light of the fact that they rarely need antibradycardia pacing. It has been previously reported, that pacing of the right ventricle in patients with systolic dysfunction will induce ventricular dyssynchrony and may increase symptoms of HF.²⁵ In our study we proved that RV pacing may have deleterious consequences after short period not only in patients with HF, but also in asymptomatic patients. This observation corresponds with the results of the PACE study, where patients with normal EF after twelve months of right ventricular apical pacing had significantly lower EF and higher LV end-systolic volume in comparison with patients with biventricular pacing.²⁶

Patients in our study had normal baseline values of CPX, EF and BNP and in spite of higher mean age, their exercise tolerance was good. The dominant concomitant disease was arterial hypertension, which was present in 75% of patients. Age and arterial hypertension were the only aggravating factors in this group. However, they do not explain this rapid deterioration after 4 months of increased RVP. Ventricular pacing with 150 ms AV delay seems to be the only factor responsible for worse outcomes in CPX and ECHO. Exercise tolerance, circulatory and respiratory system adaptation to exercise and some ECHO parameters improved when MRVP program was implemented.

LIMITATIONS

Right ventricular apical pacing (RVA), most commonly applied, was used in our patients. At the same time, RVA pacing is hemodynamically least favorable of all possible lead placement sites.

Another limitation was the small number of patients. However, crossing over doubles this number and leads to comparison of every patient in both programming modes. Due to small number of patients, during estimation of parameters responsible for worse outcomes in 150 ms AVD group in logistic regression multivariable analysis, convergence criterion was not satisfied.

Pacing frequencies from the device counters include ventricular pacing and fusion or pseudofusion beats. We were unable to investigate the underlying mechanism of LV dysfunction.

Possible mechanisms are: pacing induced left bundle branch block and electrical and mechanical dyssynchrony.

CONCLUSION

This study suggest that predominant RVP may be responsible for worse performance in CPXs and decrease of left ventricle function. Moderate HF symptoms may appear in relatively short period of time and they are reversible. Optimal DDD pacemaker programming promotes intrinsic AV conduction and prevents the development of pacing-induced HF.

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