Influence of Atrioventricular Optimization on Hemodynamic Parameters and Quality of Life in Patients with Dual Chamber Pacemaker with Ventricular Lead in Right Ventricular Outflow Tract

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Background: The aim of this study was to ascertain whether individual atrioventricular delay (AVD) optimization using impedance cardiography (ICG) offers beneficial hemodynamic effects as well as improved exercise tolerance and quality of life in patients with requiring constant right ventricular pacing.

Methods: There were 37 patients with advanced AV block included in the study. Several examinations were performed at the beginning. Next, the optimization of AVD by ICG was done. The next step of the study patients have been randomized into optimal AVD group (AVDopt) or factory setting group (AVDfab). After 3 months, the follow-up all data were collected again and crossover was performed. After another 3 months, during the final follow-up all these measures were repeated.

Results: In 87.5% patients, AVDopt were different than factory value. Cardiac output (CO), cardiac index (CI), and stroke volume (SV) were significantly ($P < 0.001$) higher in AVDopt group than in AVDfab group (CO: 6.0 ± 1.4 L/minute vs. 5.3 ± 1.2 L/minute; SV: 85.8 ± 25.7 mL vs. 76.9 ± 22.5 mL; CI: 3.2 ± 0.7 L/minute/m² vs. 2.7 ± 0.6 L/minute/m²). There was a statistical significant ($P < 0.05$) reduction of proBNP and NYHA class in patients with AVDopt compared to AVDfab (proBNP: 196.4 ± 144.7 pg/mL vs. 269.4 ± 235.8 pg/mL; NYHA class: 1.7 ± 0.5 vs. 2.3 ± 0.6). Six-minute walking test was significantly ($P < 0.05$) higher in AVDopt group (409 ± 90 m) than in AVDfab group (362 ± 93 m). There were no statistically significant differences in echocardiographic parameters between AVDopt and AVDfab settings.

Conclusion: Our study results suggest that AVD optimization in patients with DDD pacemaker with ICG improves hemodynamic when compared to the default factory settings. Furthermore, optimally programmed AVD reduces BNP and improves exercise tolerance and functional class.

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pacing; optimization; atrioventricular delay; impedance cardiography; atrioventricular block

Cardiac pacing over the past decades allowed saving numerous lives of patients with bradycardia and complete heart block. Nevertheless, long observation of patients with implanted pacemaker showed unfavorable electrical and structural re-

modeling of the heart muscle.¹ Although clear benefits of alternative right ventricular pacing sites remain unresolved,² the pacing site should allow for the depolarization to mimic that achieved via native conduction system. The right ventricular

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outflow tract (RVOT) probably carries the smaller risk of unfavorable hemodynamic effect and electrical remodeling.^{3,4}

Although longterm structural remodeling and dyssynchrony may be avoided with optimal right ventricular pacing site, correct programming of atrioventricular delay (AVD) may offer additional hemodynamic benefits. The optimal AVD (AVDopt) differs among patients and requires individual setting.^{5,6} Programming of AVD influences contractile function of left ventricle through preload modulation,⁷ and if done incorrectly, can have unfavorable hemodynamic results.⁸

The problem of the individual AVD optimization was noticed already in the 1980s.⁶ Various methods for determination of the AVDopt have been developed during last few decades (right heart catheterization, ventriculography, peak endocardial acceleration, echocardiography, impedance cardiography [ICG]), however, only echocardiography and ICG (reocardiography) are currently in general use.⁹ ICG is noninvasive, repetitive, undemanding of qualified personnel, and cheaper than the echocardiography and, therefore, can be readily used in selection of AVDopt in patients with dual-chamber pacemakers.^{10,11}

The aim of this study was to ascertain whether individual AVD optimization offers beneficial hemodynamic effects as well as improved exercise tolerance and quality of life (QoL) in patients with requiring constant right ventricular pacing.

MATERIAL AND METHODS

There were 37 patients with advanced AV block (all the patients have percent of ventricular pacing >95% after pacemaker implantation) included in the study (28 men, nine women). All patients were implanted with a dual-chamber pacemaker at least 4 weeks before the beginning of the study. All patients were implanted with Biotronik dual chamber pacemakers (manufactured in Berlin, Germany). Atrial lead was implanted in the right atrial appendage and ventricular lead was implanted in the RVOT. To verify the RVOT position of ventricular lead the fluoroscopic images during implantation and associated ECG patterns were used.¹² Ventricular lead was placed approximately two-thirds of the distance from the apex to the pulmonary valve in the posteroanterior fluoroscopic view and pointing toward the septum in the left-anterior oblique view. The 12-lead ECG

helped identify the pacing site. Pacing at the RVOT septum was manifested by a negative QRS morphology in lead aVL and an upright QRS in leads II, III, and aVF.

All devices were programmed in the DDD mode with a lower rate limit of 50 beats per minute, to avoid atrial pacing.¹³

The exclusion criteria were: moderate to severe left ventricular dysfunction (LVEF < 40%), history of atrial fibrillation, significant valvular heart disease, sick sinus syndrome, or/and percent of atrial pacing >5%, abnormal (>120 ms) duration of P wave.

Before randomization all patients enrolled in the study underwent 6 minute walking test (6MWT), assessment of proBNP concentration in plasma, as well as had transthoracic echocardiogram. Next, the optimization of AVD by ICG was done. ICG was performed with a commercially available NIC-COMO system (the CardioScreen[®]-device, Medizinische Messtechnik GmbH, Ilmenau, Germany) used for noninvasive hemodynamic measurements and the monitoring of hemodynamic parameters. Changes in volume and velocity of blood in the aorta cause variations in the thoracic impedance which is measured and displayed as the ICG waveform. With each cardiac cycle, thoracic fluid volume changes, which affects the impedance of the electrical signal transmitted by the sensors. This signal is processed via physiological adaptive signal analysis to provide key hemodynamic parameters noninvasively and continuously.¹⁴ Four pairs of electrodes (one pair at the left and right neck, one pair on the left and right side of the lower thoracic aperture) were used for recording the thoracic impedance field. Cardiac index (CI) and other hemodynamic parameters were calculated beat-to-beat from the transthoracic impedance signal.¹⁵

AVD was set successively to the following values (in 5-minute intervals): 100, 120, 140, 160, 180, 200, 250, and finally 300 ms. The ICG recording was performed for each AVD value and cardiac output (CO), stroke volume (SV) and CI were recorded. The AVD, for which CO was the highest value, was considered as the AVDopt. The next step of the study was randomization. Pacemakers with even serial number were programmed to AVDopt and pacemakers with odd serial number were programmed to factory value of AVD (AVDfab). After 3 months, the follow-up transthoracic echocardiogram was repeated as well as assessment of functional class (NYHA), 6MWT,

Figure 1. Study protocol.

AVD—atrio-ventricular delay, ICG—impedance cardiography, AVDopt—optimal setting of AVD, AVDfab—factory setting of AVD.

and proBNP concentration and patients filled out QoL questionnaire—The Minnesota Living with Heart Failure. At this stage crossing-over was done: pacemakers with even serial number were programmed to AVDfab and pacemakers with odd serial number were programmed to AVDopt. After another 3 months during the final follow-up all these measures were repeated.

The medication remained unchanged when ever clinically feasible.

Statistica 5.0 PL software was used for statistical analysis. Shapiro-Wilk W test was used for gathering evidence about the “nonnormality” of a sample. Paired *t*-test was used for variables with normal distribution and Wilcoxon’s signed-rank test was used for nonparametric data. $P < 0.05$ was regarded as statistically significant.

Study protocol is shown in Figure 1. The study protocol was approved by the local Ethics Committee and informed consent was obtained from all patients.

RESULTS

During the study, five patients dropped out from the study because of various causes (new onset of atrial fibrillation, upgrade to cardiac resynchronization therapy, myocardial infarction, significant modification of pharmacotherapy, or missed follow-up visits). Finally, 32 patients were completed all follow-up visits. Clinical characteristic of these patients is shown in Table 1.

In 28 (87.5%) patients, AVDopt was different than factory value. Optimization of AVD by ICG resulted in better hemodynamic (measured during ICG optimization) as compared to the factory settings (Table 2).

Table 1. Clinical Characteristic of Patients

Number of Patients	32
Age	67.8 ± 11.3 years
Males	24 (75%)
Hypertension	21 (66%)
Diabetes type 2	8 (25%)
History of myocardial infarction	5 (16%)
LVEF	59.7 ± 6.2%
Mean NYHA class	2.3

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association class of heart failure.

During 3 months of observation, there were no statistically significant differences in echocardiographic parameters (EDV, ESV, EF, TEI) between AVDopt and AVDfab settings.

There was a statistical significant reduction of pro-BNP in patients with AVDopt settings compared to AVDfab settings (Table 3).

Patients with AVDopt settings were able to walk a longer distance (in 6MWT) compared to AVDfab settings (Table 4).

Patients with AVDopt settings have also a significant lower NYHA class compared to AVDfab settings (Table 5).

Finally, QoL in patients with AVDopt settings were significant better than in AVDfab settings (Table 6).

Summary of the comparison of the main parameters are shown in Table 7.

DISCUSSION

In this study, optimization of AVD by ICG provides better hemodynamics (CO, SV, CI) in the majority of patients as compared to the factory settings. Furthermore, optimal programmed AVD

Table 2. Impedence Cardiography Parameters (Measured during ICG Optimization) in AVDfab and AVDopt Settings

Variables	CI fab	CI opt	SV fab	SV opt	CO fab	CO opt
Mean	2.67	3.18	76.89	85.84	5.26	6.00
SD	0.55	0.65	22.54	25.70	1.23	1.36
Median	2.55	3.1	78	85.5	5.4	6.1
Lower quartile	2.25	2.8	62	69.25	4.35	5.08
Upper quartile	3.08	3.48	89.75	102.5	6.1	6.75
	P < 0.0001		P < 0.0001		P < 0.0001	

CI = Cardiac index (L/minute/m²); SV = stroke volume (mL); CO = cardiac output (L/minute).

Table 3. proBNP in AVDfab and AVDopt Settings

Variables	proBNP fab	proBNP opt
Mean	269.38	196.42
SD	235.81	144.67
Median	148.3	189.6
Lower quartile	107.08	94.58
Upper quartile	342.2	269.35
	P = 0.016	

proBNP = level of proBNP in plasma [pg/mL].

Table 4. Six-Minute Walking Time Test Results in AVDfab and AVDopt Settings

Variables	6MWT fab	6MWT opt
Mean	361.84	409.75
SD	92.72	90.38
Median	332.5	420
Lower quartile	280	319.5
Upper quartile	446.25	473.75
	P = 0.0013	

6MWT = six-minute walking test (m).

causes a statistically significant reduction in BNP, NYHA functional class and improves 6MWT.

Negative consequences of long-term right ventricular pacing have been known for a long time^{16,17} and may result in mechanical remodeling and increase in BNP. Lengthening of the programmed AVD or automated algorithms can allow for native depolarization of ventricles and potentially minimize the unfavorable results of long-term right ventricular pacing. However, excessive lengthening the delay in patients with atrioventricular block can paradoxically lead to the fall of CO, which by itself may be more detrimental than the right ventricular pacing.^{18,19} On the other hand, programming too short of AVD will shorten the filling time and may provoke retrograde conduction.^{18,19} When AVD is

Table 5. NYHA Class in AVDfab and AVDopt Settings

Variables	NYHA fab	NYHA opt
Mean	2.31	1.69
SD	0.64	0.54
	P < 0.001	

NYHA = New York Heart Association class of heart failure.

Table 6. QoL in AVDfab and AVDopt Settings

Variables	QoL fab	QoL opt
Mean	15.15	4.35
SD	10.90	4.25
Median	12.5	3
Lower quartile	7.75	0.75
Upper quartile	21.25	8.25
	P < 0.001	

QoL = quality of life (points).

programmed optimally, it may improve CO by 13–40%.⁸

Patients with second and third degree atrioventricular block are inevitably destined to depend on the right ventricular pacing. In these patients, ventricular lead placement in other position than right ventricular apex (RVA) may significantly reduce negative influence of permanent ventricular stimulation. Many data suggest that RVOT pacing may offer significant benefits over RVA pacing.^{3,20}

Because the percent of ventricular stimulation in patients with atrioventricular block is always close or equal to 100%, the role of appropriate AVD optimization is particularly important. Echocardiography and ICG are two noninvasive methods that are commonly used to AVD optimization. ICG is free of some of the limitations compared to echocardiography—it is replicable, undemanding of qualified personnel, and cheaper than the echocardiography, and therefore it is good alternative to echocardiography in AVD optimization.^{10,11}

Table 7. Summary of the Effects of Optimal AV Delay Programming

proBNP = level of proBNP in plasma; CI = cardiac index; 6MWT = six-minute walking test; QoL = quality of life; LVEF = left ventricle ejection fraction.

The measurement of the transthoracic impedance during cycle of the heart beat is the essence of the ICG. Thanks to the changes of the resistance of the blood pool in the aorta during the cycle of the heart beat it is possible to calculate CO and other hemodynamic parameters.¹¹

With one notable exception,¹⁵ the majority of studies comparing the effects of the optimization of AVD by ICG with different methods collaborate the utility of this modality.²¹⁻²⁴ That is the reason why the ICG is applied more and more often as the helpful tool finding the most optimal setting of the AV delay. Furthermore, the ease of use makes possible finding of AVDopt in about 20 minutes. It seems that the combination of RVOT ventricular pacing and AVD optimization is the key method of management of patients with atrioventricular block.

Atrioventricular optimization in this study was performed only at rest similarly to other published data.^{25,26} There are very little data regarding the hemodynamic effects of AVD optimization during exercise.²⁷ It is still not clear as to whether AVD optimization performed during exercise may provide further hemodynamic benefits in comparison with only resting optimization. Most modern DDD pacemakers offer the function called "Dynamic AVD," which provide dynamic AVD shortening with the increase of the heart rate. These algorithms were designed to approximate natural changes in AV conduction during exercise.⁹ However, recently published data²⁸ seems to

suggest that shortening or lengthening of the AVD during exercise has no considerable impact on CI hence programming of dynamic AVD may not offer additional benefits.

Our study was performed in patients with the intrinsic sinus rhythm (percentage of atrial pacing was <5%). When patient needs atrial pacing, e.g., because of significant bradycardia, AVD optimization is much more difficult. Optimal length of AVD differs whether the atrial event is paced (AP) or sensed (AS). Those two types AVD (AsVp and ApVp) differ on average by 16-134 ms, therefore some investigators consider that in patients with relevant percentage of atrial pacing, AVD should be optimized separately for sensed and paced P waves.^{29,30}

In our study, no significant difference were seen in echocardiographic parameters. It is plausible that the 3 month follow-up may be too short to develop significant remodeling^{28,31,32} or the RVOT location of the lead had "protective" effect (carries the smaller risk of unfavorable hemodynamic effect compared to right ventricle apex pacing). There has been much confusion among investigators defining optimal site for the right ventricular pacing.¹² True RVOT (especially right ventricular septum) pacing can be difficult to achieve. The technique for RVOT pacing, fluoroscopic appearances and ECG patterns have been elegantly reviewed recently.³³

CONCLUSIONS

Successful AV sequential pacing involves not only appropriate right ventricular lead placement but also involves programming of an individual, AVDopt. Our study results suggest that AVD optimization in patients with DDD pacemaker with ICG improves hemodynamic when compared to the default factory settings. Furthermore, optimally programmed AVD reduces BNP and improves exercise tolerance and functional class.

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